1. What is the principal component of the motor system?

- The principal component of the motor system is the motor unit.

2. What is a motor unit composed of?

- A motor unit is composed of one lower motor neuron together with the associated axon, its neuromuscular junctions, and the skeletal muscle fibers it innervates.

3. How is skeletal muscle classified in terms of fiber types?

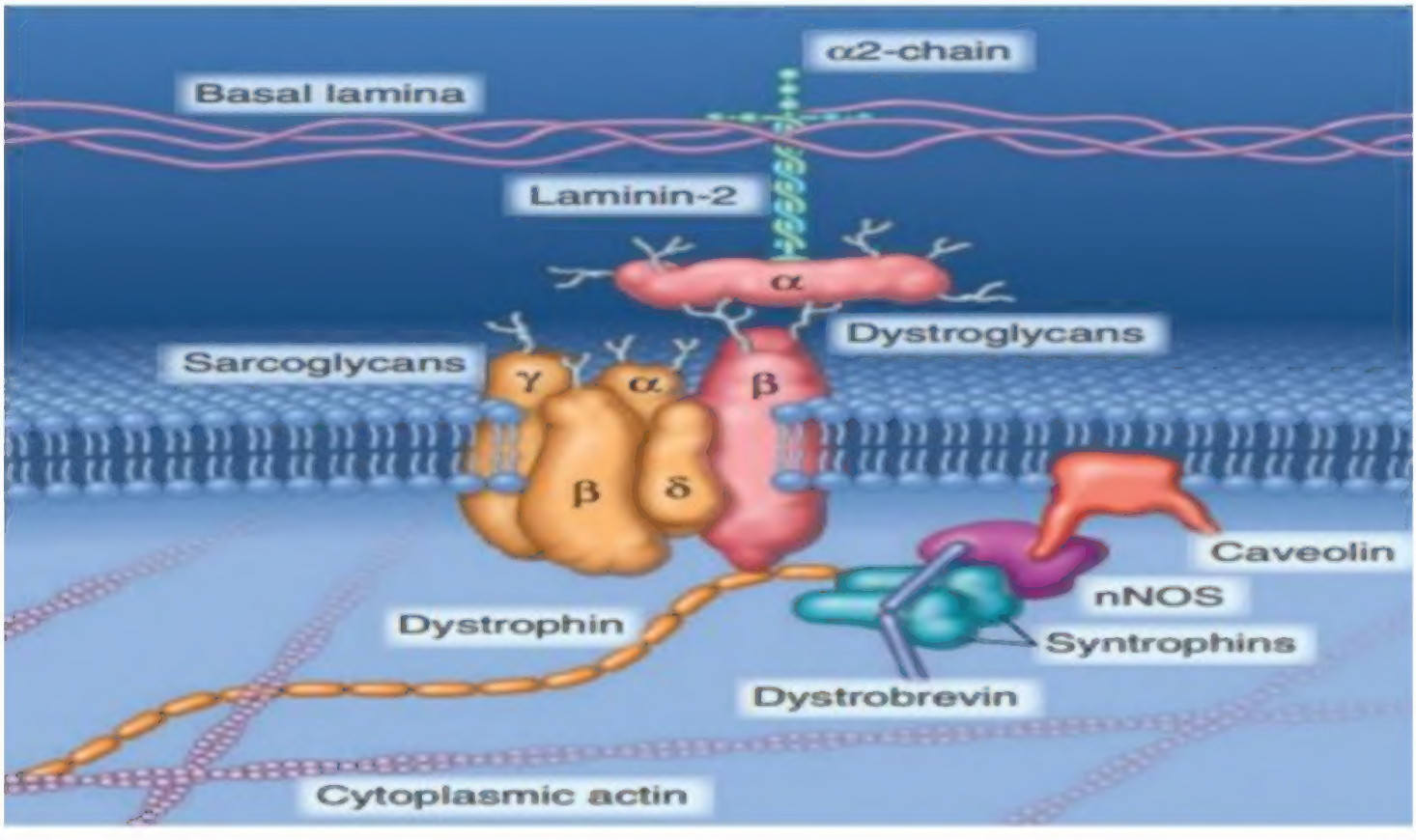
- Skeletal muscle is classified into different fiber types broadly classified as slow twitch type I and fast twitch type II fibers.

1. What proteins are crucial for the unique structure mentioned?

- Proteins that make up the sarcomeres

and the dystrophin-glycoprotein complex are crucial for the unique structure.

2. What are some examples of proteins involved in the unique structure?
- Some examples of proteins involved in the unique structure are those that make up the sarcomeres and the dystrophin-glycoprotein complex.



