"RIABILITAZIONE DELLE MALATTIE NEUROMUSCOLARI"
Neuromuscular Disorders
### Neurological disorders: approximate point prevalence rates per 100,000 population, all ages. 1. Most common entities

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2,000&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Other severe headache&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1,500&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Brain injury</td>
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<tr>
<td>Epilepsy</td>
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<tr>
<td>Acute cerebrovascular disease</td>
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<td>Lumbosacral pain syndrome&lt;sup&gt;a&lt;/sup&gt;</td>
<td>500&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Alcoholism&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Ménière’s disease</td>
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<td>Lumbosacral herniated nucleus pulposus</td>
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<tr>
<td>Cerebral palsy</td>
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<td>Dementia</td>
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<td>Parkinsonism</td>
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<td>Transient ischemic attacks</td>
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<td>Febrile fits</td>
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<td>Multiple sclerosis&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Benign brain tumor</td>
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<td>Cervical pain syndrome&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Down syndrome</td>
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<td>Subarachnoid hemorrhage</td>
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<tr>
<td>Spinal cord injury</td>
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</tbody>
</table>

<sup>a</sup>Rate for those who should be seen by a physician competent in neurology (20% of migraine, 10% of all others).

<sup>b</sup>Narcolepsies and hypersomnias (with sleep apnea).

<sup>c</sup>Rate for high-risk areas.


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### Neurological disorders: approximate point prevalence rates per 100,000 population, all ages. 2. Less common entities

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Rate</th>
</tr>
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<tbody>
<tr>
<td>Tic douleuroux</td>
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<tr>
<td>Neurological symptoms without defined disease</td>
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<tr>
<td>Mononeuropathies</td>
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<tr>
<td>Polynuropathies</td>
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<tr>
<td>Dorsolateral sclerosis</td>
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<td>Peripheral nerve trauma</td>
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<tr>
<td>Other head injury&lt;sup&gt;*&lt;/sup&gt;</td>
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<tr>
<td>Acute transverse myelopathy</td>
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<td>Chronic progressive myelopathy</td>
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<td>Optic neuritis</td>
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<td>Encephalitides</td>
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<td>Vascular disease spinal cord</td>
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<tr>
<td>Hereditary ataxias</td>
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<tr>
<td>Syringomyelia</td>
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<td>Motor neuron disease</td>
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<td>Polymyositis</td>
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<td>Progressive muscular dystrophy</td>
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<td>Metastatic cord tumor</td>
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<td>Meningitides</td>
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<td>Huntington’s disease</td>
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<td>Intracranial abscess</td>
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<td>Cranial nerve trauma</td>
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<td>Myotonic dystrophy</td>
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<td>Spinal muscular atrophy</td>
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<tr>
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<tr>
<td>Acute disseminated encephalomyelitis</td>
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<tr>
<td>Dystonia musculorum deformans</td>
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<sup>*</sup>Rate for those who should be seen by a physician competent in neurology (10% of total).

### Incidence per 100,000 per year

#### Most Common

<table>
<thead>
<tr>
<th>Disorder</th>
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</thead>
<tbody>
<tr>
<td>Herpes zoster</td>
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<td>Migraine</td>
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<td>Brain trauma</td>
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<td>Other severe headache</td>
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<td>Acute cerebrovascular disease</td>
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<td>Other head injury</td>
<td>150a</td>
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<tr>
<td>Transient postconcussive syndrome</td>
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<tr>
<td>Lumbosacral herniated nucleus pulposus</td>
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<td>Lumbosacral pain syndrome</td>
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<tr>
<td>Epilepsy</td>
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<td>Febrile fits</td>
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<td>Dementia</td>
<td>50</td>
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<tr>
<td>Ménie’s disease</td>
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<tr>
<td>Mononeuropathies</td>
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<td>Polyneuropathy</td>
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<td>Transient ischemic attacks</td>
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<td>Bell’s palsy</td>
<td>25</td>
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<td>Single seizures</td>
<td>20</td>
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<td>Parkinsonism</td>
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<td>Alcoholism</td>
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<td>Meningitides</td>
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<td>Encephalitides</td>
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<tr>
<td>Sleep disorders</td>
<td>15b</td>
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<tr>
<td>Subarachnoid hemorrhage</td>
<td>15</td>
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<td>Cervical herniated nucleus pulposus</td>
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<td>Metastatic brain tumor</td>
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<tr>
<td>Peripheral nerve trauma</td>
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<td>Blindness</td>
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<tr>
<td>Benign brain tumor</td>
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<tr>
<td>Deafness</td>
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*Rate for those who should be seen by a physician competent in neurology (10% of total).


#### Less Common

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Rate</th>
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<tbody>
<tr>
<td>Cerebral palsy</td>
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<tr>
<td>Mental retardation, other</td>
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<tr>
<td>Malignant primary brain tumor</td>
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<tr>
<td>Metastatic cord tumor</td>
<td>5.0</td>
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<tr>
<td>Tic douloureux</td>
<td>4.0</td>
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<tr>
<td>Multiple sclerosis</td>
<td>3.0b</td>
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<tr>
<td>Optic neuritis</td>
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<td>Dorsolateral sclerosis</td>
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<td>Functional psychosis</td>
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<td>Spinal cord injury</td>
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<td>Motor neuron disease</td>
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<tr>
<td>Down syndrome</td>
<td>2.0</td>
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<tr>
<td>Guillain-Barré syndrome</td>
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<tr>
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<td>1.0</td>
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<td>Cranial nerve trauma</td>
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<tr>
<td>Charcot-Marie-Tooth disease</td>
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<td>Spinal muscular atrophy</td>
<td>0.2</td>
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<td>Familial spastic paraplegia</td>
<td>0.1</td>
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<tr>
<td>Wilson’s disease</td>
<td>0.1</td>
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<tr>
<td>Malignant primary cord tumor</td>
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</tr>
<tr>
<td>Vascular disease cord</td>
<td>0.1</td>
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</tbody>
</table>

*Rate for those who should be seen by a physician competent in neurology (10% of total).

