

“RIABILITAZIONE DELLE MALATTIE NEUROMUSCOLARI”

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Neuromuscular Disorders

Table 44.4: Neurological disorders: approximate point prevalence rates per 100,000 population, all ages. 1. Most common entities

Disorder	Rate
Migraine ^a	2,000 ^a
Other severe headache ^a	1,500 ^a
Brain injury	800
Epilepsy	650
Acute cerebrovascular disease	600
Lumbosacral pain syndrome ^a	500 ^a
Alcoholism ^a	500 ^a
Sleep disorders ^b	300
Ménière's disease	300
Lumbosacral herniated nucleus pulposus	300
Cerebral palsy	250
Dementia	250
Parkinsonism	200
Transient ischemic attacks	150
Febrile fits	100
Persistent postconcussive syndrome	80
Herpes zoster	80
Congenital malformations of central nervous system	70
Single seizures	60
Multiple sclerosis ^c	60
Benign brain tumor	60
Cervical pain syndrome ^a	60 ^a
Down syndrome	50
Subarachnoid hemorrhage	50
Cervical herniated nucleus pulposus	50
Transient postconcussive syndrome	50
Spinal cord injury	50

^aRate for those who should be seen by a physician competent in neurology (20% of migraine, 10% of all others).

^bNarcolepsies and hypersomnias (with sleep apnea).

^cRate for high-risk areas.

Source: Modified from JF Kurtzke. The current neurologic burden of illness and injury in the United States. Neurology 1982;32:1207-1214.

**Prevalence
per 100.000
Most Common**

Table 44.5: Neurological disorders: approximate point prevalence rates per 100,000 population, all ages. 2. Less common entities

Disorder	Rate
Tic douloureux	40
Neurological symptoms without defined disease	40
Mononeuropathies	40
Polyneuropathies	40
Dorsolateral sclerosis	30
Peripheral nerve trauma	30
Other head injury*	30*
Acute transverse myelopathy	15
Metastatic brain tumor	15
Chronic progressive myelopathy	10
Optic neuritis	10
Encephalitides	10
Vascular disease spinal cord	9
Hereditary ataxias	8
Syringomyelia	7
Motor neuron disease	6
Polymyositis	6
Progressive muscular dystrophy	6
Malignant primary brain tumor	5
Metastatic cord tumor	5
Meningitides	5
Bell's palsy	5
Huntington's disease	5
Charcot-Marie-Tooth disease	5
Myasthenia gravis	4
Familial spastic paraplegia	3
Intracranial abscess	2
Cranial nerve trauma	2
Myotonic dystrophy	2
Spinal muscular atrophy	2
Guillain-Barré syndrome	1
Wilson's disease	1
Acute disseminated encephalomyelitis	0.6
Dystonia musculorum deformans	0.3

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

Source: Modified from JF Kurtzke. The current neurologic burden of illness and injury in the United States. Neurology 1982;32:1207-1214; and JF Kurtzke, LT Kurland. The Epidemiology of Neurologic Disease. In A Baker, LH Baker (eds), Clinical Neurology (Vol. 4). Philadelphia: Harper & Row, 1983;1-143.

**Prevalence
per
100.000
Less
Common**

Table 44.2: Neurological disorders: approximate average annual incidence rates (per 100,000 population), all ages.

1. Most common entities

Disorder	Rate
Herpes zoster	400
Migraine	250
Brain trauma	200
Other severe headache ^a	200 ^a
Acute cerebrovascular disease	150
Other head injury ^a	150 ^a
Transient postconcussive syndrome	150
Lumbosacral herniated nucleus pulposus	150
Lumbosacral pain syndrome ^a	150 ^a
Neurological symptoms (with no defined disease)	75
Epilepsy	50
Febrile fits	50
Dementia	50
Ménière's disease	50
Mononeuropathies	40
Polyneuropathy	40
Transient ischemic attacks	30
Bell's palsy	25
Single seizures	20
Parkinsonism	20
Cervical pain syndrome ^a	20 ^a
Persistent postconcussive syndrome	20
Alcoholism ^a	20 ^a
Meningitides	15
Encephalitides	15
Sleep disorders ^b	15 ^b
Subarachnoid hemorrhage	15
Cervical herniated nucleus pulposus	15
Metastatic brain tumor	15
Peripheral nerve trauma	15
Blindness	15
Benign brain tumor	10
Deafness ^a	10 ^a

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

^bNarcolepsies and hypersomnias (with sleep apnea).

Source: Modified from JF Kurtzke. The current neurologic burden of illness and injury in the United States. *Neurology* 1982;32:1207-1214

**Incidence per 100.000 per year
Most Common**

Table 44.3: Neurological disorders: approximate average annual incidence rates (per 100,000 population), all ages.

2. Less common entities

Disorder	Rate
Cerebral palsy	9.0
Congenital malformations of central nervous system	7.0
Mental retardation, severe	6.0
Mental retardation, other ^a	6.0 ^a
Malignant primary brain tumor	5.0
Metastatic cord tumor	5.0
Tic douloureux	4.0
Multiple sclerosis ^b	3.0 ^b
Optic neuritis ^b	3.0 ^b
Dorsolateral sclerosis	3.0
Functional psychosis ^a	3.0 ^a
Spinal cord injury	3.0
Motor neuron disease	2.0
Down syndrome	2.0
Guillain-Barré syndrome	2.0
Intracranial abscess	1.0
Benign cord tumor	1.0
Cranial nerve trauma	1.0
Acute transverse myelopathy	0.8
All muscular dystrophies	0.7
Chronic progressive myelopathy	0.5
Polymyositis	0.5
Syringomyelia	0.4
Hereditary ataxias	0.4
Huntington's disease	0.4
Myasthenia gravis	0.4
Acute disseminated encephalomyelitis	0.2
Charcot-Marie-Tooth disease	0.2
Spinal muscular atrophy	0.2
Familial spastic paraplegia	0.1
Wilson's disease	0.1
Malignant primary cord tumor	0.1
Vascular disease cord	0.1

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

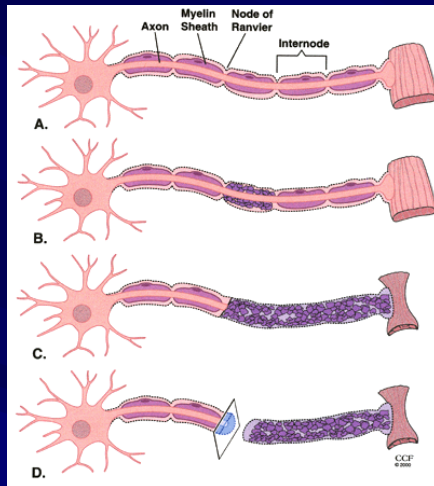
^bRate for high-risk areas.

Source: Modified from JF Kurtzke. The current neurologic burden of illness and injury in the United States. *Neurology* 1982;32:1207-1214; and JF Kurtzke, LT Kurland. The Epidemiology of Neurologic Disease. In A Baker, LH Baker (eds), *Clinical Neurology* (Vol. 4). Philadelphia: Harper & Row, 1983;1-143.

**Incidence per 100.000 per year
Less Common**

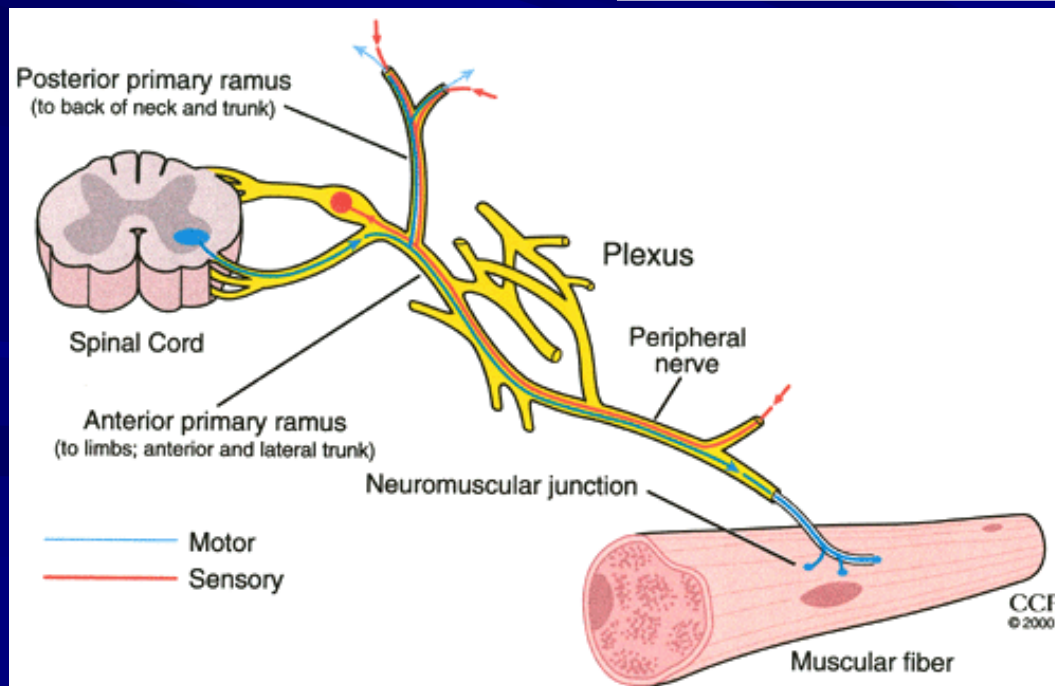
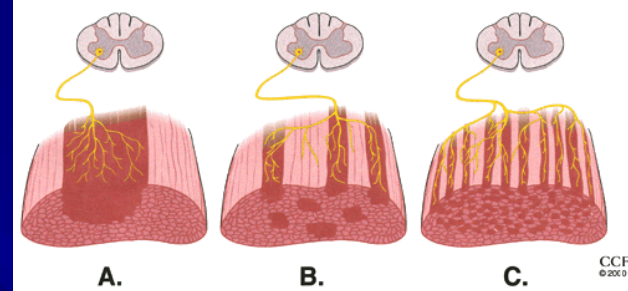
NEUROMUSCULAR DISEASES

(acquired or hereditary)



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

Concepts Regarding Motor Unit



- 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
- Fasciculation (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 dysarthrias (speech), dysphagias (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

Causes

■ 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 polyneuropath)
 - “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 acetylcholine receptors** in the postsynaptic neurons of the neuromuscular junction.
- Characterized by excessive weakness & fatigability of voluntary muscles & those innervated by cranial nerves.
- Myasthenia gravis 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
- Loss of acetylcholine receptors in the synaptic neurons of the neuromuscular junction
- 80% have elevated titers of antibodies to acetylcholine receptors

