DIFFERENTIAL DIAGNOSIS OF NEUROGENIC DISORDERS & MYOPATHIES

<table>
<thead>
<tr>
<th>NEUROPATHY</th>
<th>MYOPATHY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>distal</td>
</tr>
<tr>
<td>Sensory dysfunction</td>
<td>proximal</td>
</tr>
<tr>
<td>Loss of reflexes</td>
<td>0</td>
</tr>
<tr>
<td>Serum enzymes</td>
<td>+/-</td>
</tr>
<tr>
<td>CSF protein</td>
<td>+/+</td>
</tr>
<tr>
<td>Electromyography</td>
<td>neurogenic</td>
</tr>
<tr>
<td></td>
<td>myopathic</td>
</tr>
</tbody>
</table>

CLASSIFICATION OF PERIPHERAL NERVE DISEASES

Myelinopathy
- Acute inflammatory polyneuropathy (Guillain-Barré syndrome or GBS)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Charcot-Marie-Tooth, type 1 (CMT-1)

Axonopathy
- Wallerian degeneration (trauma, vasculitis etc.)
- Distal axonopathies (dying back neuropathies)

Neuronopathy
- Amyotrophic lateral sclerosis (ALS)

CLINICAL ROLE OF NERVE BIOPSY IS VERY LIMITED

- Identify the cause of a neuropathy (vasculitis, amyloidosis).
- Nerve conduction studies are more useful than nerve biopsy for distinguishing between a demyelinating neuropathy and an axonal disorder.

PATHOLOGICAL ANALYSIS OF SURAL NERVE BIOPSY

- ROUTINE HISTOLOGY
- SEMITHIN PLASTIC SECTIONS
- TEASED MYELINATED FIBERS
- ELECTRON MICROSCOPY

SURAL NERVE, SEMITHIN PLASTIC SECTION (TOLUIDINE BLUE)

TEASED MYELINATED FIBER: NORMAL
PERIPHERAL NERVE, ELECTRON MICROGRAPH

SEQUENCE OF SEGMENTAL DEMYELINATION & REMYELINATION

NERVE STIMULATION EVOKES ACTION POTENTIAL IN HAND MUSCLE

TEASED MYELINATED FIBER: SEGMENTAL REMYELINATION

SAME TEASED FIBER AT HIGHER MAGNIFICATION

SEQUENCE OF SEGMENTAL AXONAL DEGENERATION & REGENERATION

Conduction slowing
Conduction block of action potentials

NORMAL COMPOUND MUSCLE ACTION POTENTIAL
REDUCED AMPLITUDE OF CMAP

TEASED MYELINATED FIBER: AXONAL DEGENERATION

CLASSIFICATION OF PERIPHERAL NERVE DISEASES

Myelinopathy
- Acute inflammatory polyneuropathy (Guillain-Barré syndrome or GBS)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Charcot-Marie-Tooth, type 1 (CMT-1)

Axonopathy
- Wallerian degeneration (trauma, vasculitis etc.)
- Distal axonopathies (dying back neuropathies)

Neuronopathy
- Amyotrophic lateral sclerosis (ALS)

ACUTE INFLAMMATORY POLYNEUROPATHY (GUILLAIN-BARRE SYNDROME OR GBS)

- Rapidly progressive neuropathy, chiefly motor, reaching maximum weakness usually within 1 to 2 weeks.
- Severe respiratory weakness is a major danger and may require treatment in an intensive care unit.
- An acute infectious illness precedes weakness in two thirds, consisting of influenza-like symptoms or diarrhea. The respiratory disorder is linked to infection by viruses whereas diarrhea is often caused by Campylobacter jejuni.
- Recovery takes weeks or months. Permanent handicap occurs in 15%-20% of patients.

GBS: DIAGNOSIS & TREATMENT

- Electrophysiology: early block of conduction of action potentials along motor nerves. Slowing of conduction velocity develops later as segmental remyelination appears.
- Electrodiagnostic studies often show evidence of co-existing axonal degeneration, usually of mild degree.
- Cerebrospinal fluid typically has mildly elevated protein and no cells.
- Sural nerve biopsy does not have a role in diagnosis but has provided information about etiology and pathogenesis.
- Plasmapheresis or intravenous gamma globulin speeds recovery.

PATHOLOGY OF GUILLAIN-BARRÉ SYNDROME

- Immune complexes (C3, IgG, IgM) are detectable on the surface of myelin sheaths in the early stage.
- Sparse T cells, chiefly CD4 subset, infiltrate endoneurium.
- Monocytes and macrophages appear to attack myelin sheaths.
- Myelinated fibers show segmental demyelination during the first few days. Segmental remyelination occurs subsequently.
- The lesions have a perivenular distribution and tend to affect the DRG, nerve roots and adjacent nerves where blood-nerve barrier is normally more permeable than elsewhere.