*Rate for high-risk areas.

NEUROMUSCULAR DISEASES
(acquired or hereditary)

C. Current concept: individual muscle fibers of same motor unit are scattered throughout muscle

- Muscle
- Neuromuscular junction
- Nerve
  - Nerve plus Central Nervous System
Neuromuscular disorders:

- **Muscle weakness:**
  - Amyotrophic lateral sclerosis ALS (Lou Gerig’s Disease)
  - Charcot-Marie-Tooth syndrome
  - Myasthenia gravis
  - Muscular Dystrophy

- **Movement disorders**
  - Parkinson’s Disease

- **Combined muscle weakness and movement disorder**
  - Multiple sclerosis
Amyotrophic lateral sclerosis (ALS- Lou Gehrig’s disease)

- Is a degenerative disease that affects the **upper and/or lower motor neurons** (nerve cells controlling muscles) in the anterior (motor) horns of the spinal cord, and/or motor nuclei of the lower brain.

- A disease of progressive loss of motor nerve cells in the brain and spinal cord, causing progressive loss of motor control.

- As nerves die, the muscles atrophy.
Symptoms of ALS

- Symptoms usually do not develop until after age 50, usually 5th or 6th decade of life.

- Affects males more than females.

- Symptoms begin with muscle weakness, muscle cramps, and decrease in muscle strength and coordination that eventually lead to paralysis.

- There may be muscle tremors, spasms, twitching, or muscle atrophy.

- Reflexes may be abnormal, including loss of the gag reflex.

- Some patients have "emotional incontinence"
Weakness often begins in one limb or in proximal groups with gradual onset.

As the disease progresses, more muscle groups are affected and patients become progressively incapacitated.

Progressive loss of muscle strength and coordination eventually interfere with the ability to perform routine activities, such as lifting, going up steps, getting out of a chair, walking, swallowing, and eventually breathing.

Other complications include:

- Loss of ability to care for self, inhaling food or fluid, pneumonia, respiratory failure, skin breakdown, weight loss

There is no effect on the ability to think or reason.
ALS

Weakness typically begins in the upper extremities & progressively involves the upper arms & shoulders & then the muscles of the neck & throat. Trunk & lower extremities are usually not affected until late in the disease.

- **Lower Motor Neuron**
  - Weakness
  - Atrophy
  - Cramps
  - Fasciculatoin (irregular twitching of muscle fibers or bundles)

- **Upper Motor Neurons**
  - Spasticity
  - Hyper reflexia
  - Involvement of corticobulbar tracts causes dysphagia (difficulty swallowing) & dysarthria (slurred speech)
ALS—Lou Gehrig’s disease

Signs and Symptoms

- Fatigue
- Difficult doing motor task
  - Buttoning a shirt
- Progressive muscle weakness & wasting, atrophy
  - When intercostal muscles & diaphragm become involved, resp are shallow & coughing is ineffective.
- Dysphagia-swallowing
- Dysarthria -speech
  - Weakness begins in brain stem causing problems with speech & swallowing = bulbar ALS
  
- Wt loss
- Tongue fasciculation-twitching
- Jaw clonus --involuntary tightening/ relaxing of muscles
- Spasticity of flexor muscles
- Respiratory difficulty - death occurs 2dary to resp infection
ALS—Lou Gehrig’s disease
S/S continued

- Involvement of upper and lower extremities
- One side more than other
- No sensory loss
- Patient remains alert
- Death occurs 5 to 10 years post diagnosis
- Death usually results from respiratory infection secondary to compromised respiratory function. Caused by respiratory or bulbar paralysis
**Chief Symptoms of ALS**

- Progressive muscle weakness
- Atrophy/fasciculations (tongue twitching)
- Spasticity with brisk overactive stretch reflex
- Anal/bladder muscle weakness
- With cranial nerves, resulting dyarthrias (speech), dysphagia’s (difficulty swallowing) and dyspnea (SOB)
  - *Aspiration is a big problem*
ALS—Lou Gehrig’s disease
diagnostic test

No specific test is available to dx ALS

Electromyography (EMG) may be done to rule out other neuromuscular disease
Guillain-Barre Syndrome - GBS

Guillain-Barre Syndrome (GBS) is an inflammatory disorder of the peripheral nerves.

The peripheral nerves convey sensory information (Ex-pain, temp, etc) from the body to the brain & motor (Ex-movement) signals from the brain to the body.

GBS may be an autoimmune disorder in which the body produces antibodies that damage the myelin sheath that surrounds peripheral nerves. The myelin sheath is a fatty substance that surround axons. It increases the speed at which signals travel along the nerves.