Myasthenia Gravis

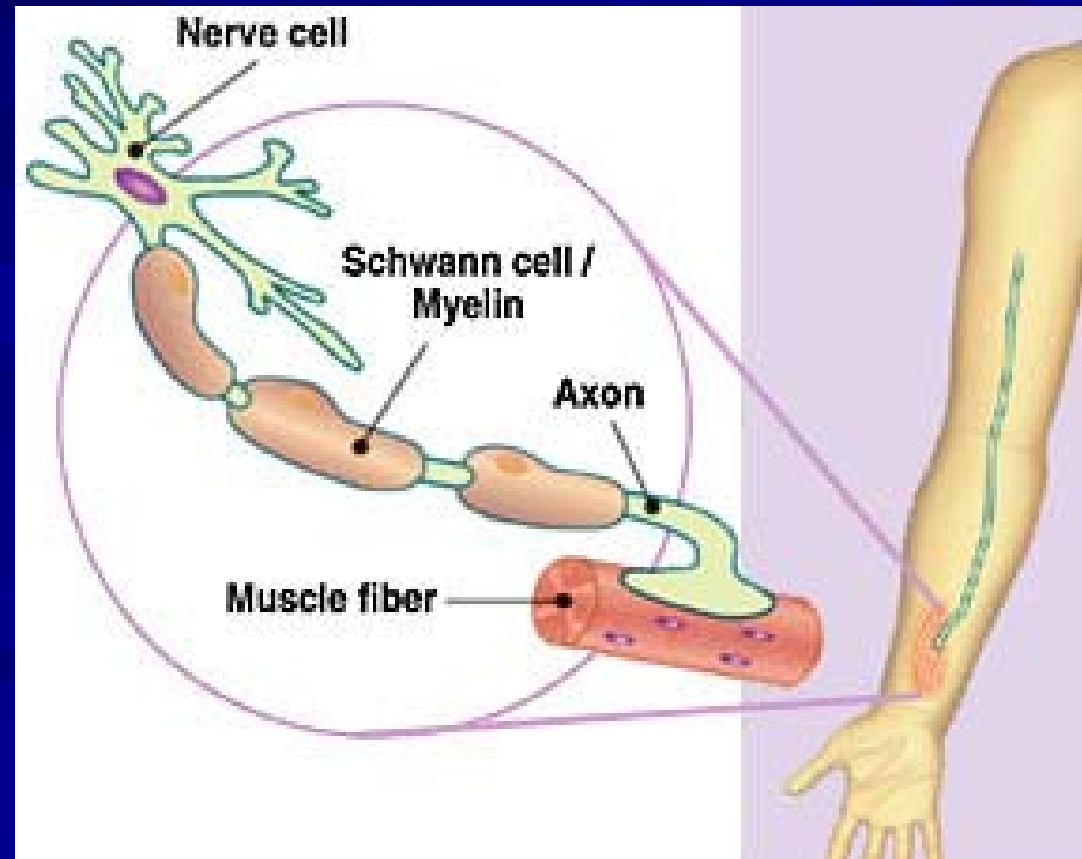
Pathophysiology-continued

- 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.

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Myasthenia gravis

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



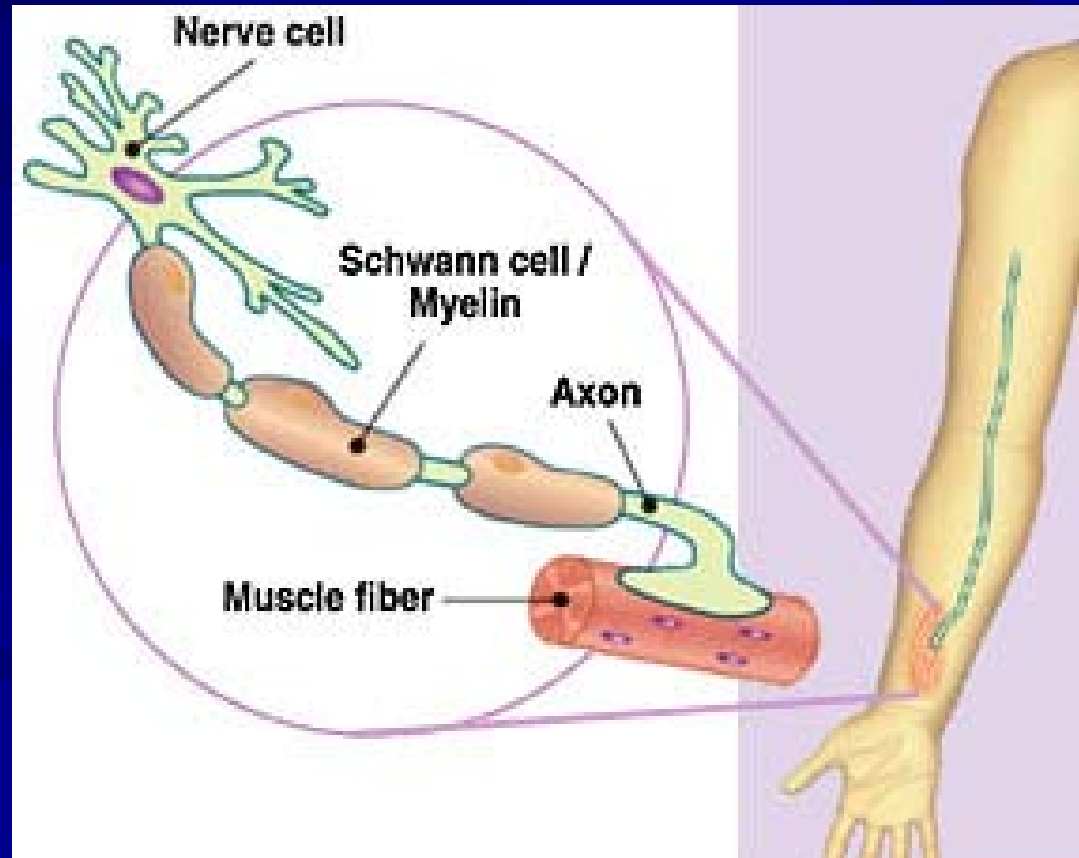
Myasthenia Gravis

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.

Myasthenia gravis

- 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.

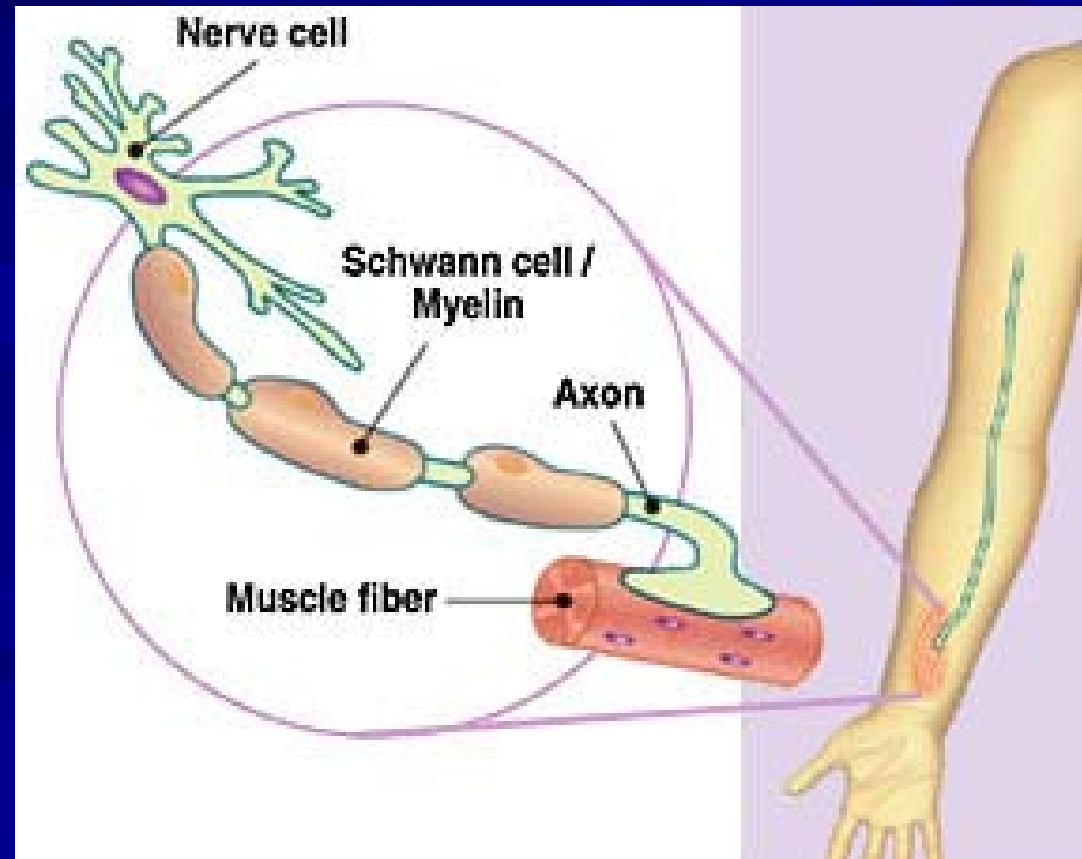


Myasthenia Gravis

- 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

Myasthenia gravis

- 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-acetylcholine taken or used up by movement, pt gets weaker & weaker. While at rest, not using as much acetylcholine.
 - 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 breathe 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) Overmediation of anticholinergic drugs***

causes **acute**
exacerbation of
muscle weakness

=

Cholinergic Crisis

MYOPATHIES

TABLE 1

CLASSIFICATION OF MYOPATHIES

Hereditary:

- Muscular dystrophies
- Myotonias and Channelopathies
- Congenital myopathies
- Metabolic myopathies
- Mitochondrial myopathies

Acquired:

- Inflammatory myopathies
- Endocrine myopathies
- Myopathies associated with other systemic illness
- Drug-induced/Toxic myopathies

MYOPATHIES

TABLE 2

SYMPTOMS ASSOCIATED WITH MYOPATHIES

“Negative”:

Weakness
Fatigue and exercise intolerance

“Positive”:

Myalgias
Cramps
Contractures
Myotonia
Myoglobinuria

(*) Gowers' Muscle (pseudo) hypertrophy

(*) Sir William Richard Gowers: British neurologist, born March 20, 1845, London; died May 4, 1915, London.