GBS, DORSAL ROOT GANGLION, H&E
GBS, MOTOR NERVE, H&E

GBS, MOTOR NERVE, SEMITHIN SECTION

GBS, ELECTRON MICROGRAPH

GBS, SEGMENTAL REMYELINATION

GBS, C3 COMPONENT ON MYELIN SHEATHS

EVIDENCE FOR AUTOIMMUNE ETIOLOGY IN GUILLAIN-BARRE SYNDROME

- Demyelinating neuropathy can be induced in experimental animals by immunization with myelin, purified myelin protein or galactocerebroside.

- Antibody titers to nerve myelin in patients correlate with disease activity.

- The antibodies recognize specific glycolipids or glycoproteins of peripheral myelin in a minority of patients.

- Immune complexes are found at surface of myelin sheaths.

- Plasmapheresis or intravenous gamma globulin speeds recovery when treatment is started early.
AXONAL VARIANT OF GUILLAIN-BARRÉ SYNDROME

• Clinical syndrome resembles Guillain-Barre syndrome, but is often purely motor.
• It is common in Asia and other countries but accounts for only 5% of patients in the US or Europe.

AXONAL VARIANT OF GBS, Possible molecular mimicry

• The patients often have elevated serum autoantibodies that recognize the terminal oligosaccharide of GM1 & GD1a ganglioside.
• The chemical structure of lipopolysaccharide of C. jejuni has the same oligosaccharide chain present in GD1a and GM1.
• This suggests that the immune response to C. jejuni induces antibodies that crossreact to a self-antigen of the axolemma. This axonal variant of autoimmune neuropathy is postulated to be caused through molecular mimicry.

CLASSIFICATION OF PERIPHERAL NERVE DISEASES

Myelinopathy
Acute inflammatory polyneuropathy (Guillain-Barré syndrome or GBS)
Chronic inflammatory demyelinating polyneuropathy (CIDP)
Charcot-Marie-Tooth, type 1 (CMT-1)

Axonopathy
Wallcerian degeneration (trauma, vasculitis etc.)
Distal axonopathies (dying back neuropathies)

Neuronopathy
Amyotrophic lateral sclerosis (ALS)

CHRONIC INFLAMMATORY Demyelinat-ING POLYNEUROPATHY (CIDP)

• Chronic progressive or relapsing neuropathy, motor > sensory.
• An antecedent infectious illness is uncommon.
• Electrophysiology: conduction block and slowing of velocity.
• Pathology: segmental demyelination and remyelination, onion bulbs, fibrosis and little or no lymphocytic infiltration of tissue.
• Probably an autoimmune disorder of myelin but pathogenesis is not well understood.
• Patients respond to plasmapheresis, intravenous gamma globulin or corticosteroid treatment.

ONION BULB

CIDP WITH ONION BULBS
CLASSIFICATION OF PERIPHERAL NERVE DISEASES

Myelinopathy
- Acute inflammatory polyneuropathy (Guillain-Barré syndrome or GBS)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Charcot-Marie-Tooth, type 1 (CMT-1)

Axonopathy
- Wallerian degeneration (trauma, vasculitis etc.)
- Distal axonopathies (dying back neuropathies)

Neuronopathy
- Amyotrophic lateral sclerosis (ALS)

CHARCOT-MARIE-TOOTH, TYPE 1
- Slowly progressive distal limb weakness begins in first decade with great variation in onset; few sensory complaints.
- Autosomal dominant, mutations commonly affect PMP22.
- Neurological exam:
  - Atrophy of distal leg muscles (stork leg appearance).
  - Palpable nerve enlargement in 50%.
  - Pes cavus and hammer toes is common.
- Pathology: Similar to CIDP.

AMYOTROPHIC LATERAL SCLEROSIS
(LOU GEHRIG’S DISEASE)
- Progressive weakness, muscle wasting and fasciculations; often asymmetrical in the beginning.
- Symptoms usually begin after the age of 40.
- Hyperactive tendon reflexes, clonus and Babinski signs.
- Electromyogram: Signs of denervation in muscle. Normal or slightly reduced conduction.
- Most are sporadic; about 10% are familial.
- Death occurs usually within 3 to 5 years from onset.

