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 loss</td>
<td>+</td>
</tr>
<tr>
<td>Loss of reflexes</td>
<td>early</td>
</tr>
<tr>
<td>CSF protein</td>
<td>elevated</td>
</tr>
<tr>
<td>Electromyography</td>
<td>neurogenic</td>
</tr>
<tr>
<td>Serum enzymes</td>
<td>+/-</td>
</tr>
</tbody>
</table>

CLASSIFICATION OF PERIPHERAL NERVE DISEASES

Myelinopathy
- Acute inflammatory polyneuropathy (AIP)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Charcot-Marie-Tooth, type 1 (CMT-1)

Axonopathy
- Vasculitis, amyloidosis
- Metabolic neuropathies (diabetic neuropathy)
- Toxic neuropathy (acrylamide neuropathy)

Neuroropathy
- Amyotrophic lateral sclerosis (ALS)

TEASED MYELINATED FIBER: NORMAL
TEASED MYELINATED FIBER: SEGMENTAL REMYELINATION

SAME TEASED FIBER AT HIGHER MAGNIFICATION

TEASED MYELINATED FIBER: AXONAL DEGENERATION

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ACUTE INFLAMMATORY POLYNEUROPATHY (GUILLAIN-BARRE SYNDROME [GBS])

- Rapidly progressive neuropathy, chiefly motor, reaching maximum weakness usually within 1 to 2 weeks.
- An acute infectious illness precedes weakness in two thirds.
- Electrophysiology: slow conduction velocity & conduction block but also show axonal degeneration, usually of mild degree.
- Recovery takes weeks or months. Permanent handicap in 5%.
- Plasmapheresis or intravenous gamma globulin speeds recovery.
PATHOLOGY OF ACUTE INFLAMMATORY POLYNEUROPATHY (GBS)

• Immune complexes (C3, IgG, IgM) are detectable on the surface of myelin sheaths in the early stage.
• 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.
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, P2 myelin basic protein or galactocerebroside.
• Antibody titers to nerve myelin in patient correlate with disease activity.
• The antibodies recognize glycolipids of peripheral myelin.
• Immune complexes are found at the surface of myelin sheaths.
• Plasmapheresis or intravenous gamma globulin speeds recovery when treatment is started early.

AXONAL VARIANT OF GUILLAIN-BARRE SYNDROME

• Clinical syndrome resembles Guillain-Barre syndrome, but is often purely motor.
• It was first described in children in China by investigators from John Griffin and others from Johns Hopkins.
• Electrodiagnostic studies suggested a purely axonal disorder with little slowing of conduction velocity or block.
• Some of the patients died within a few days of the onset of weakness allowing autopsy study of the nerves.

AXONAL VARIANT OF GUILLAIN-BARRE SYNDROME

• Autopsy showed axonal degeneration with little or no demyelination or lymphocytic infiltration.
• Immune complexes were found at the nodes of Ranvier.
• The disorder was often preceded by a gastrointestinal illness caused by the bacterium, Campylobacter jejuni.
• Elevated serum antibodies to GD1 & GM1 ganglioside; these antibodies recognized the terminal oligosaccharide chain, which is a component of both gangliosides.

AXONAL VARIANT OF GUILLAIN-BARRE SYNDROME

• It turned out that the chemical structure of the lipopolysaccharide of the bacterium includes the same oligosaccharide chain present in GD1a and GM1.
• This suggests that the immune response to the infection could react to both Campylobacter jejuni and gangliosides expressed on axons.
• This data provides support for the idea that molecular mimicry can be the basis for this autoimmune neuropathy.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

• Chronic progressive or relapsing neuropathy, motor > sensory.
• An antecedent infectious illness is uncommon.
• Electrophysiology: slow conduction velocity & conduction block.
• Pathology: segmental demyelination and remyelination, onion bulbs, fibrosis and little or no lymphocytic infiltration of tissue.
• Autoimmune disorder of myelin, probably antibody-mediated.
• Patients respond to plasmapheresis, intravenous gamma globulin or corticosteroid treatment.
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VASCUITIC NEUROPATHY

SURAL NERVE BIOSY, CONGO RED

CIDP WITH ONION BULBS

SURAL NERVE BIOSY, CONGO RED, BIREFRINGENCE
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AMYOTROPHIC LATERAL SCLEROSIS (LOU GEHRIG’S DISEASE)

- Progressive weakness and wasting with fasciculations, often asymmetrical in the beginning.
- Hyperactive tendon reflexes, clonus and Babinski signs.
- Symptoms usually begin after the age of 40.
- Electrodiagnostic: denervation & normal nerve conductions.
- Most are sporadic; 5-10% are familial.
- Death usually within 3 to 5 years from onset.