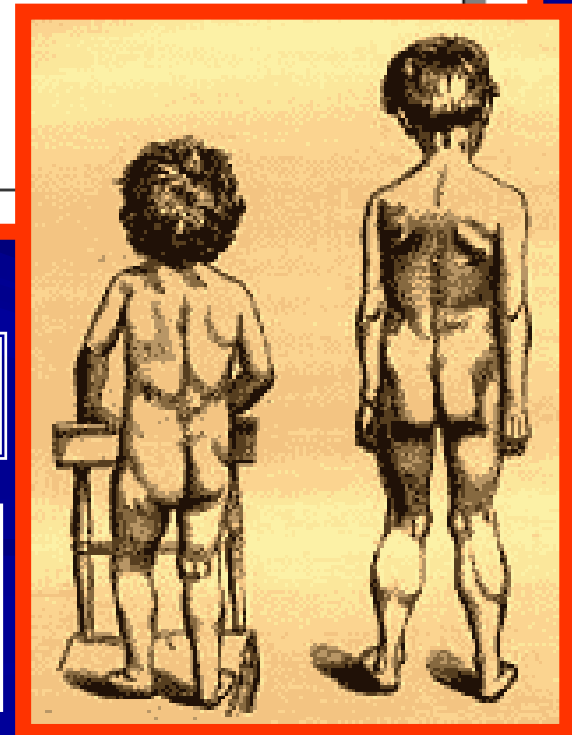


TABLE 7

ASSESSMENT OF MUSCLE WEAKNESS

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

(*) Gowers' sign

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

Sir William Richard Gowers: British neurologist, born March 20, 1845, London; died May 4, 1915, London.

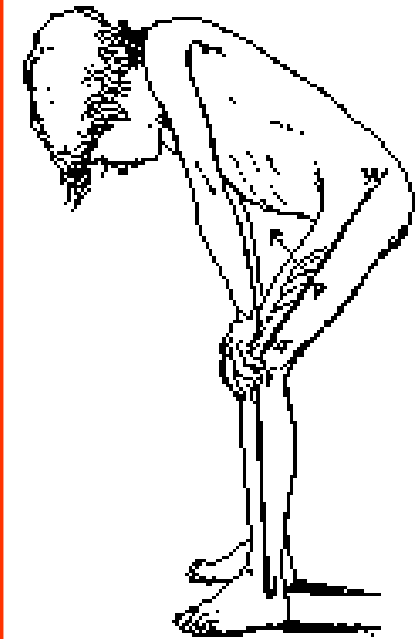


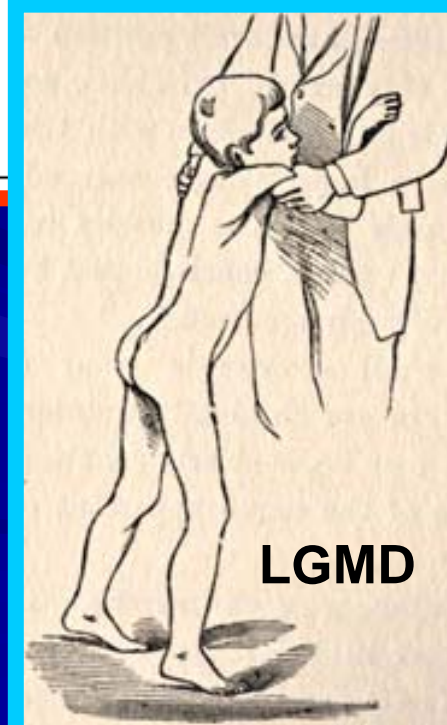
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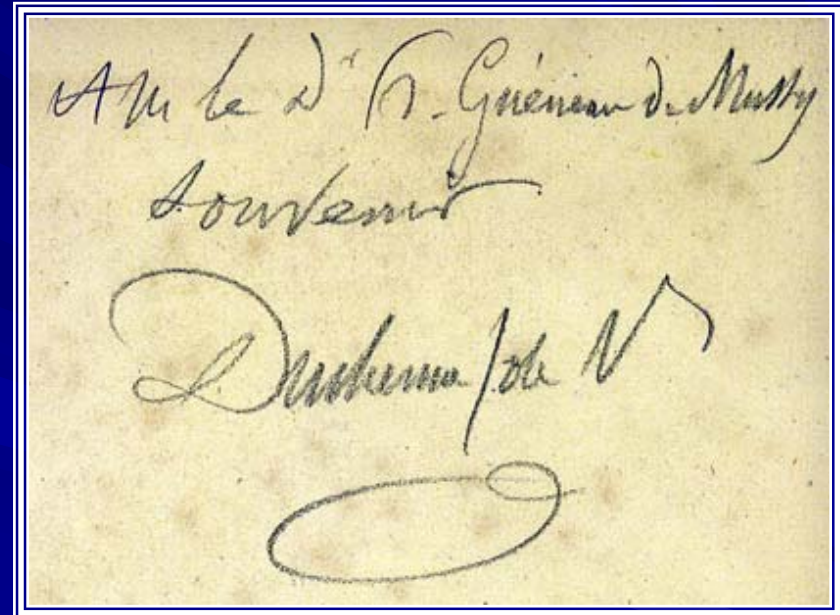


DYSTROPHINOPATHIES

Duchenne muscular dystrophy



Guillaume-Benjamin
Duchenne de Boulogne



Autographed copy of: De la
Paralysie Musculaire Pseudo-
hypertrophique...1868

Duchenne Dystrophy

Overview

- Most common lethal XLR
 - 1:3500 males (Live birth)
- Xp21 dystrophin gene mut.
 - 90% now detectable
- Usual onset 3-5 years
 - Slow progression
- Non-ambulatory ~age 12
- Untreated: death ~age 20
 - Pulmonary compromise



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



macroglossia

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



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

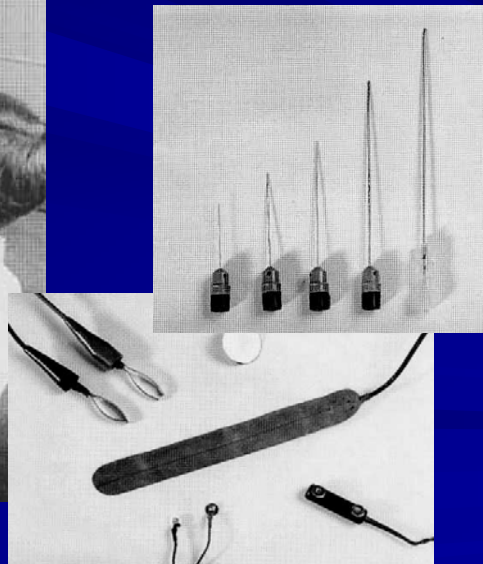
■ EMG

■ 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

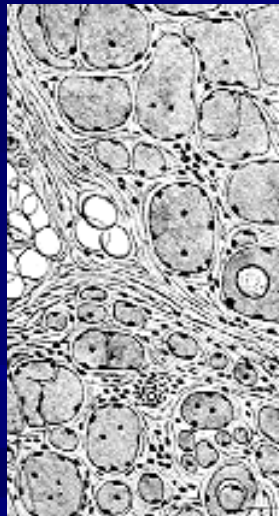
Hypercontracted (opaque) muscle fibers

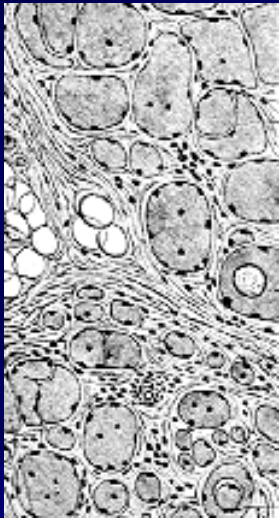
Necrosis “Myopathic grouping”

Muscle fiber degeneration & regeneration:

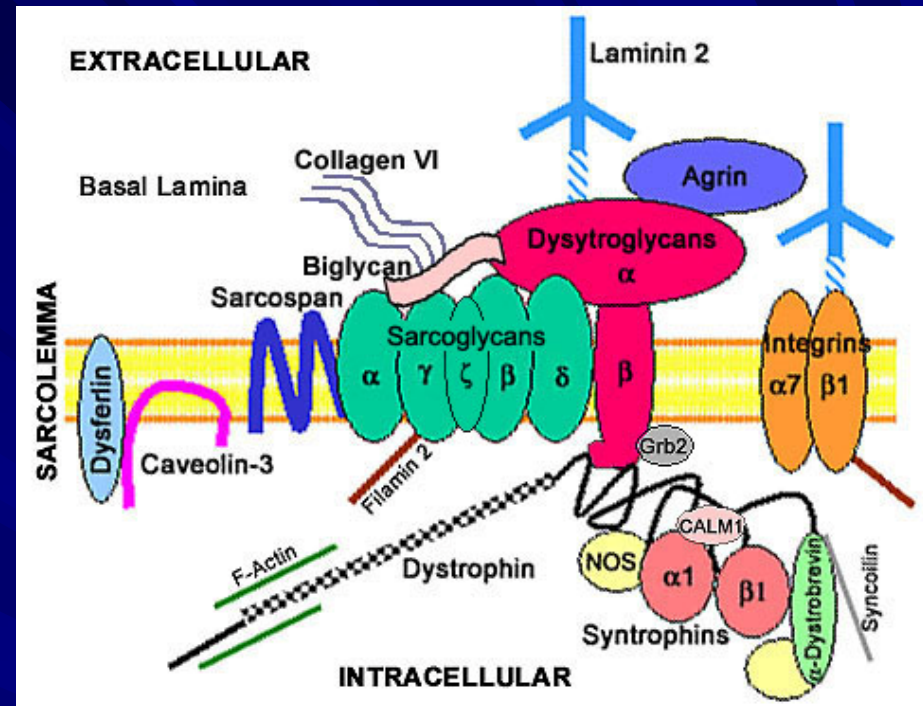
Especially early

Muscle fiber internal architecture:
Normal or immature

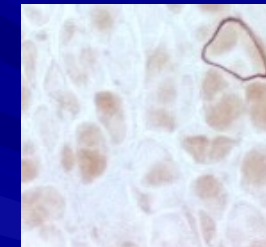
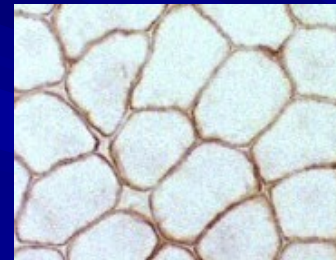