ALS: FASCICULATIONS & BABINSKY REFLEXES

ALS: LOWER MOTOR NEURON PATHOLOGY
- Loss of motor neurons in ventral horns and nuclei of cranial nerve V, VII, IX-XII.
- Sparing of motor nuclei of cranial nerves III, IV & VI and Onuf’s nucleus.
- Surviving motor neurons show atrophy & inclusions.
- Few chromatolytic-like nerve cells.
- Little or no evidence of axonal regeneration.
**ALS: LOSS OF MOTOR NEURONS IN VENTRAL HORN**

**ALS & SARCOIDOSIS, SPINAL CORD, TDP-43**

- Intracytoplasmic aggregates of granules and loosely-arranged fibrils (skein-like inclusions) occur in motor neurons of spinal cord and brain stem. Rare in Betz motor cells of precentral gyrus.
- Invisible in routine histology (H&E) and are not argyrophilic.
- The inclusions are composed of TDP-43, a protein that is normally expressed in the nucleus.
- The skein-like inclusions are ubiquinated.
- Sensitivity: 90-100%; specificity: >95%.

**SKEIN-LIKE INCLUSIONS**

- Intracytoplasmic aggregates of granules and loosely-arranged fibrils (skein-like inclusions) occur in motor neurons of spinal cord and brain stem. Rare in Betz motor cells of precentral gyrus.
- Invisible in routine histology (H&E) and are not argyrophilic.
- The inclusions are composed of TDP-43, a protein that is normally expressed in the nucleus.
- The skein-like inclusions are ubiquinated.
- Sensitivity: 90-100%; specificity: >95%.

**ALS: UPPER MOTOR NEURON PATHOLOGY**

- Loss of Betz cells (upper motor neurons) in precentral gyrus.
- Pyramidal degeneration with gradually increasing myelin pallor in a caudal direction due to loss of axons.
- The tract degeneration is marked by macrophages (removing myelin debris) and numerous activated microglia.
Mutations of the Cu/Zn superoxide dismutase (SOD1) cause ALS of 20% of familial cases. Expression of mutant human SOD1 in transgenic mice produces MND by a toxic or gain of function mechanism. This mouse model has yielded two major hypotheses of toxicity:

- Aberrant oxidation
- Intracellular aggregates
- Glutamate toxicity, disrupted calcium homeostasis, abnormal nitration and glycation of proteins, apoptotic death

**AIMS OF MUSCLE BIOPSY**

- Distinguish a neurogenic disorder from a myopathy.
- Screen inherited myopathies for molecular analysis.
- Subclassify acquired myopathies.
MODIFIED GOMORI TRICROME

SUCCINATE DEHYDROGENASE

DIAGNOSTIC HISTOLOGICAL FEATURES OF A NEUROGENIC DISORDER

• LARGE GROUPS OF ATROPHIC FIBERS
• FIBER TYPE GROUPING
• TARGET FIBERS

GROUPS OF ATROPHIC MYOFIBERS, H&E

FIBER TYPE GROUPING

NADH-DEHYDROGENASE

ATPase

TARGET FIBERS, NADH DEHYDROGENASE

DIAGNOSTIC HISTOLOGICAL FEATURES OF MYOPATHIES

• ABSENCE OF NEUROGENIC ABNORMALITIES
• NECROTIC MUSCLE FIBERS
• BASOPHILIC (REGENERATING) MYOFIBERS
• FIBROSIS OF THE ENDOMYSIUM
• SPECIAL PATHOLOGICAL FEATURES (INFLAMMATORY CELLS, RAGGED RED FIBERS ETC.)
GOWER’S SIGN

Gowers, 1879

DUCHELLE MUSCULAR DYSTROPHY

- X-linked recessive inheritance
- Onset of weakness noticeable at 2-5 years of age.
- Progressive weakness, proximal>distal
- Hypertrophy of calves
- High serum creatine kinase activity
- Fatal in 3rd decade
**DUCHENNE MUSCULAR DYSTROPHY**

- Dystrophin is a 427 kD protein that binds to the inner face of the surface membrane.
- The protein has amino acid sequence similarities with alpha-actinin, an actin binding protein.
- The protein links actin to the surface membrane and the basal lamina acting through dystroglycan and merosin (alpha 2-laminin).
- Interrupting this linkage causes the surface membrane to be unstable leading to fiber injury.

---

**DUCHENNE DYSTROPHY, SPECTRIN**

**DUCHENNE DYSTROPHY, DYSTROPHIN**

---

**INFLAMMATORY MYOPATHIES**

- Polymyositis
- Inclusion body myositis
- Dermatomyositis

---

**POLYMYOSITIS**
**DIAGNOSTIC FEATURES OF POLYMYOSITIS**

- Subacute progressive weakness, proximal>distal. Usually adults, women more common than men.
- Elevated serum creatine kinase activity.
- Electromyogram: myopathic potentials, spontaneous activity.
- Muscle biopsy: inflammatory myopathy affecting chiefly the endomysium.
- Usually respond to glucocorticoids.

