Pathogenesis and Mechanism of Action of Inflammatory Neuropathies
Pathogenic processes significant to inflammatory neuropathies

- There are common pathogenic processes involved in acute and chronic inflammatory immune neuropathies:
  
  **Axonal dysfunction**
  - Axonal dysfunction causes alterations in impulse propagation at the Nodes of Ranvier which slows / blocks conduction
  - Changes in conduction results in transient weakness which can be reversible with treatment; however, may lead to axonal degeneration

  **Demyelination**
  - Leads to dysfunction at inter- / para- nodes affecting conduction
  - Transient weakness can be reversible with treatment; may lead to permanent axonal damage

  **Axonal structural damage**
  - If axonal degeneration occurs, it is less amenable to treatment and is more likely to cause permanent disability

CIDP: chronic inflammatory demyelinating polyneuropathy, GBS: Guillain-Barré Syndrome
Temporal evolution of disease: The GBS to CIDP continuum

- It is currently unclear what causes acute or chronic forms of disease

CIDP: chronic inflammatory demyelinating polyneuropathy, GBS: Guillain-Barré Syndrome
Current understanding of GBS pathogenesis

- At least 2 GBS variants have a complement-mediated stage where a membrane-attack complex (MAC) is formed.
- Acute motor axonal neuropathy (AMAN)
  
  IgG anti-GM1 / GD1a auto-antibodies bind to membrane antigens leading to MAC formation
  
  - Sodium channel clusters are disrupted or disappear at lengthened nodes in addition to the disruption of paranodal junctions.
  - This disruption may result in myelin detachment leading to nerve-conduction failure, muscle weakness, and possibly axonal degeneration. Macrophages subsequently invade and scavenge injured axons.
- Acute inflammatory demyelinating polyneuropathy (AIDP)
  
  Auto-antibodies bind to unidentified myelin antigens and activate complement. MAC forms on outer surface of Schwann cells and initiates vesicular degeneration. Macrophages later scavenge myelin debris.


Current understanding of CIDP pathogenesis

- May be caused by abnormal immune response mediated by lymphocytes and macrophages, in addition to auto-antibodies and complement

- In CIDP patients:
  - Pro-inflammatory and regulatory cytokines – elevated in the CSF
  - Serum TNF-α levels are raised – correlate with disease activity
  - Activated T-cells, mainly CD4⁺ – increased in the circulation
  - Antigen-driven, major histocompatibility complex class I restricted, CD8⁺ T-cell-mediated attack

- T-cells may activate residing macrophages, leading to:
  - Enhanced phagocytosis
  - Production of pro-inflammatory molecules, e.g.:
    - Reactive oxygen species
    - Proteases
    - Pro-inflammatory cytokines

- Auto-antibodies may contribute to disease process by complement activation or antibody-dependent cellular toxicity

CIDP: chronic inflammatory demyelinating polyneuropathy, CSF: cerebral spinal fluid, MoA: mechanism of action, TNF: tumor necrosis factor

Current understanding of MMN pathogenesis

- In up to 60% of MMN patients, antibodies against gangliosides including GM1 are present\(^1\)
- Antibodies may bind to GM1 and cause disruption of ion channel clusters, which leads to conduction block;\(^2\) a defining physiologic feature of this disease
- The resultant progressive axonal damage may lead to progressive axonal loss and permanent disability\(^2\)


Acute and chronic immune-mediated neuropathies

**Acute**
- AIDP
- AMAN
  - IgG anti-GM1
  - Fisher Syndrome
  - IgG anti-GQ 1B

**Chronic**
- CIDP
- MMN
  - IgM anti-GM1
  - CANOMAD
  - IgM anti-GQ 1B
  - Anti-MAG neuropathy

Gangliosides and disease pathogenesis

- Gangliosides are a group of glycosphingolipids widely distributed in membrane components of the nervous system\(^1\)
- Auto-antibodies targeting gangliosides can be associated with clinical symptoms that imply selective nerve damage\(^2\)

<table>
<thead>
<tr>
<th>Auto-antibody</th>
<th>Neuropathy</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM1</td>
<td>Multifocal or lower motor</td>
<td>MMN, AMAN, AIDP, CIDP</td>
</tr>
<tr>
<td>Asialo-GM1</td>
<td>Motor and sensorimotor</td>
<td>AIDP</td>
</tr>
<tr>
<td>GD1a</td>
<td>Motor and sensorimotor</td>
<td>AIDP, AMAN</td>
</tr>
<tr>
<td>GD1b</td>
<td>Sensory w/ or w/o ataxia</td>
<td>SAN, ASAN, CANOMAD</td>
</tr>
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<td>GQ1b</td>
<td>Motor and sensorimotor</td>
<td>Fisher, ASAN, CANOMAD</td>
</tr>
</tbody>
</table>


   Accessed May 2013
Current understanding of Plasma exchange MoA

- Plasma exchange (PE) removes:
  - Auto-antibodies
  - Cytokines
  - Complement
  - Unknown humoral factors that alter lymphocyte function

- The result is:
  - Improvement of axonal functions
  - Reduced nerve injury through decreased complement attack and axonal damage
  - Clinical improvement compared to no treatment

PE: plasma exchange, MoA: mechanism of action
Current understanding of IgG MoA

- IgG is thought to act by:\(^1,^2\)
  - Neutralizing pathogenic auto-antibodies
  - Inhibiting auto-antibody-mediated complement activation
  - Altering FcR expression and redressing altered cytokine patterns

- The result is:\(^1\)
  - Improvement of axonal functions
  - Reduced nerve injury through decreased complement attack and axonal damage
  - Faster clinical improvement compared with no treatment

FcR: fragment crystallizable receptor, IgG: immunoglobulin G, MoA: mechanism of action
**Additional thoughts**

- MMN must be distinguished from other degenerative motor neuron diseases and CIDP due to differences in prognosis and therapy
  - Certain therapies may exacerbate weakness in MMN patients
- Increasing evidence suggests that IgM antibodies to GM1 are biomarkers for MMN
- As GM1 is only found in up to 80% of patients, there may be antibodies of other specificities that perform a similar function
  - Sensitivity of current assays may affect antibody detection

CIDP: chronic inflammatory demyelinating polyneuropathy, GM1: ganglioside GM1, IgM: immunoglobulin M, MMN: multifocal motor neuropathy