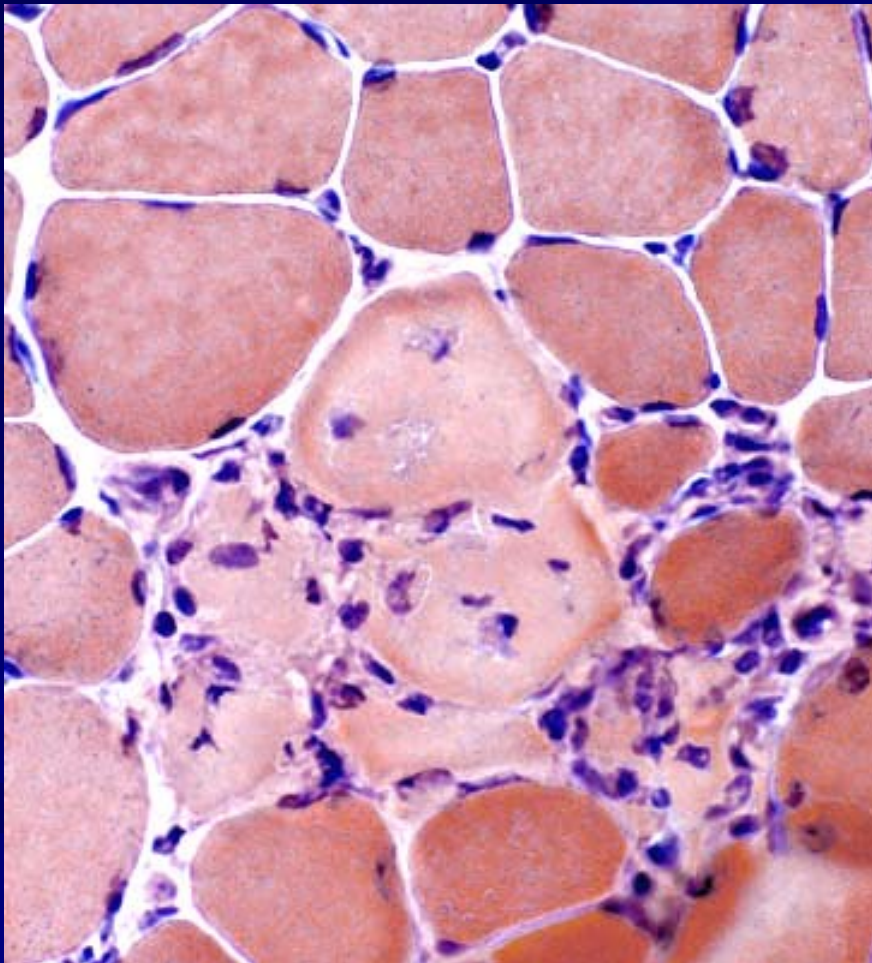
Duchenne muscular dystrophy



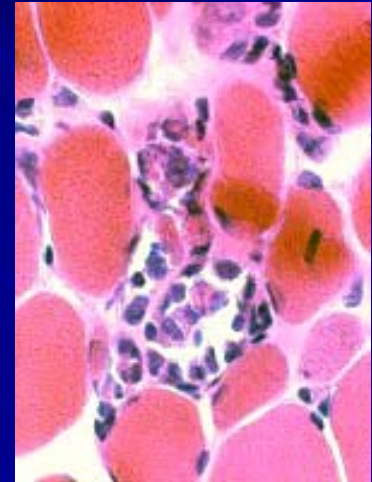
- Dystrophin: Absent staining
- Other membrane proteins
 - Sarcoglycans: Reduced
 - Aquaporin 4: Reduced
- Endomysial fibrosis: More with late pathology



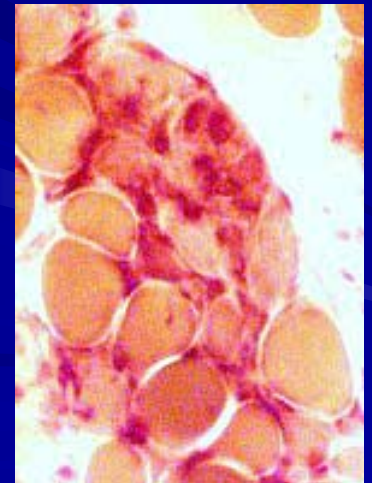
Duchenne Muscular Dystrophy: Early Pathology.1



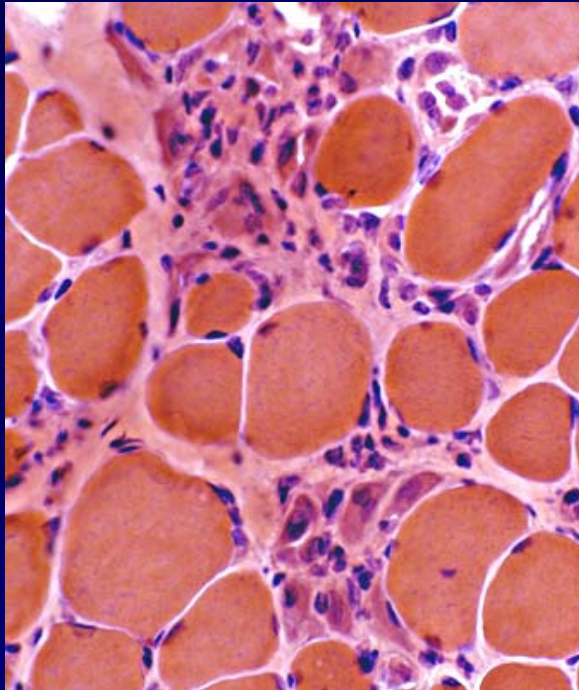
**Necrotic
muscle fibers:
Grouped**



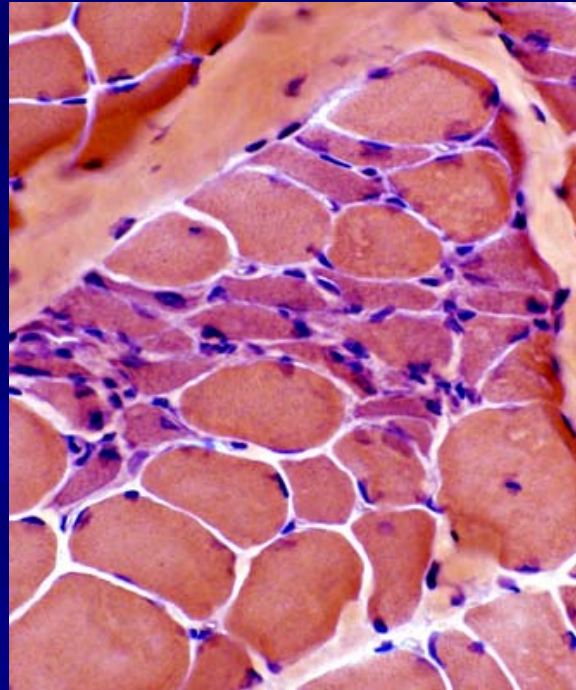
**Phagocytosis
: Invasion of
fibers by
macrophages**



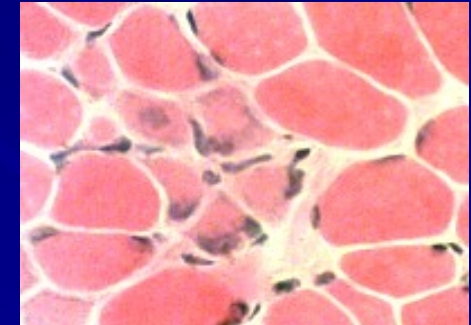
Duchenne Muscular Dystrophy: Early Pathology. 2



Many small regenerating fiber



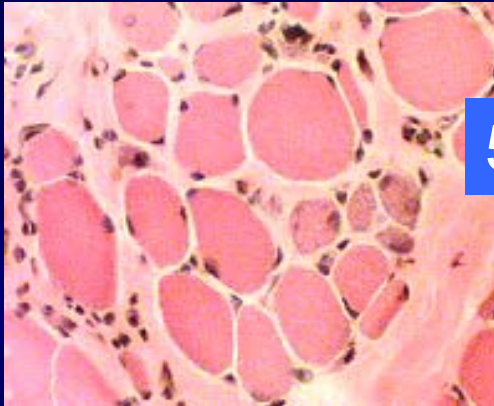
Intermediate-sized regenerating muscle fibers: Myopathic grouping



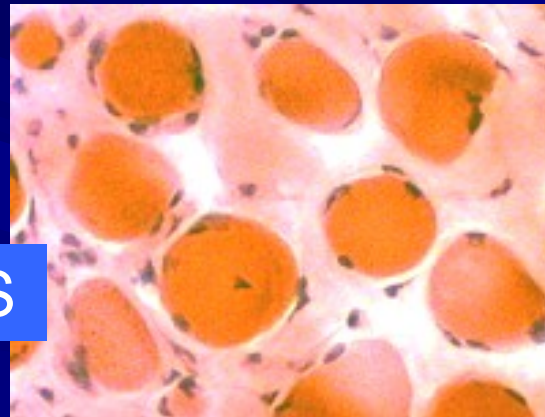
**Immature muscle fibers:
Numerous**

Myopathic grouping of regenerating muscle fibers

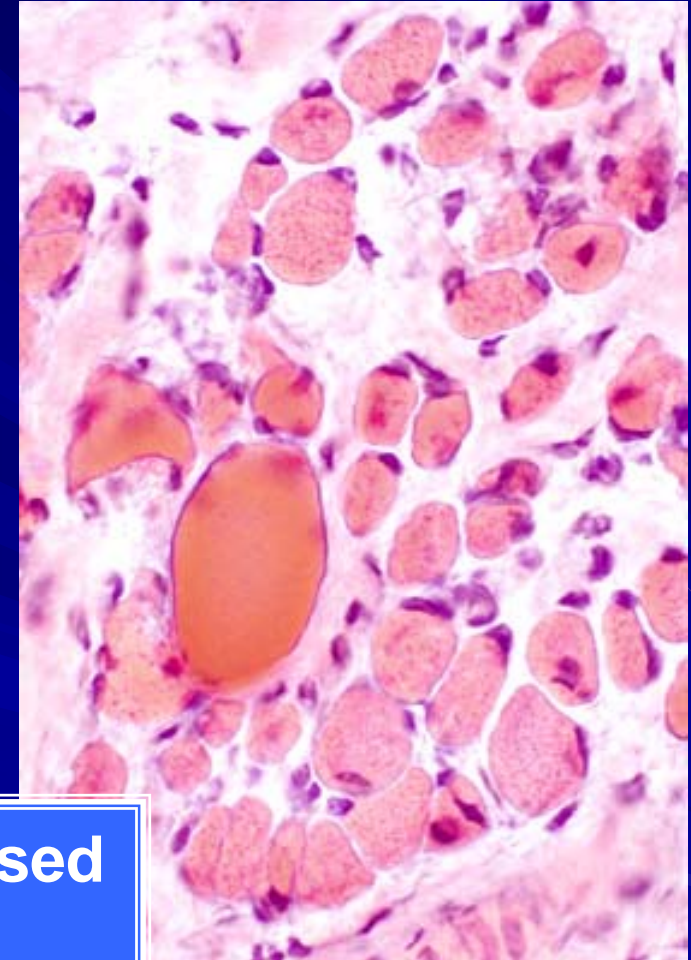
Duchenne Muscular Dystrophy: Later Pathology