GBS characterized by ascending weakness & numbness or tingling in the legs & arms & possible loss of movement & feeling in the legs, arms, upper body, & face. Ascending weakness begins in lower extremities & spreads to trunk, upper extremities, & face.
**Guillain-Barre Syndrome**

**Incidence**
- Rare
- 1-2 cases in every 100,000 people per year
- Men & women, young & old are equally prone to contracting GBS

**Causes**
- Not heredity or contagious
- Cause-unknown

**Causes - continued**
- Half of all cases onset follows a viral or bacterial infection or inflammation, such as:
  - Flu, common cold
  - GI viral infection
  - Infectious mononucleosis
  - Viral hepatitis
  - Campylobacteriosis (usually from eating undercooked poultry)
Symptoms of Guillain-Barre Syndrome - GBS

1st symptoms of GBS are usually numbness or tingling (paresthesia) in the toes & fingers, with progressive weakness in the arms & legs over the next few days.

Some patients experience paresthesia only in their toes & legs; others only experience symptoms on one side of the body.

Symptoms may start out causing only mild difficulty in walking, requiring crutches or a walking stick.

As illness progresses, leads to complete paralysis of arms & legs.

1/4 of pt experience paralysis up to chest & paralyses of respiratory muscles, leaving pt dependant on a ventilator.

Swallowing muscles also affected, & feeding tube may be needed.
Guillain-Barre Syndrome

- **Initial problem can become chronic**
  
  - **Acute** Inflammatory Demyelinating Polyneuropathy  
    (AIDP-acute inflammatory demyelinating polyneuropathy)
  
  - **Chronic** Inflammatory Demyelinating Polyneuropathy  
    (CIDP-Chronic inflammatory demyelinating polyneuropathy)
  
    “Similar” to GB Syndrome

- **Chronic problem**

- **Treated the same way**
  
  - Steroids (may be used for CIDP but *not* Guillain-Barre) and immune suppressants
Guillain-Barre Syndrome - Diagnosis

- Symptoms vary & cause unknown, therefore GBS can be extremely difficult to dx. If symptoms occur uniformly across body & progress rapidly, dx is easier.
- Observe pt symptoms & evaluation of medical history prove the basis for dx, although no single observation is suitable to make dx.

Evaluation
- Must include history & physical examination
- Blood work-may show leukocytosis early in illness. ESR typically WNL
- Lumbar puncture (Spinal tap) see next slide
- Electromyogram (EMG) see next slide
- Nerve conduction velocity (NCV) see next slide
- Can also do MRI of the entire spine
Guillian-Barre Syndrome - Dx Evaluation
Three tests confirm dx

(1) Lumbar puncture (spinal tap) - Pt given local anesthesia. Needle inserted between two lumbar vertebrae in lower back & sample of cerebrospinal fluid (CSF) is drawn. An elevated level of protein or +protein in the CSF is a characteristic of GBS. Cerebrospinal fluid would have +protein

(2) Electromyogram (EMG) - Records muscle activity & can show the loss of reflexes due to the disease’s characteristic slowing of nerve responses

(3) Nerve conductin velocity (NCV) - this test is performed with the EMG. NCV records the speed at which signals travel along the nerves. Guillian Barre syndrome would show a decreased nerve conduction velocity
Myasthenia gravis

Myasthenia gravis is a neuromuscular autoimmune disease which affects how nerve impulses are transmitted to voluntary muscles at the neuromuscular junction. There is a loss of acethycholine receptors in the postsynaptic neurons of the neuromuscular junction.

Characterized by excessive weakness & fatigability of voluntary muscles & those innervated by cranial nerves.

Myasthenia gravia defined: weakness of voluntary or striated muscles or “grave muscle weakness”

Considered to be autoimmune, presents as muscular weakness & fatigue that worsens with exercise & improves with rest.
Myasthenia gravis
Pathophysiology

- Defect in transmission of impulses from nerves to muscle cells due to loss of available receptors on the post synaptic membrane junction

- \textit{Loss of acetylcholine receptors} in the synaptic neurons of the neuromuscular junction

- 80% have elevated titers of antibodies to acetylcholine receptors
The glitch in myasthenia has to do with the transmission of nerve signal to muscles.

Nerves release a chemical messenger called acetylcholine.

Acetylcholine has to swim a small gap between nerve and muscle and land at a muscle receptor, a docking station.

When it arrive there, the muscle contracts.
Myasthenia gravis

- Weakness occurs when the nerve impulse to initiate or sustain movement does not adequately reach the muscle cells.
Myasthenesia Gravis
Pathophysiology - continued

In myasthenia, the receptor docking stations are blocked with antibodies.

Acetylcholine can *not* activate the muscle properly.

The result is a feeble muscle contraction.
Immune cells target and attack the body's own cells, producing antibodies that attach to affected areas. This prevents muscle cells from receiving chemical messages from the nerve cell.
Myasthenia Gravis

- Eyelids can droop
- Eye muscles can no longer coordinate right & left eye synchronous movement, so double vision often occurs
- Chewing & swallowing becomes difficult
- Arms & legs can be affected
Patients with myasthenia gravis have a higher risk of having other autoimmune disorders. The cause of autoimmune disorders is unknown.
Myasthenia Gravis
Clinical Manifestations

- Primary features is increasing weakness with sustained muscle contraction

- Extreme muscle weakness and generalized fatigue
  - Increase fatigue - acethycholine taken or used up by movement, pt gets weaker & weaker. While at rest, not using as much acethycholine.
    - Worse following effort
    - Relieved with rest

- Symptoms vary according to muscles involved
Myasthenia Gravis
Clinical Manifestations