**POLMYOSITIS, H&E**

**POLMYOSITIS, PARAFFIN SECTION, H&E**

**POLMYOSITIS, IMMUNOPEROXIDASE, CD8**

**POLYMYOSITIS: PATHOLOGY**

- Necrotic fibers and regenerating fibers randomly distributed throughout the muscle specimen.
- CD8 cytotoxic cells infiltrate predominantly the endomysium with invasion of rare myofibers.
- Little fibrosis or myofiber hypertrophy, consistent with a subacute disorder.

**INCLUSION BODY MYOSITIS**
**DIAGNOSTIC FEATURES OF IBM**

- Most common inflammatory myopathy in patients over the age of 50 years and affects mostly men.
- Slowly progressive weakness, proximal and distal.
- Mildly elevated serum creatine kinase or normal.
- Electromyogram: myopathic potentials, spontaneous activity.
- Muscle biopsy: resembles polymyositis, but chronic and exhibits rimmed vacuoles and amyloid inclusions.
- Usually does not respond to glucocorticoids.

**INCLUSION BODY MYOSITIS, H&E**

**IBM, RIMMED VACUOLES, H&E**

**IBM, EOSINOPHILIC INCLUSION IN A RIMMED VACUOLE**

**IBM, CONGO RED, FLUORESCENCE, RHODAMINE OPTICS**

**ELECTRON MICROSCOPY, 15-20 nm FILAMENTS**
IBM PATHOLOGY
- IBM resembles polymyositis but has hypertrophic fibers and prominent endomysial fibrosis indicating it is chronic.
- Rimmed vacuoles.
- Congophilic fibrillar inclusions, composed of abnormal (? paired-helical) filaments.
- Lymphocytic infiltration suggests an autoimmune disorder, but disorder is usually unresponsive to immunosuppression.

DERMATOMYOSITIS

DIAGNOSTIC FEATURES OF DERMATOMYOSITIS
- Subacute progressive weakness, proximal>distal. Children and adults, women more common than men.
- Characteristic rash on face, chest & extensor surfaces.
- Elevated serum creatine kinase activity.
- Electromyogram: myopathic potentials, spontaneous activity.
- Muscle biopsy: inflammatory myopathy affecting chiefly the perimysium with perifascicular atrophy.
- Usually respond to glucocorticoids or IVGG.

DERMATOMYOSITIS: LYMPHOCYTE PHENOTYPES
- CD4 T cells and B cells located chiefly in connective tissue and around vessels of perimysium.
- Inconstant and usually sparse CD8 T cells located mainly in endomysium.

DM, IMMUNE COMPLEXES (C5b-9) IN BLOOD VESSEL WALL
TUBULORETICULAR AGGREGATE IN ENDOTHELIAL CELL

DERMATOMYOSITIS: PATHOLOGY

- Perifascicular atrophy of muscle fibers, with or without necrotic fibers or regenerating fibers.
- Immune complexes of immunoglobulins and complement components in the walls of blood vessels.
- Endothelial tubuloreticular aggregates.
- Reduced number of capillaries at periphery of fascicle.
- Lymphocytes are often sparse and located in chiefly perimysium.

INFLAMMATORY MYOPATHIES: PATHOPHYSIOLOGY

- Polymyositis and inclusion body myositis (IBM) have autoaggressive CD8 lymphocytes that appear to attack myofibers and suggest an autoimmune role. However, a major question exists about the etiology and pathogenesis of IBM.
- Dermatomyositis is thought to be caused by autoantibodies, possibly targeting an antigen of the endothelium. The pathological findings suggest that myofiber injury may be caused by ischemia.

HYPOTONIA IN INFANCY

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>INHERITED</th>
<th>PROGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Werdnig-Hoffmann disease</td>
<td>Autosomal recessive</td>
<td>Fatal</td>
</tr>
<tr>
<td>Central core disease</td>
<td>Autosomal</td>
<td>Not pro-</td>
</tr>
<tr>
<td>Nemaline myopathy</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Mitochondrial disorder</td>
<td>Maternal or autosomal</td>
<td>Variable</td>
</tr>
</tbody>
</table>

WERDNIG-HOFFMANN DISEASE

CENTRAL CORE DISEASE, NADH DEHYDROGENASE
MITOCHONDRIAL MYOPATHY

MUTATIONS OF mtDNA RAGGED “RED” FIBER

CYTOCHROME C OXIDASE DEFICIENT MYOFIBER

RRF, SUCCINATE DEHYDROGENASE