5 YEARS

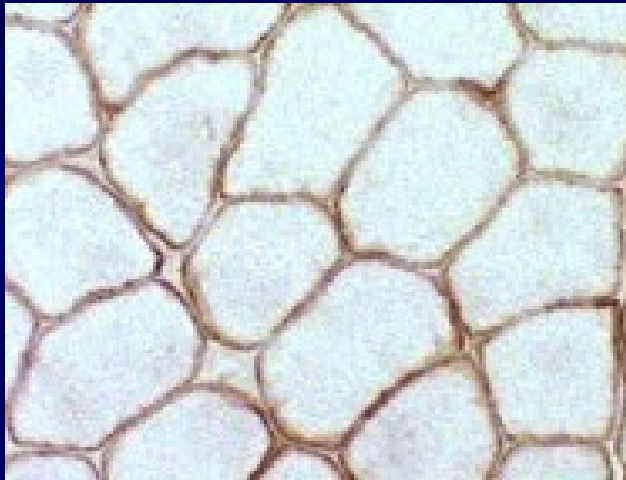


10 YEARS

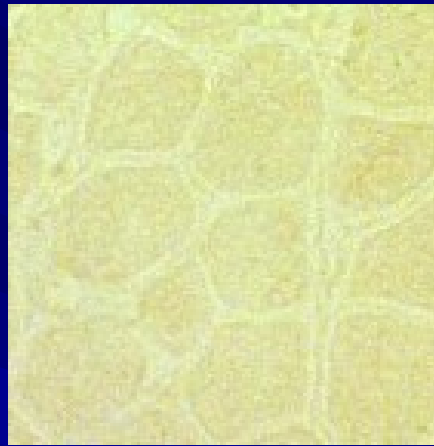


Endomysial connective tissue increased
Variable fiber size.
Small fibers are **rounded**.
Many **hypercontracted** muscle fibers

Duchenne Muscular Dystrophy: Dystrophin staining



Normal dystrophin staining
around the rim of
muscle fibers



Absent dystrophin: Duchenne
muscular dystrophy

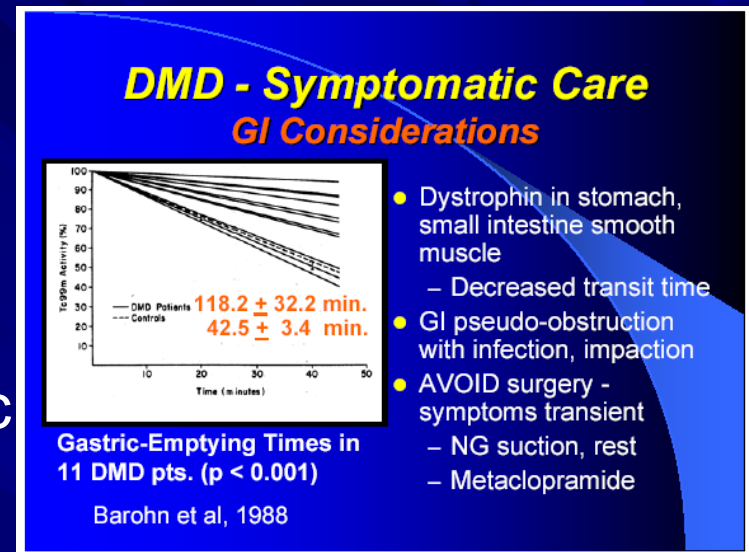
Left: No staining around the rim of
muscle fibers.

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



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

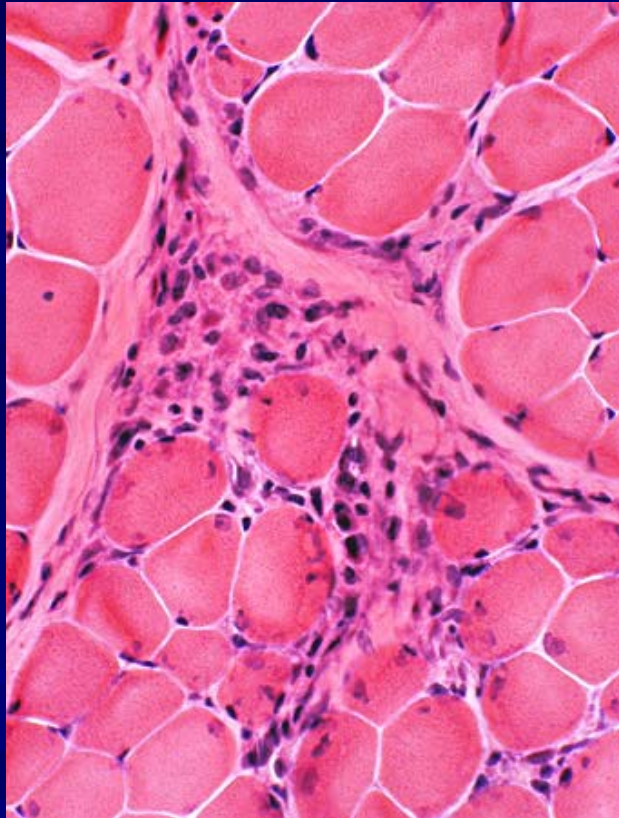


- Toe walking

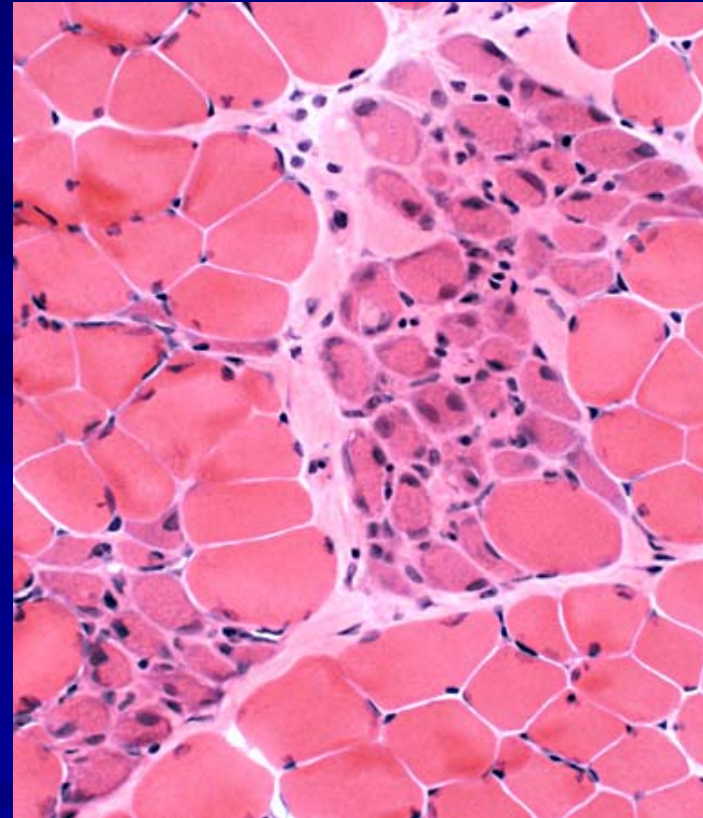
Becker muscular dystrophy

- 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

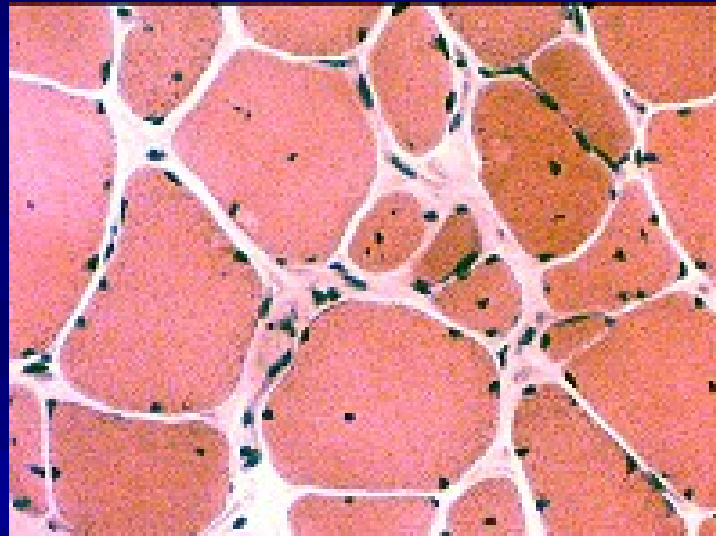
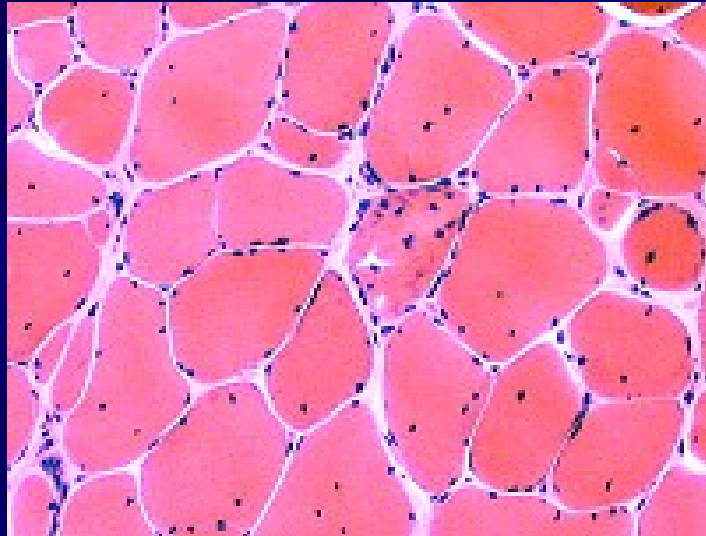