- Symmetric muscles involved, especially those innervated by cranial nerves
  - Diplopia - double vision
  - Ptosis - droopy eyelid
  - Sleepy mask like expression
  - Dysphonia - diff speaking, hoarseness
  - Dysphagia - inability or difficulty in swallowing
    tendency for mouth to hang open
  - Progressive weakness of diaphragm/intercostals
  - Variable course with exacerbation’s/remissions
Myasthenia Gravis
Motor & Sensory Clinical Manifestations

Motor Manifestations
- Progressive muscle weakness (proximal) that usually improves with rest
- Poor posture
- Ocular palsies
- Ptosis/Weak or incomplete eye closure
- Diplopia
- Respiratory compromise secondary to ineffective coughing, swallowing, muscle weakness, etc.
- Loss of bowel & bladder control

Sensory Manifestation
- Muscle achiness
- Paresthesias
- Decreased smell and taste
Dx of Myasthenia gravis

- **History & Physical**
  - **Tensilon Testing** - Confirmed by *injection of anticholinesterase drugs*, usually *Tensilon* (edrophonium) & patients response to cholinergic drugs *(see next slides)*
  - **Lab Studies**
    - Thyroid function tested
    - Serum protein electrophoresis evaluates pt for immunologic disorder
    - Thyrotoxicosis (excessive thyroid hormone) is present in approx 5% of MG patients
  - **Other dx associated with MG** - Rheumatoid arthritis, systemic lupus erythematosus, & polymyositis
  - **EMG - Electromyography**
    - Electrical testing of normal neuromuscular junction should produce no change in the amplitude of muscle contraction. In MG, the amplitude of the muscle’s response diminishes with progressive stimulation = MG
Myasthenia Gravis - Crisis

Both types of Crisis - Sudden increase in weakness & inability to clear secretions, swallow, or breath adequately. Patient will choke on their own secretions.

2 types of Crisis:
- Myasthenic Gravis Crisis
- Cholinergic Crisis
Myasthenia Gravis

2 types of Crisis:

1. **Undermedication of anticholinesterase drugs**
   - causes exacerbation of Myasthenia Gravis symptoms
   - = **Myasthenic Gravis Crisis**

2. **Overmedication of anticholinergic drugs**
   - causes acute exacerbation of muscle weakness
   - = **Cholinergic Crisis**
<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLASSIFICATION OF MYOPATHIES</strong></td>
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<tr>
<td><strong>Hereditary:</strong></td>
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<tr>
<td>Muscular dystrophies</td>
</tr>
<tr>
<td>Myotonias and Channelopathies</td>
</tr>
<tr>
<td>Congenital myopathies</td>
</tr>
<tr>
<td>Metabolic myopathies</td>
</tr>
<tr>
<td>Mitochondrial myopathies</td>
</tr>
<tr>
<td><strong>Acquired:</strong></td>
</tr>
<tr>
<td>Inflammatory myopathies</td>
</tr>
<tr>
<td>Endocrine myopathies</td>
</tr>
<tr>
<td>Myopathies associated with other systemic illness</td>
</tr>
<tr>
<td>Drug-induced/Toxic myopathies</td>
</tr>
</tbody>
</table>
## MYOPATHIES

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SYMPTOMS ASSOCIATED WITH MYOPATHIES</strong></td>
</tr>
<tr>
<td><strong>“Negative”:</strong></td>
</tr>
<tr>
<td>Weakness</td>
</tr>
<tr>
<td>Fatigue and exercise intolerance</td>
</tr>
<tr>
<td><strong>“Positive”:</strong></td>
</tr>
<tr>
<td>Myalgias</td>
</tr>
<tr>
<td>Cramps</td>
</tr>
<tr>
<td>Contractures</td>
</tr>
<tr>
<td>Myotonia</td>
</tr>
<tr>
<td>Myoglobinuria</td>
</tr>
</tbody>
</table>

(*) Gowers’ Muscle (pseudo) hypertrophy

TABLE 7

ASSESSMENT OF MUSCLE WEAKNESS

<table>
<thead>
<tr>
<th>Location</th>
<th>Signs or Symptoms of Weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial</td>
<td>Inability to “bury eyelashes”, “horizontal smile”, inability to whistle</td>
</tr>
<tr>
<td>Ocular</td>
<td>Double vision, ptosis, dysconjugate eye movements</td>
</tr>
<tr>
<td>Bulbar</td>
<td>Nasal speech, weak cry, nasal regurgitation of liquids, poor suck, difficulty swallowing, recurrent aspiration pneumonia, cough during meals</td>
</tr>
<tr>
<td>Neck</td>
<td>Poor head control</td>
</tr>
<tr>
<td>Trunk</td>
<td>Scoliosis, lumbar lordosis, protuberant abdomen, difficulty sitting up</td>
</tr>
<tr>
<td>Shoulder girdle</td>
<td>Difficulty lifting objects overhead, scapular winging</td>
</tr>
<tr>
<td>Forearm/hand</td>
<td>Inability to make a tight fist, finger or wrist drop, inability to prevent escape from hand grip</td>
</tr>
<tr>
<td>Pelvic girdle</td>
<td>Difficulty climbing stairs, waddling gait, Gower’s sign</td>
</tr>
<tr>
<td>Leg/foot</td>
<td>Foot drop, inability to walk on heels or toes</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Use of accessory muscles</td>
</tr>
</tbody>
</table>

(*) Standing up with the aid of hands pushing on knees
# TABLE 7

## ASSESSMENT OF MUSCLE WEAKNESS

<table>
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<tr>
<th>Location</th>
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</tr>
</tbody>
</table>

