Therapeutic Plasma Exchange in the Treatment of Stiff Person Syndrome: Report of Nine Cases and Literature Review

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Outline

• Disease Description
• ASFA Guidelines
• Hopkins Case Series
• Literature Review
• Discussion
Stiff Person Syndrome, SPS

- Chronic neurologic disorder
- 1:1,250,000
- Middle age women and men
- Characterized
  - Progressive stiffness and painful muscle spasms
  - Imbalance, gait abnormalities, dysarthria
- Associated
  - Autoimmune endocrinopathies
  - 5% Paraneoplastic syndrome
Associated Antibodies
GABAergic Transmission

Anti-GAD65 85%
Anti-Amphiphysin 5%
Anti-GABARAP 65%
Anti-Gephyrin 1 case

=> Functional blockade on inhibitory neurotransmitters

Dalakas, M Cur Neurol Neuros Reports 2008
Anti-GAD65 and Disease

- Are not exclusive of SPS
  - Cerebellar ataxia, Diabetes Mellitus
  - Different epitope specificity
  - Titers
    - Very high titers in SPS, usually >1000
    - Low titers in diabetes

- Can be present in Serum and CSF
  - Good markers of disease
SPS Treatment

• GABA enhancing drugs:
  – Sedative anxiolytics: Diazepam
  – Antispasticity: Baclofen

• Immunotherapies
  – Corticosteroids
  – Immunosuppressive agents: Azathioprine
  – IV Immunoglobulin
  – Rituximab
  – Therapeutic Plasma Exchange
Immunotherapies

• Immunoglobulin
  – RCT, crossover: n=16, IVIG x 3 months vs. placebo
    • Improvement in stiffness and frequency of spasms
    • Antibody levels declined
    • Clinical response 6 weeks – 1 year

• Therapeutic plasma exchange
  – No RCT
  – ASFA Guidelines

*Dalakas, N Engl J Med 2001;345:1870-6*
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Role of Plasmapheresis in SPS

ASFA Guidelines 2007:

<table>
<thead>
<tr>
<th>STIFF-PERSON SYNDROME</th>
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<tbody>
<tr>
<td><strong>Disease Group:</strong> Neurological</td>
</tr>
<tr>
<td><strong>Incidence:</strong> 0.1 per 100,000/year</td>
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</table>

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Category</th>
</tr>
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<tbody>
<tr>
<td>TPE</td>
<td>III</td>
</tr>
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</table>

# of reported patients*: <100

<table>
<thead>
<tr>
<th>RCT</th>
<th>CT</th>
<th>CS</th>
<th>CR</th>
<th>Strength of evidence</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8  (9)</td>
<td>Type III</td>
</tr>
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</table>

Category III
There is a **suggestion of benefit** for which existing evidence is insufficient. TPE may reasonably be used when **conventional therapies** do not produce an adequate response **or as part of an IRB-approved research protocol**.

Level of evidence
Type III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
ASFA Guidelines 2010

Stiff Person Syndrome:

**Category IV**

**Evidence** suggests **no benefit or harm**. IRB-approval is desirable if TPE is undertaken.

**Level of Evidence**
Not described

**Recommendation Grade**
2C: Weak recommendation, low-quality of very low-quality evidence
Category IV Interpretation

For physicians and third party payers:

TPE in these disorders is “experimental”

Questions:
- Does TPE provide no benefit?
- Is TPE really harmful?
- What is the evidence?
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## Case series

Retrospective chart review  
n=9 Age: 55, range 34 - 72

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Female</td>
<td>7 (78 )</td>
</tr>
<tr>
<td>Anti-GAD65</td>
<td>8 (89 )</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (33 )</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>0</td>
</tr>
<tr>
<td>Cancer *</td>
<td>3 (33 )</td>
</tr>
<tr>
<td>Anti-Amphiphysin</td>
<td>1 (11 )</td>
</tr>
<tr>
<td>IVIG</td>
<td>6 (67 )</td>
</tr>
<tr>
<td>Immunosuppressive medication</td>
<td>4 (44 )</td>
</tr>
</tbody>
</table>

* Melanoma, Breast, Colon
TPE Treatments

• Every other day
• Replacement fluid: 50% Albumin 5%/ 50% NS
• Volume replaced: 110%
• Central line, ACD

• 7 patients: 5 treatments
• 1 patient: 5 x 2 treatments
• 1 patient: 5 x 3 treatments
Response to TPE Treatment

Severity score (Dalakas, NEJM 2001)

- Distribution-of-stiffness index
  - 0 to 6
  - reflect the extent of stiffness
  - lower trunk, upper trunk, legs, arms, face, and abdomen.