ALS: UPPER MOTOR NEURON PATHOLOGY

- Loss of Betz cells in precentral gyrus.
- Pyramidal degeneration with gradually increasing myelin pallor in caudal direction due to loss of axons.
- The tract degeneration is marked by macrophages (removing myelin debris) and numerous activated microglia.
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.
- Motor neurons show atrophy & inclusions.
- Few, if any, chromatolytic nerve cells.
- Little or no evidence of axonal regeneration.

ALS, SKEIN-LIKE INCLUSIONS, UBIQUITIN

- Intracytoplasmic aggregates of loosely-arranged fibrils in motor neurons of spinal cord and brain stem. Rare in Betz cells.
- Invisible in routine histology (H&E) and are not argyrophilic.
- Ubiquitin presumably conjugated to a protein but not identified yet.
- Sensitivity: 90-100%.
- Specificity: >95%.

UBIQUTINATED SKEIN-LIKE INCLUSIONS

ALS, NEUROFILAMENT PROTEIN
PATHOGENESIS OF ALS

Mutations of the Cu/Zn superoxide dismutase (SOD1) cause ALS of 20% of familial cases. Expression of mutant human SOD1 produces MND in transgenic mice 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

CRYOSECTIONS OF SKELETAL MUSCLE, H&E

CRYOSECTIONS OF SKELETAL MUSCLE, ATPase

MODIFIED GOMORI TRICHOE

SUCCINATE DEHYDROGENASE

DIAGNOSTIC HISTOLOGICAL FEATURES OF A NEUROGENIC DISORDER

- GROUPS OF ATROPHIC FIBERS
- FIBER TYPE GROUPING
- TARGET FIBERS

GROUPS OF ATROPHIC MYOFIBERS, H&E
FIBER TYPE GROUPING

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.)

NECROTIC FIBER, H&E

REGENERATING FIBER, H&E

DUCHENNE MUSCULAR DYSTROPHY

• X-linked recessive inheritance
• Onset of weakness before age 5
• Progressive weakness, proximal>distal
• Hypertrophy of calves
• High serum creatine kinase activity
• Fatal in 3rd decade
Duchenne Muscular Dystrophy

Duchenne Muscular Dystrophy (DMD) is a genetic disorder that affects the muscles. It is caused by mutations in the DMD gene, which is located on the X chromosome. The gene codes for a protein called dystrophin, which plays a crucial role in maintaining muscle integrity.

Dystrophin is a 427 kD protein that binds to the inner face of the surface membrane. It 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.

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.
MUSCLE BIOPSY DIAGNOSES OF POLYMYOSITIS (46 CASES)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Inflammatory myopathy</td>
<td>52%</td>
</tr>
<tr>
<td>Myopathy</td>
<td>10%</td>
</tr>
<tr>
<td>Muscle fiber atrophy</td>
<td>15%</td>
</tr>
<tr>
<td>Normal</td>
<td>23%</td>
</tr>
</tbody>
</table>

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

- Slowly progressive weakness, proximal and distal. Usually in adults, mostly men.
- Mildly elevated serum creatine kinase or normal.
- Electromyogram: myopathic potentials, spontaneous activity.
- Muscle biopsy: inflammatory myopathy affecting chiefly the endomysium, but chronic and has rimmed vacuoles and amyloid inclusions.
- Usually does not respond to glucocorticoids.
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.

DERMATOMYOSITIS

- Subacute progressive weakness, proximal>distal. Children and adults, women more common than men.
- Characteristic rash and periorbital heliotrope.
- 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.

DIAGNOSTIC FEATURES OF DERMATOMYOSITIS
DERMATOMYOSITIS, PERIFASCICULAR ATROPHY, H&E

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.
- Tubuloreticular aggregates (undulating tubules).
- 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 of IBM.
- Dermatomyositis is thought to be caused by autoantibodies, possibly targeting an antigen of the endothelium. Fiber 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 dominant</td>
<td>Not progresive</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

![Werdnig-Hoffmann Disease](image1)

## Central Core Disease, NADH Dehydrogenase

![Central Core Disease](image2)

## Mitochondrial Myopathy

![Mitochondrial Myopathy](image3)

## Mutations of mtDNA Ragged “Red” Fiber

![Mutations of mtDNA Ragged “Red” Fiber](image4)

## Cytochrome C Oxidase Deficient Myofiber

![Cytochrome C Oxidase Deficient Myofiber](image5)
RRF, SUCCINATE DEHYDROGENASE