![LGMD](image1.png)

![LGMD](image2.png)

![LGMD](image3.png)

![LGMD](image4.png)

![LGMD](image5.png)

![FSH](image6.png)
Duchenne muscular dystrophy

Guillaume-Benjamin Duchenne de Boulogne

Autographed copy of: De la Paralysie Musculaire Pseudo-hypertrophique...1868
Duchenne Muscular Dystrophy is unique in being the only muscular dystrophy for which a therapy (prednisone and deflazacort) has been proven effective in randomized, controlled trials.
Duchenne muscular dystrophy

- Chromosome: Xp21; Recessive
- Onset: 3 to 5 yrs

Clinical
- Weakness Distribution
  - Proximal > Distal
  - Symmetric
  - Legs & Arms
- Most involved muscles:
  - Adductor magnus in legs
- Relatively spared muscles:
  - Gracilis & Sartorius

- Course
  - Reduced motor function by 2 to 3 years
  - Steady decline in strength: After 6 to 11 years
  - **Gowers sign**
  - Failure to walk: 9 - 13 years; Later with steroid treatment

**Standing from supine position**
Duchenne muscular dystrophy

• **Muscle (pseudo)hypertrophy**

- Especially calf
- May be generalized
- Increases with age
- Most commonly due to muscle fibrosis
- Some relatively spared muscles may have true hypertrophy

*macroglossia*
Duchenne muscular dystrophy

Musculoskeletal symptoms

- Contractures
  - Especially ankles; Also hips & knees

Treatment

  Non-surgical

  Night splints on ankles: More effective than passive stretch

  Surgical

Scoliosis

  Onset: After loss of ambulation
  May be reduced if walking & standing is prolonged to 17 - 18 years

Treatment

  Surgical insertion of spinal rod
Duchenne muscular dystrophy

Other clinical features

**Cardiomyopathy**: Dilated; Especially > 15 years

**Mental retardation**: Mean IQ ~ 88

Night blindness

Altered response to flashes of light in dark adapted state

ERG: b-wave, Reduced amplitude

Dp260: Isoform of dystrophin in retina

- Reduced verbal IQ
- Selective defects:
  - Shorter digit span memory
  - Developmental delay

Death

Most common between 15 - 25 years

Due to respiratory or **cardiac failure**

Life prolonged by ~ 6 years to 25 years with respiratory support

Life shortened by 2 years with cardiomyopathy
Duchenne muscular dystrophy

- EMG
- Laboratory
- Serum  CK: Very high

Troponin I: Elevated above normal but not to levels in cardiac ischemia
Liver enzymes: High AST & ALT

Diagnostic testing
- Muscle: Staining for dystrophin protein absent
- Genetic: Deletion, Duplication, Small mutation, Point mutation
Duchenne muscular dystrophy

- Muscle biopsy: General features
  - Variable fiber size: Small fibers rounded
  - Hypercontracted (opaque) muscle fibers
  - Necrosis "Myopathic grouping"
  - Muscle fiber degeneration & regeneration:
    - Especially early
  - Muscle fiber internal architecture:
    - Normal or immature
Duchenne muscular dystrophy

- **Dystrophin**: Absent staining
- Other membrane proteins
  - **Sarcoglycans**: Reduced
  - **Aquaporin 4**: Reduced
- Endomysial fibrosis: More with late pathology
Duchenne Muscular Dystrophy: Early Pathology.1

Necrotic muscle fibers: Grouped

Phagocytosis: Invasion of fibers by macrophages
Duchenne Muscular Dystrophy: Early Pathology. 2

- Immature muscle fibers: Numerous
- Many small regenerating fiber
- Intermediate-sized regenerating muscle fibers: Myopathic grouping

Myopathic grouping of regenerating muscle fibers
Duchenne Muscular Dystrophy: Later Pathology

Endomysial connective tissue increased
Variable fiber size.
Small fibers are **rounded**.
Many **hypercontracted** muscle fibers
Duchenne Muscular Dystrophy: Dystrophin staining

Normal dystrophin staining around the rim of muscle fibers

Absent dystrophin: Duchenne muscular dystrophy
Left: No staining around the rim of muscle fibers.
Right: No staining of most muscle fibers. One "revertant" fiber with dystrophin staining.
Dystrophin isoforms.
Cell types.

- Cell type specificities: Determined by promoters
  - Muscle: 427 kDa mol. weight
    Expressed in Skeletal, Cardiac & Smooth Muscle + Retina
  - Cortical: 427 kDa; B isoform
    Cortical post-synaptic densities, Retina, ? Skeletal Muscle
    Different first exon from muscle isoform
    Functionally homologous to muscle isoform
  - Purkinje Cell: 427 kDa; Cerebellar; CP isoform
    Different first exon from muscle isoform
    Functionally homologous to muscle isoform
    ? Present in adult muscle

DMD - Symptomatic Care
GI Considerations

- Dystrophin in stomach, small intestine smooth muscle
  - Decreased transit time
- GI pseudo-obstruction with infection, impaction
- AVOID surgery - symptoms transient
  - NG suction, rest
  - Metoclopramide
Dystrophin localization. Cell types.