- Frequency of spasms
  - 1 to 7
  - Type of Stimulus (noises, visual, somatosensory, others)
Response to TPE Treatment

• No standardized severity score was used by the neurologists
• A more global non specific description of improvement was used

Descriptive Score:
1: No response
2: Minimal, some, partial improvement
3: Dramatic change
Response to TPE Treatment, n=9

Score:
1: No response
2: Minimal, some, partial improvement
3: Dramatic change

- Score 3: 5 (56%)
- Score 2: 2 (22%)
- Score 1: 2 (22%)
Patients with Adverse Events, n=9

- Catheter Infection: 7 (78%)
- Transient Hypotension: 1 (11%)
- No complications: 1 (11%)

Total: 9 patients
Summary of Hopkins Case Series

- 9 patients refractory to standard treatment
- Most of the patients had at least some response to TPE treatment
- Those patients with high antibody levels were likely to have a response to TPE
- Overall, TPE was well tolerated
- No other conclusions possible due to small number of observations
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## Literature Review

18 publications  
n=26  
Age: 53 (range 10 – 79)

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>Information available, n</th>
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<tbody>
<tr>
<td>Female</td>
<td>15 (63)</td>
<td>24</td>
</tr>
<tr>
<td>Anti-GAD65</td>
<td>14 (61)</td>
<td>23</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (29)</td>
<td>24</td>
</tr>
<tr>
<td>Autoimmunity*</td>
<td>6 (25)</td>
<td>24</td>
</tr>
<tr>
<td>Cancer†</td>
<td>4 (17)</td>
<td>24</td>
</tr>
<tr>
<td>Anti-Amphiphysin</td>
<td>1 (100)</td>
<td>1</td>
</tr>
<tr>
<td>IVIG</td>
<td>6 (23)</td>
<td>26</td>
</tr>
<tr>
<td>Immunosuppressive drugs</td>
<td>16 (62)</td>
<td>26</td>
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</table>

*Hashimoto, Graves (2), Vitiligo, Pernicius Anemia, Rheumatoid Arthritis

†Thymoma, Breast, Lung, Mesopharyngeal carcinoma
TPE Treatment

![Bar graph showing TPE Treatment](image.png)

- TPE Treatment: 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 treatments per patient.
- Number of patients: 1, 1, 1, 2, 2, 1, 1, 4, 8.

TPE: Therapeutic Plasma Exchange
Response to TPE Treatment, n=26

Score:
1: No response
2: Minimal, some, partial improvement
3: Dramatic change

Score 1: 10 (38%)
Score 2: 5 (19%)
Score 3: 11 (42%)
# Response to Treatment vs. Clinical Variables

<table>
<thead>
<tr>
<th></th>
<th>Response</th>
<th>Correlation</th>
<th>p</th>
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<tbody>
<tr>
<td># TPE</td>
<td></td>
<td>0.230</td>
<td>0.300</td>
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<tr>
<td>Immunosuppressive drugs</td>
<td></td>
<td>0.188</td>
<td>0.350</td>
</tr>
<tr>
<td>IVIG</td>
<td></td>
<td>0.058</td>
<td>0.770</td>
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<tr>
<td>Anti-GAD65</td>
<td></td>
<td>-0.375</td>
<td>0.080</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>0.065</td>
<td>0.764</td>
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<tr>
<td>Autoimmune disease</td>
<td></td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td>0.316</td>
<td>0.132</td>
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</tbody>
</table>
Patients with Adverse Events, n=26

- No complications: 19 (73%)
- Lymphoid leakage: 1 (4%)
- Line Infection: 1 (4%)
- Technical problems: 2 (8%)
- Not specified: 3 (12%)
Literature Review Summary

• No prospective, randomized trials
• The majority of patients had at least a minimal improvement
• Prolonged treatment seems to correlate with positive response
• Adverse events were infrequent
• Unanswered questions:
  – Timing to start TPE treatment, duration
  – Combination with other therapies (immunosuppressive drugs, IVIG, BZD, physical therapy)
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Discussion

• In observational studies, TPE seems to provide some benefit to the majority of patients who were refractory to standard treatment.

• A Category IV recommendation could exclude patients from receiving TPE after they failed first and second line therapy, leaving these patients without therapeutic options.

• Current data represents low quality evidence (2C recommendation), but it does not demonstrate harm and suggests some benefit.
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Questions?

Thanks