Cluster of degenerated muscle fibers replaced by phagocytic cells



Grouped regenerating muscle fibers (7 yrs old boy)

Becker muscular dystrophy

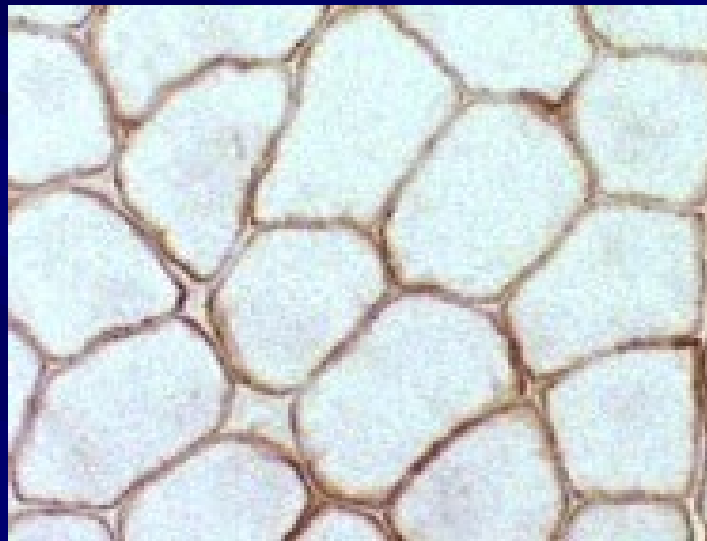


**27 yrs old
male**

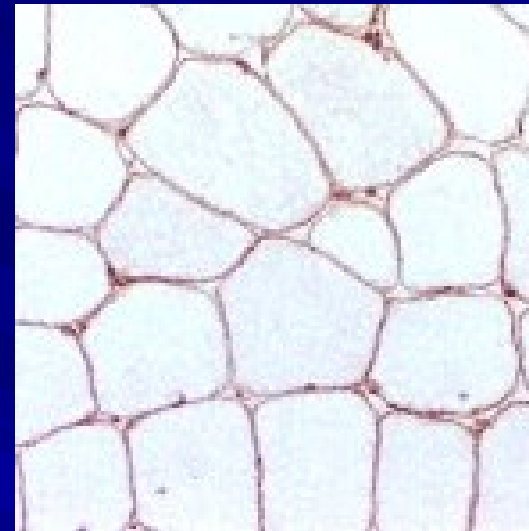
- **chronic dystrophy:**
 - **Increased endomysial connective tissue**
 - **Variable fiber size: Small muscle fibers are rounded**
 - **Internal nuclei**
 - **The largest muscle fibers are hypertrophied**
 - **Occasional fibers: Degeneration; Regeneration; Hypercontraction; Split**

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

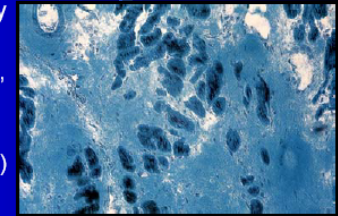
**Tachycardia: > 100;
Common even < 10 years age
Dilated cardiomyopathy
Symptomatic: 57% by age 18
Progression: Variable
May be associated with only:
Myalgias after exercise & High CK**

EKG

**Changes due to atrophy
Age 10: EKG changes in 60%; No clinical
manifestations. Age 18: EKG or ECHO
changes in most**

DMD - Supportive Care Cardiac Considerations

- LV fibrotic cardiomyopathy
 - Big LV, decreased EF
- EKG - tachycardia; tall Rs, deep Qs precordial leads
- Atrial arrhythmia in 50%
- EKG/ECHO ~age 10 (WC)
 - Cardiac consultation
 - Afterload reduction rx.
 - Steroid effects ?



Left ventricle – 21 y.o. DMD

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

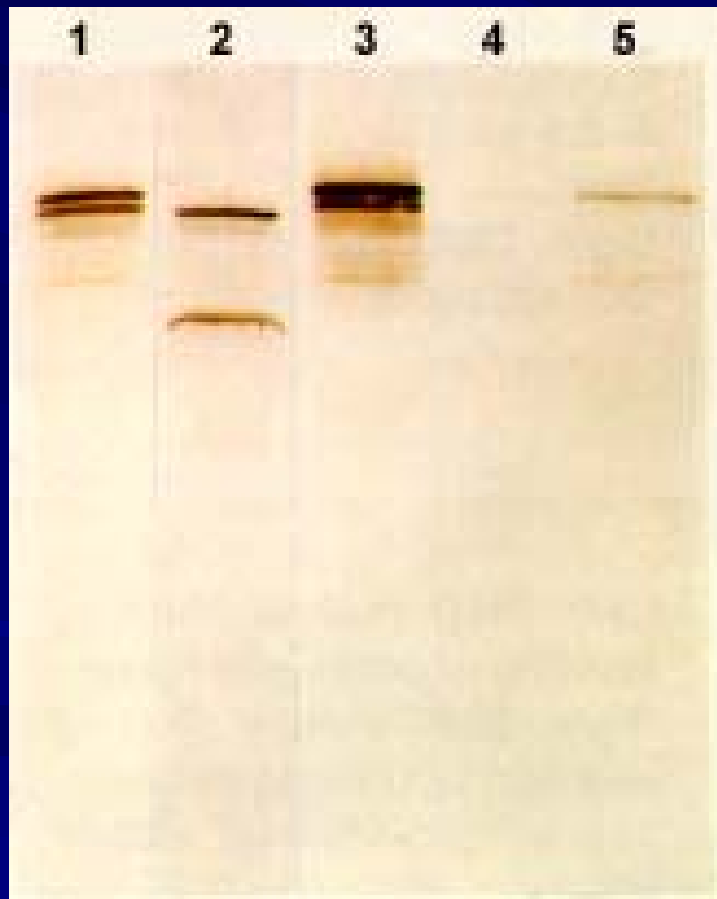
Onset: 5th decade

Congestive heart failure

Chest pain: Atypical

Slowly progressive over > 10 years

Duchenne Muscular Dystrophy: Dystrophin recognition



Western blot of dystrophin
from dystrophinopathies.

Lane 1: Becker dystrophy; Dystrophin has reduced abundance but normal size.

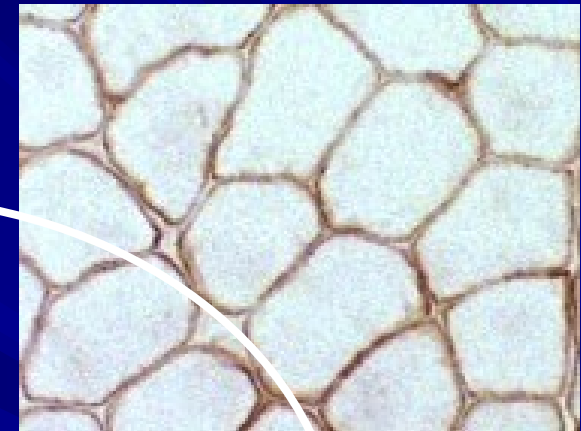
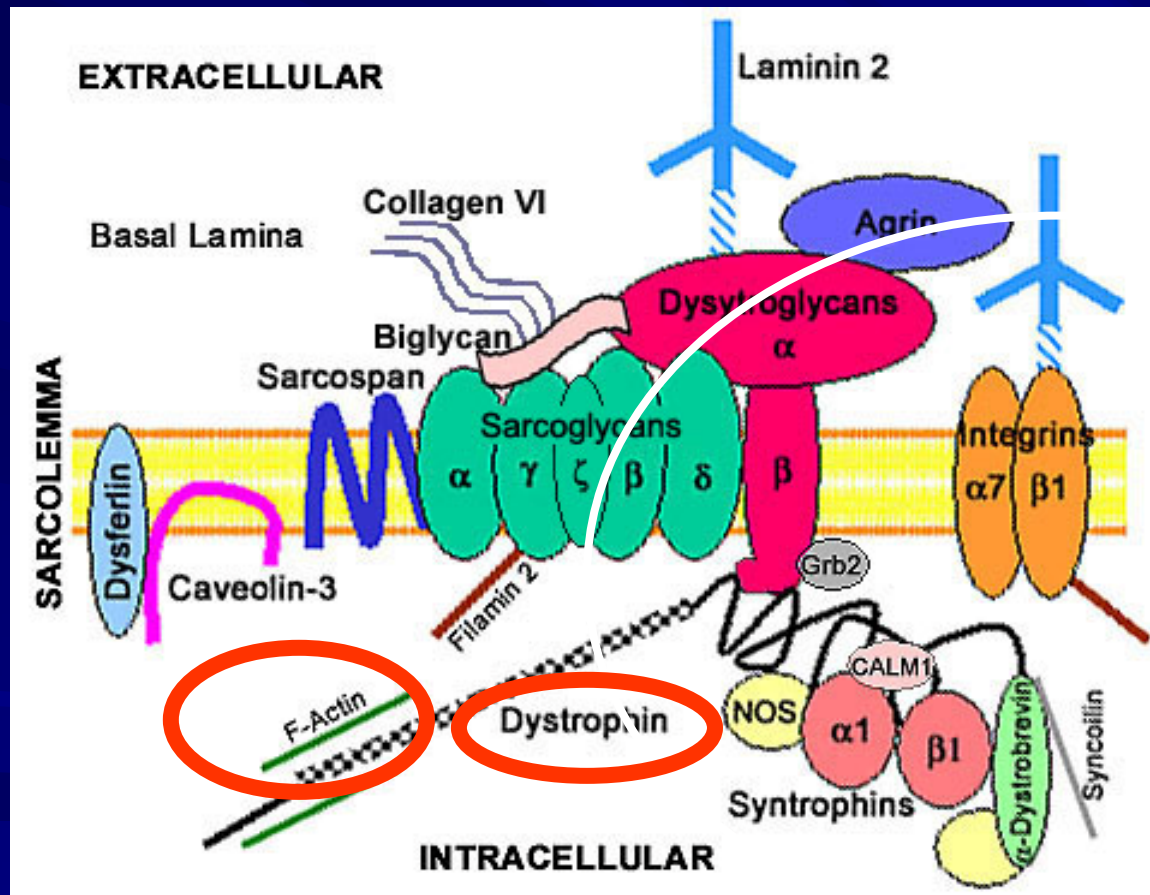
Lane 2: Becker dystrophy; Dystrophin has reduced size and abundance.

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.