- **Retinal**: 260 kDa
  Retinal exon 1 spliced to exon 30
  Mouse retina: outer plexiform layer
- **Brain (Fetal) & Kidney**: 140 kDa
  Promoter & first exon: In large intron between exon 44 and 45
- **Schwann cell (S-dystrophin)**: 116 kDa
  Onset exon 56
  Submembrane of external (abaxonal) layer; Nodes of Ranvier
  Mouse model: Reduced dystrophin in peripheral nerve causes demyelinating neuropathy
- **Glial**: 71 kDa
  Onset exon 63
  Brain (Glia), Viscera (Lung, Liver, Kidney), Cardiac Muscle
Becker muscular dystrophy

- Clinical features
  - Onset > 7 yrs
  - Weakness
    - Proximal > Distal;
    - Symmetric;
    - Legs & Arms
      - May be especially prominent in quadriceps or hamstrings
    - Slowly progressive
    - Calf pain on exercise
  - Muscle hypertrophy:
    - Especially calves
  - Failure to walk 16 – 80 years

- Enlarged calves
- Toe walking
Becker muscular dystrophy

- **Genotype:** Dystrophin mutations
  - Deletion 70% of patients: Usually In-frame
    - 16% with frameshift mutation
  - Point mutations
    - > 70 identified; new mutation rare
  - Worse course: Additional mutation in Myogenic factor 6

- **Systemic**
  - Joint contractures: Ankles & Other
  - Cardiomyopathy: May occur before severe weakness
  - Mental retardation
    - Associated with deletion of Dp140 transcription unit

- **Serum CK**
  - Very high: 5,000 to 20,000
  - Lower levels with increasing age & disability
Becker muscular dystrophy

Cluster of degenerated muscle fibers replaced by phagocytic cells

Grouped regenerating muscle fibers (7 yrs old boy)
Becker muscular dystrophy

- chronic dystrophy:
  - Increased endomysial connective tissue
  - Variable fiber size: Small muscle fibers are rounded
  - Internal nuclei
  - The largest muscle fibers are hypertrophied
  - Occasional fibers: Degeneration; Regeneration; Hypercontraction; Split

27 yrs old male
Becker muscular dystrophy

Dystrophin staining

Normal dystrophin staining around the rim of muscle fibers

Reduced dystrophin staining Severity & onset age correlate with muscle dystrophin levels
Dystrophinopathies: Cardiomyopathy

- Cardiomyopathy with Becker or Duchenne MD syndromes: Common
  - Common mutations: Deletions in Exons 48-53 region (Spectrin-like region)
  - Clinical features
    - Tachycardia: > 100; Common even < 10 years age
    - Dilated cardiomyopathy
    - Symptomatic: 57% by age 18
    - Progression: Variable
    - May be associated with only: Myalgias after exercise & High CK
  - EKG
    - Changes due to atrophy
      - Age 10: EKG changes in 60%; No clinical manifestations. Age 18: EKG or ECHO changes in most
Dystrophinopathies: Cardiomyopathy

- Selective Cardiomyopathy: Minimal or mild weakness
  
  Clinical features
  
  Weakness: Minimal or Mild
  
  Cardiomyopathy: Males
  
  Onset: Late teens
  
  Congestive heart failure
  
  Rapidly progressive: 1 to 2 years
  
  More severe cardiomyopathy with mutations at 5' end of dystrophin gene
  
  Cardiomyopathy: Manifesting females
  
  Onset: 5th decade
  
  Congestive heart failure
  
  Chest pain: Atypical
  
  Slowly progressive over > 10 years
Duchenne Muscular Dystrophy: Dystrophin recognition

[Image: Western blot of dystrophin from dystrophinopathies.]

Lane 1: **Becker dystrophy**; Dystrophin has reduced abundance but normal size.
Lane 2: **Becker dystrophy**; Dystrophin has reduced size and abundance.
Lane 3: **Normal**; Dystrophin has normal size and amount.
Lane 4: **Duchenne dystrophy**; Almost no protein is present.
Lane 5: **Duchenne outlier**; Dystrophin has severely reduced abundance.
MEMBRANE-ASSOCIATED PROTEIN COMPLEXES IN SKELETAL MUSCLE FIBERS

EXTRACELLULAR
- Basal Lamina
- Collagen VI
- Biglycan
- Sarcospan
- Dysferlin
- Caveolin-3

SARCOLEMA
- F-Actin
- Dystrophin

INTRACELLULAR
- Sarcoglycans α, γ, ζ, β, δ
- Integrins α7, β1
- NOS
- Syntrophins α1, β1
- Grb2
- CALM1
- SYT1

Costameres

Extrajunctional muscle membrane Associated proteins
**Dystrophin functions**

**Mechanical**
- Stabilization of membrane during contraction & relaxation
- Part of link between intracellular cytoskeleton & extracellular matrix

**Functional**
- Plays role in ability of muscle fibers to differentiate into fast glycolytic type
- May play a role in organization of postsynaptic membrane & AChRs

**Molecular Weight (KDa):** 427 (3685 AA)
Dystrophphin function

- Cytoskeleton binding:
  - via F-actin (NH₂-terminus; 1st to 420 AA)
- Actin binding
  - (Rod: Coiled-coiled 2400 amino acids)
- Binds to calmodulin (WW domain - AA 3056-3088 and 3080 to 3360)
- Membrane attachment to cytoskeleton via binding to β-Dystroglycan (AA 3080 to 3360)
- Binds to Dystrobrevins, Syntrophins, DAGs, β-Dystroglycan (Last 420 AA)
Ca\textsuperscript{++} ions release from sarcoplasmic reticulum is regulated by 2 large membrane protein complexes:
- **Dihydropyridine receptor** (DHPR)
- **Ryanodyne receptor** (RyR)

**Action potential**
- travels along muscle surface membrane
- enters transverse tubule system (t-tubules)
Contains Actin

Contains Myosin

- Myosin light chains: 4 types
  - Bind Ca\(^{++}\): High affinity

- Non-myosin components in thick filament
  - Titin (myogenesis)
  - Z disc; Theletonin

Regulatory protein of thin filament

- Troponin: Complex of 3 subunits

- Myosin heavy cheins form cross-bridges
Contractile apparatus activated
• Ca^{++} binds to troponin complex
• Tropomyosin binding to contractile apparatus changes
• Actin allowed to bind to myosin heads
• Muscle contraction occurs via myofilament sliding
Dystrophin gene mutations: Size & Types

- Point mutations along entire gene
- Often cause premature truncation of translation
- May occur with Duchenne or Becker phenotype
- Frequency: Detected in ~73% of patients without deletions or duplications

Deletions or Duplications

- Majority of deletions at the 3' end region; 5' end deletions in 18%
- More than one exon usually deleted

Clinical correlations:
- Exon 1 & promoter region: Mild weakness ± severe cardiomyopathy
- Deletions of more than 36 exons produce severe phenotype

Disease frequency
- Duchenne: 65% of patients have gene deletions
- Becker: 55% to 85% of patients have gene deletions or duplications

- Very large chromosomal deletions
  - Multisystem disorders
  - Duchenne muscular dystrophy phenotype

Dystrophin abnormalities
Effects of dystrophin mutations: Other

Dystrophin absence

DMD phenotype: Severe

Reduction in sarcoglycans & other proteins in dystrophin-glycoprotein complex

Dysferlin increased in cytoplasm

C-terminal mutations

Severe dystrophies

Functional consequences of loss of dystrophin on muscle fibers

Increased movement of membrane impermeant molecules into and out of muscle cells

Force production: Decreased; Hypersensitive to lengthening, or eccentric contraction

Force decrement with eccentric contraction correlates with acutely increased sarcolemmal permeability

Disorganized subsarcolemmal costameres
Limb-Girdle Muscular Dystrophies

The term “limb-girdle muscular dystrophy” (LGMD) refers not to a single disease, but rather to a group of disorders, all of which usually but, paradoxically, not always, involve mainly proximal muscles.

In fact, most LGMD patients have weakness beyond a simple limb-girdle distribution (LGMD 2B).

15 forms (and their genetic defect; 5 dominant; 10 recessive) have been identified
Limb-Girdle Dystrophy

- Group of dx. that tend to involve proximal muscles
  - Exceptions (LGMD 2B)
- Prevalence \(~0.8 \text{ – } 69/10^6\)
- Variable age of onset, severity, progression
- Heart, lung involve; varies
- Precise dx. in only \(~50\%\)
- No strength therapy, little symptomatic therapy
  - Supportive care key
## LGMD-Genetic Classification

**Autosomal Dominant**

<table>
<thead>
<tr>
<th>Dx.</th>
<th>Chrom.</th>
<th>Gene</th>
<th>Protein</th>
<th>Detect.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>5q22-24</td>
<td>?</td>
<td>myotilin</td>
<td>MA</td>
</tr>
<tr>
<td>1B@</td>
<td>1q11-21</td>
<td>LMNA</td>
<td>lamin A/C</td>
<td>MA</td>
</tr>
<tr>
<td>1C</td>
<td>3p25</td>
<td>CAV3</td>
<td>caveolin-3</td>
<td>MA, IH</td>
</tr>
<tr>
<td>1D</td>
<td>6q23</td>
<td>?</td>
<td>?</td>
<td>Linkage</td>
</tr>
<tr>
<td>1E</td>
<td>7q</td>
<td>?</td>
<td>?</td>
<td>Linkage</td>
</tr>
</tbody>
</table>

- same locus as AD Emery-Dreifuss
- Cardiac conduction defects and/or cardiomyopathy
**LGMD-Genetic Classification**

**Autosomal Recessive**

<table>
<thead>
<tr>
<th>Dx.</th>
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<th>Gene</th>
<th>Protein</th>
<th>Detect.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2A</td>
<td>15q15.1</td>
<td>CAPN-3</td>
<td>calpain 3</td>
<td>MA</td>
</tr>
<tr>
<td>2B*</td>
<td>2p13</td>
<td>DYSF</td>
<td>dysferlin</td>
<td>MA, IH</td>
</tr>
<tr>
<td>2C</td>
<td>13q12</td>
<td>SGCG</td>
<td>γ-sarcoglycan</td>
<td>MA, IH</td>
</tr>
<tr>
<td>2D</td>
<td>17q21</td>
<td>SGCA</td>
<td>α-sarcoglycan</td>
<td>MA, IH</td>
</tr>
<tr>
<td>2E</td>
<td>4q12</td>
<td>SGCB</td>
<td>β-sarcoglycan</td>
<td>MA, IH</td>
</tr>
<tr>
<td>2F</td>
<td>5q33</td>
<td>SGCD</td>
<td>δ-sarcoglycan</td>
<td>MA, IH</td>
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<tr>
<td>2G</td>
<td>17q11-12</td>
<td>TCAP</td>
<td>telethonin</td>
<td>MA</td>
</tr>
<tr>
<td>2H</td>
<td>9q31-33</td>
<td>TRIM32</td>
<td>TRIM32</td>
<td>MA</td>
</tr>
<tr>
<td>2I</td>
<td>19q13.3</td>
<td>FKRP</td>
<td>Fukutin RP</td>
<td>MA</td>
</tr>
<tr>
<td>2J</td>
<td>2q31</td>
<td>TTN</td>
<td>Titan</td>
<td>MA</td>
</tr>
</tbody>
</table>