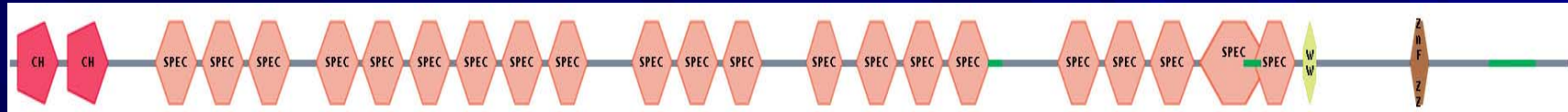
MEMBRANE-ASSOCIATED PROTEIN COMPLEXES IN SKELETAL MUSCLE FIBERS



Costameres

Extrajunctional muscle membrane Associated proteins

Dystrophin functions



Mechanical

Molecular Weight (KDa) : 427 (3685 AA)

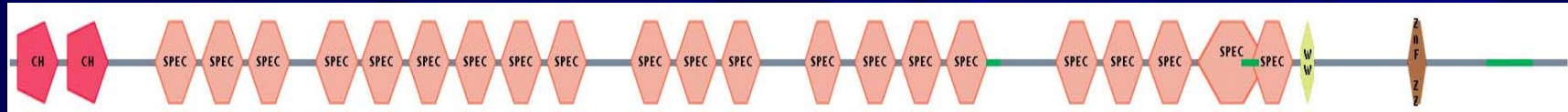
? Stabilization of membrane during contraction & relaxation

Part of link between intracellular cytoskeleton & extracellular matrix

Functional

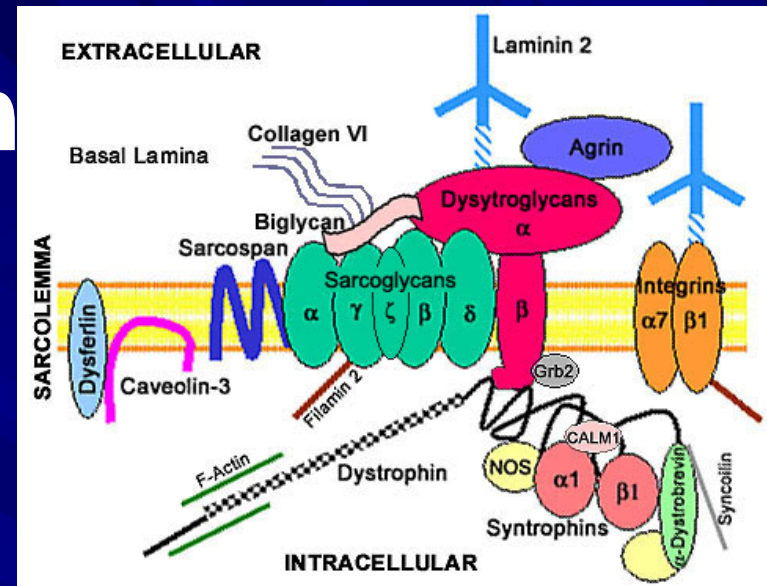
Plays role in ability of muscle fibers to differentiate into fast glycolytic type

May play a role in organization of postsynaptic membrane & AChRs

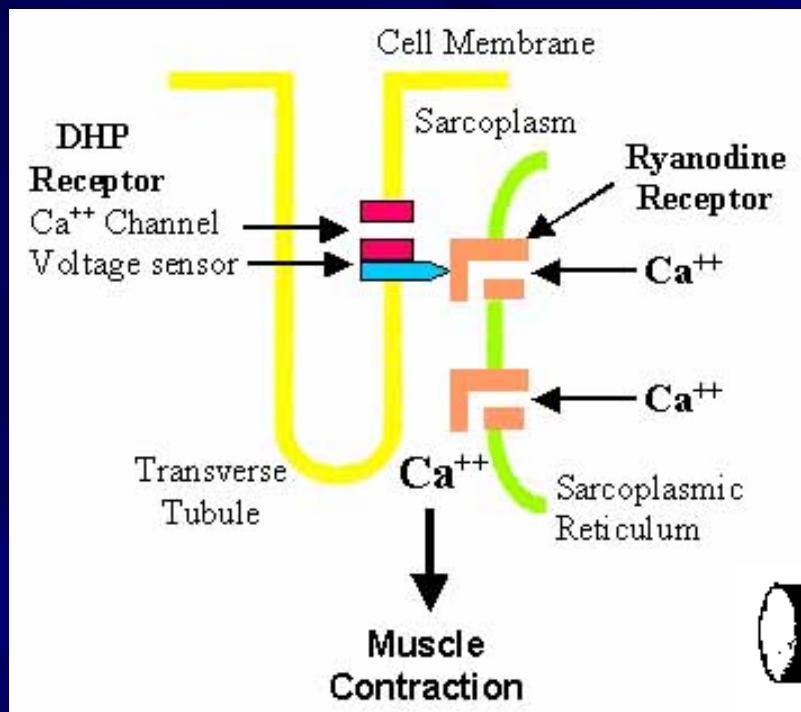


Dystrophin function

- Cytoskeleton binding:
via F-actin (NH₂-terminus;
1 st 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)



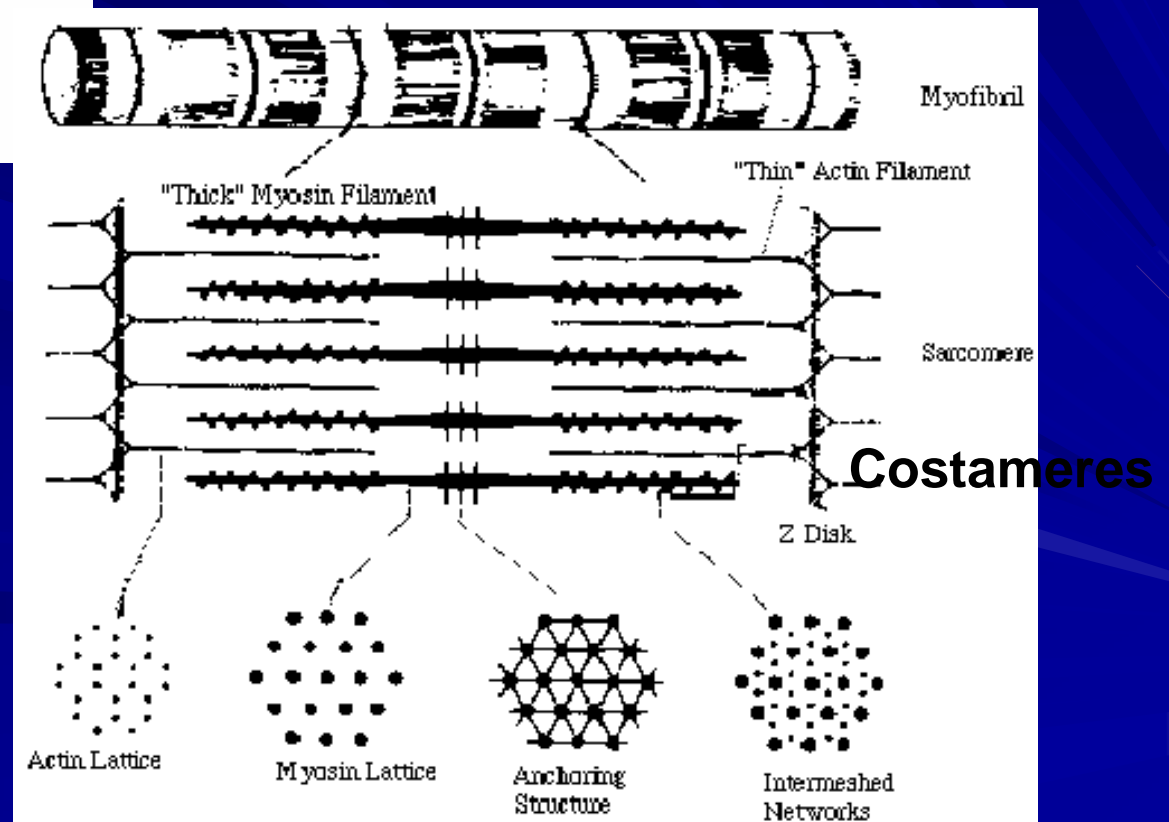
Costameres

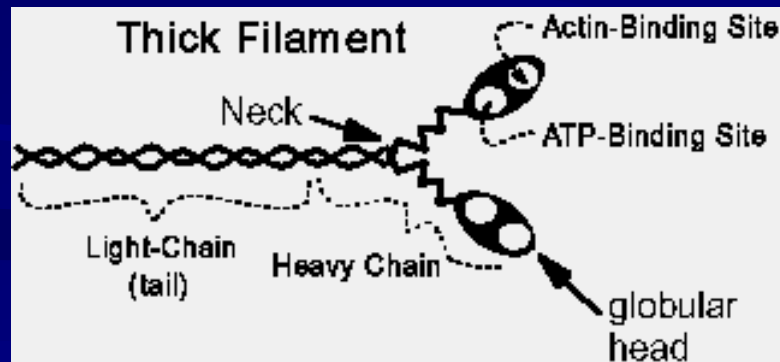
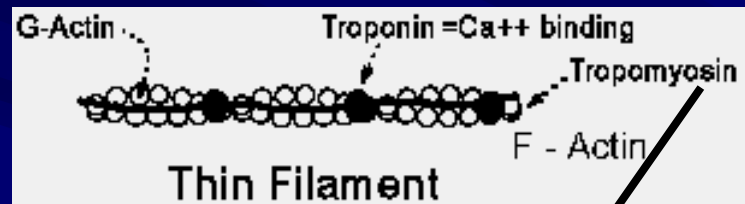
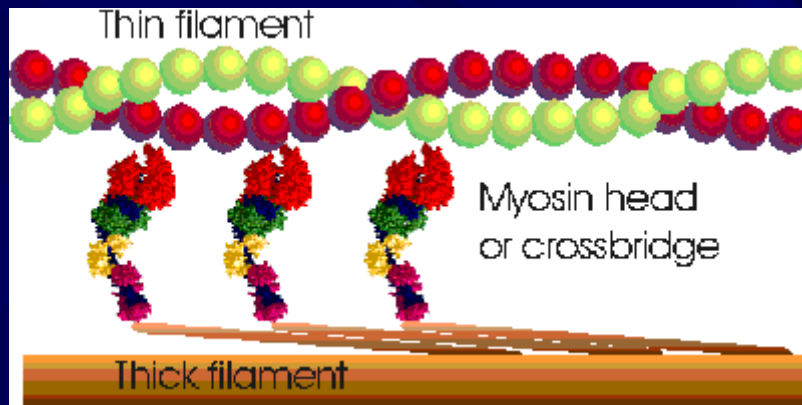