Cardiac conduction defects and/or cardiomyopathy
### MYOPATHIES WITH PTOSIS OR OPHTHALMOPLEGIA

<table>
<thead>
<tr>
<th>Ptosis Usually Without Ophthalmplegia</th>
<th>Ptosis With Ophthalmplegia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myotonic dystrophy</td>
<td>Oculopharyngeal muscular dystrophy</td>
</tr>
<tr>
<td>Congenital myopathies</td>
<td>Oculopharyngodistal myopathy</td>
</tr>
<tr>
<td>Centronuclear myopathy</td>
<td>Chronic progressive external ophthalmplegia (mitochondrial myopathy)</td>
</tr>
<tr>
<td>Nemaline myopathy</td>
<td></td>
</tr>
<tr>
<td>Central core myopathy</td>
<td></td>
</tr>
<tr>
<td>Desmin storage myopathy</td>
<td></td>
</tr>
</tbody>
</table>

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"www.fisiokinesiterapia.biz"
The myotonic dystrophies are a group of muscle disorders characterized generally by muscle weakness, myotonia, cataracts, and cardiac conduction disorders and arrhythmias.

Approximately 90% patients have myotonic dystrophy type 1 (DM1) which is the most common inherited muscle disorder affecting adults with an incidence of approximately 15 cases per 100,000 live births.
Myotonic Dystrophy

Overview

- Most common adult MD
  - 2 cases/100,000
- A.D.- presents < age 50
  - Variable severity
  - Multi-system dx.
- Expanded 19q13.3 CTG repeat - DMPK gene (98%)
  - Correlates inversely with severity
- No strength therapy yet
  - DHEAS?
Dropped head syndrome

**TABLE 11**

MYOPATHIES WITH PROMINENT NECK EXTENSOR WEAKNESS

- Isolated neck extensor myopathy
- Polymyositis
- Dermatomyositis
- Inclusion body myositis
- Carnitine deficiency
- Facioscapulomumeral dystrophy
- Myotonic dystrophy
- Congenital myopathy
- Hyperparathyroidism
Although FSHD was described over a century ago, and is the third most common dystrophy prevalence (1:20,000), it has received relatively little attention.

It appears that FSHD results from inappropriate over-expression of certain genes, rather than the absence or under-expression of genes, as in most dystrophies.

Mechanisms of toxic effect on muscle cell are unknown.
FSH Dystrophy

Overview

- AD; prevalence 1:20,000
- Sx. begin < age 20
  - 20% asymptomatic
  - 20% need WC
- Variable deletion in 3.3 kb repeat sequence at 4q35
  - Short fragment in 95%
  - Inverse correlation with severity
- No strength therapy yet
# DISTAL WEAKNESS IN MYOPATHIES

## TABLE 9

**MYOPATHIES CHARACTERIZED BY PREDOMINANTLY DISTAL WEAKNESS**

- Late adult onset distal myopathy Type 1 (Welander)
- Late adult onset distal myopathy Type 2 (Markesbery/Udd)
- Early adult onset distal myopathy Type 1 (Nonaka)
- Early adult onset distal myopathy Type 2 (Miyoshi)
- Early adult onset distal myopathy Type 3 (Laing)
- Desmin myopathy
- Childhood onset distal myopathy
- Myotonic dystrophy
- Facioscapulohumeral dystrophy*
- Scapuloperoneal myopathy*
- Oculopharyngeal dystrophy
- Emery-Dreifuss humeroperonal dystrophy*
- Inflammatory myopathies
  - Inclusion body myositis
- Metabolic myopathy
  - Debrancher deficiency
  - Acid-maltase deficiency*
- Congenital myopathy
  - Nemaline myopathy*
  - Central core myopathy*
  - Centronuclear myopathy

*scapuloperoneal pattern can occur
DISTAL WEAKNESS IN MYOPATHIES

Chromosome 2p13; Dominant
• Genetics\textsuperscript{10}
  • Not allelic with Miyoshi myopathy & LGMD 2B
  • Finnish & Swedish patients have shared haplotype
• Epidemiology: Especially mid-Sweden & Finland
• Onset
  • Age: Usually > 40 years; Median 5th decade;
    Range 20 to 77
  • Location: Arms; Wrist & Finger extensors
DISTAL WEAKNESS IN MYOPATHIES

Welander (Late onset type I) distal myopathy

- Clinical: Typical disease
  - Weakness
    - Hands > Legs in most
    - Muscles involved: Long finger extensors; Intrinsic hand; Thumb & index-finger
    - Progression to legs: Toe & ankle extensors
    - Only rarely proximal weakness
  - Tendon reflexes: Reduced at ankles
  - Slow progression with normal life span
  - Sensory loss: Some patients; Subclinical neuropathy common
  - Autonomic signs
DISTAL WEAKNESS IN MYOPATHIES

- Laboratory
- CK: Normal or mildly elevated
- EMG: Myopathic; Some irritability
- Muscle Pathology
- Chronic myopathic: Varied fiber size; Splitting
- Rimmed vacuoles: Variably present
- Tubulo-Filamentous inclusions:
  - Sarcoplasm & muscle fiber nuclei
- Eosinophilic cytoplasmic bodies
- Neurogenic changes

Welander (Late onset type I) distal myopathy