- **Ca⁺⁺ ions release from sarcoplasmic reticulum is regulated by 2 large membrane protein complexes:**
 - Dihydropyridine receptor (DHPR)
 - Ryanodyne receptor (RyR)

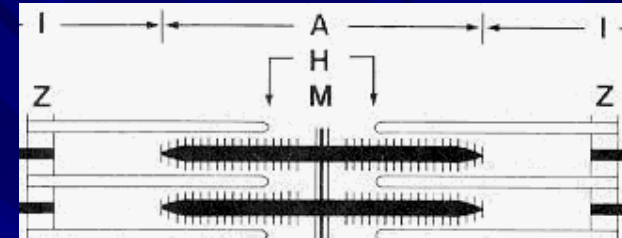
Action potential

- travels along muscle surface membrane
- enters transverse tubule system (t-tubules)





Contains Actin



Contains Myosin

• Costameres

Regulatory protein of thin filament

• Troponin: Complex of 3 subunits

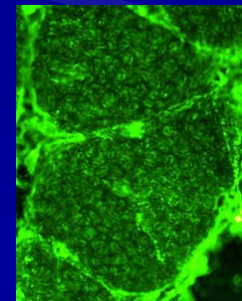
• Myosin heavy chains form cross-bridges

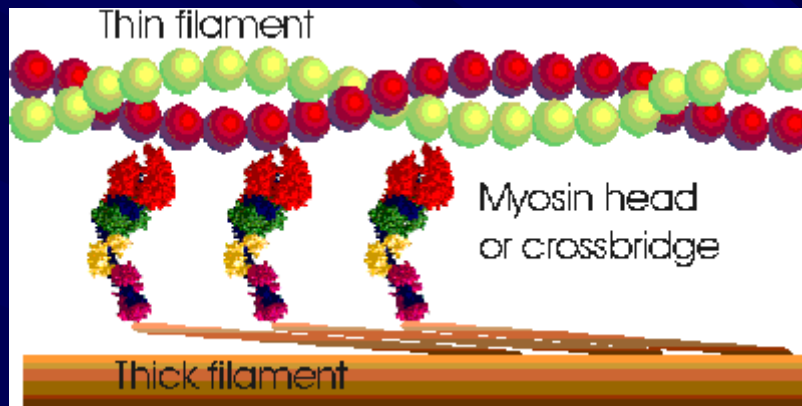
- Myosin light chains: 4 types

- Bind Ca^{++} : High affinity

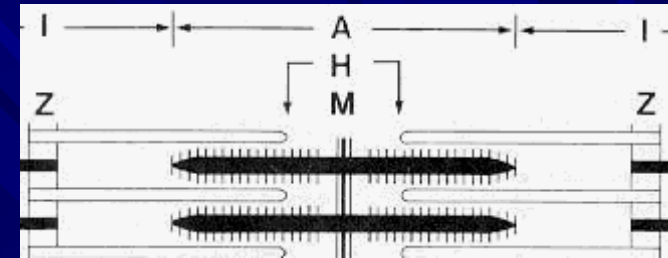
- **Non-myosin components in thick filament**

- Titin (myogenesis)
Z disc ; Theletonin

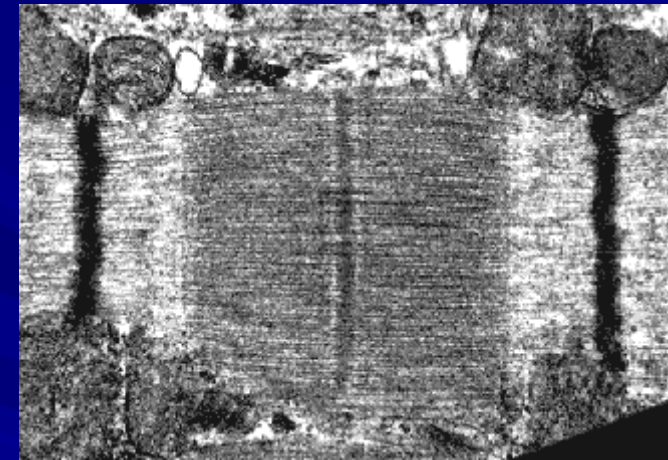
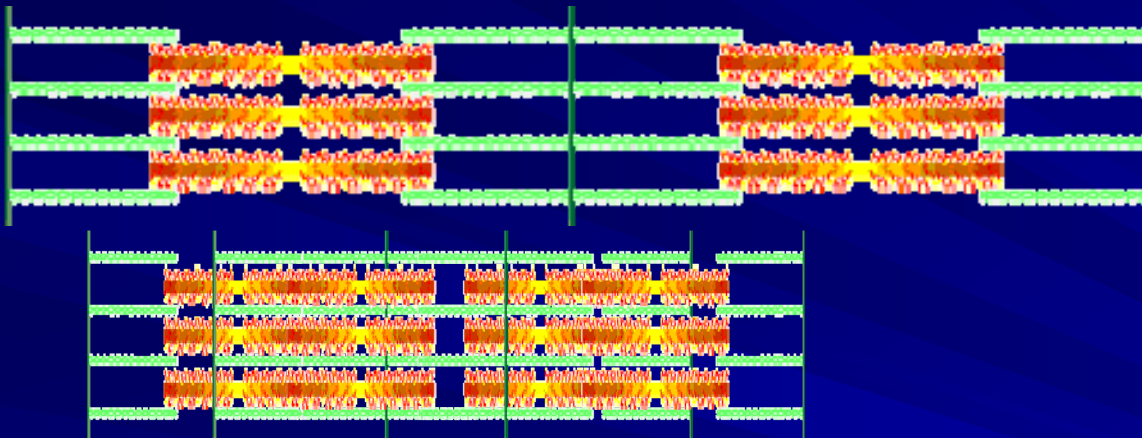




Actin



Myosin



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

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

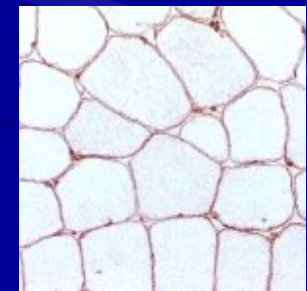
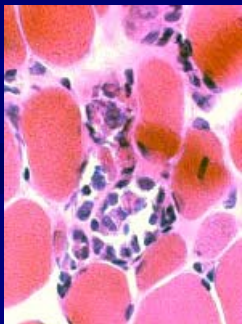
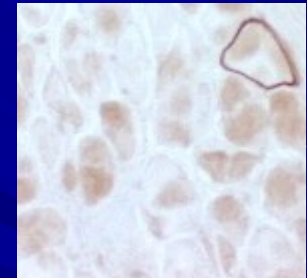
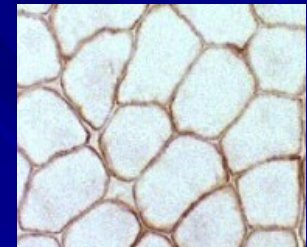
■ Functional consequences of loss of dystrophin on muscle fibers

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 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



5 y.o. with LGMD 1B

- Group of dx. that *tend* to involve proximal muscles
 - Exceptions (LGMD 2B)
- Prevalence $\sim 0.8 - 69/10^6$
- Variable age of onset, severity, progression
- Heart, lung involve. varies
- Precise dx. in only $\sim 50\%$
- No strength therapy, little symptomatic therapy
 - Supportive care key

LGMD-Genetic Classification

Autosomal Dominant

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

@-same locus as AD Emery-Dreifuss

Cardiac conduction defects and/or cardiomyopathy

LGMD-Genetic Classification

Autosomal Recessive

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

Cardiac conduction defects and/or cardiomyopathy

MYOPATHIES WITH PTOSIS +/- OPHTHALMOPLÉGIA

TABLE 10

MYOPATHIES WITH PTOSIS OR OPHTHALMOPLÉGIA

Ptosis Usually Without Ophthalmoplegia

Myotonic dystrophy
Congenital myopathies
 Centronuclear myopathy
 Nemaline myopathy
 Central core myopathy
Desmin storage myopathy



Ptosis With Ophthalmoplegia

Oculopharyngeal muscular dystrophy
Oculopharyngodistal myopathy
Chronic progressive external ophthalmoplegia (mitochondrial myopathy)



Myotonic dystrophies

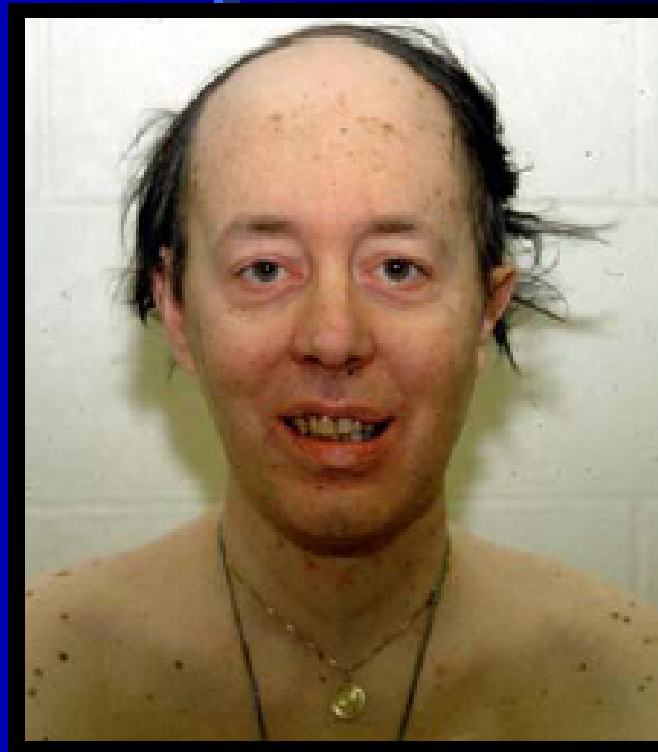
The myotonic dystrophies are a group of muscle disorders characterized generally by muscle weakness, myotonia, cataracts, and cardiac conduction disorders and arrhythmias.

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
Facioscapulohumeral dystrophy
Myotonic dystrophy
Congenital myopathy
Hyperparathyroidism



Facioscapulohumeral Dystrophy

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 humeroperoneal 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

Welander (Late onset type I) distal myopathy

Chromosome 2p13; Dominant

- Genetics¹⁰

- 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

Welander (Late onset type I) distal myopathy

- **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