1. What is the definition of myopathy?
- Myopathy is a clinical disorder

characterized by primary dysfunction of skeletal muscle.

2. What are some examples of myopathy in infancy?
- Examples of myopathy in infancy include mitochondrial and congenital myopathy, such as nemaline myopathy.

3. What are examples of myopathy in childhood?
- Examples of myopathy in childhood include Duchenne and Becker muscular dystrophy.

4. What are examples of myopathy in adulthood?
- Examples of myopathy in adulthood include endocrine myopathies and inflammatory myopathies.

1. What are the types of inherited classifications mentioned?
- The types of inherited classifications mentioned are dystrophy (including Duchenne, Becker, and fascioscapulohumeral), congenital (such as nemaline), metabolic, mitochondrial, and channelopathies.

2. What are examples of dystrophy in the inherited classification?
- Examples of dystrophy in the inherited classification include Duchenne, Becker, and fascioscapulohumeral dystrophies.

3. What types of myopathy fall under the acquired classification?
- Myopathies that fall under the acquired classification include inflammatory (such as dermatomyositis and polymyositis), infective (viral), toxic (medication-induced),

and systemic (related to endocrine disease) myopathies.

1. What is the pathophysiology of mitochondrial myopathies?
- Mitochondrial myopathies result from mutations in mitochondrial and nuclear genome proteins involved in oxidative phosphorylation. This leads to impaired ATP production, excess free radical production, and lactic acidosis in muscles and other tissues.

2. How does muscular dystrophy occur?
- Muscular dystrophy, particularly in the case of X-linked dystrophy, is characterized by the absence of dystrophin, leading to poor structural stability of the Dystroglycan complex. This results in persistent depolarization and calcium influx, ultimately leading to

degradation of muscle fibers.

3. What is the pathophysiological mechanism behind thyrotoxic myopathy?
- Thyrotoxic myopathy involves reduced levels of acetylcholinesterase, leading to overstimulation of muscle fibers.

1. How do primary muscle diseases (myopathies) differ from secondary neuropathic changes?
- Primary muscle diseases or myopathies need to be distinguished from secondary neuropathic changes caused by disorders that disrupt muscle innervation.

2. What is the commonality between myopathies and neuropathies?
- Both myopathies and neuropathies are associated with altered muscle function and morphology.

3. What distinguishes myopathies from neuropathies?
- Myopathies and neuropathies each have distinctive features despite their association with altered muscle function and morphology.

1. What are some morphological features associated with myopathic conditions?
- Myopathic conditions often exhibit segmental necrosis and regeneration of individual muscle fibers. Some myopathies may also show other morphological features, such as inflammatory infiltrates or intracellular inclusions.

2. What morphological changes indicate chronicity in both myopathic and neuropathic conditions?
- Disruption of muscle by endomysial

fibrosis and fatty replacement reflects disease chronicity, which can occur in both myopathic and neuropathic conditions.

3. What is a common effect on muscle fibers caused by both neuropathic and myopathic processes?

- Both neuropathic and myopathic processes can lead to muscle fiber atrophy.

Myopathy Vs Neuropathy

	Neuropathy	Myopathy
Pattern of weakness	distal	proximal
Reflexes	weak or absent	normal early on
Sensory symptoms	present	absent
Creatine kinase (CK) (muscle enzyme)	normal	elevated
EMG	"neuropathic"	"myopathic"
Muscle biopsy	"group atrophy/ type grouping"	"necrosis/inflammation /specific findings"

1. What are the variations in organ involvement in inherited disorders of skeletal muscle?

- In some inherited disorders, skeletal muscle is the primary site of disease, while in others, multiple organs are involved.

2. Is there a direct relationship between genotypes and phenotypes in inherited skeletal muscle disorders?

- No, there is not a simple one-to-one correspondence between genotypes and phenotypes in inherited skeletal muscle disorders.

3. How can mutations in different genes present clinically?

- Mutations in several different genes can present clinically, for example, as autosomal recessive limb-girdle muscular dystrophy.

4. Can mutations in a single gene lead to different clinical phenotypes?
- Yes, mutations in a single gene, such as dystrophin, can lead to very different clinical phenotypes, as seen in Duchenne and Becker types of muscular dystrophy.

1. What is the cause of Duchenne and Becker muscular dystrophy?
- Duchenne and Becker muscular dystrophy are caused by mutations that disrupt the function of a large structural protein called dystrophin.

2. What is the incidence of Duchenne muscular dystrophy?
- Duchenne muscular dystrophy has an incidence of about 1 per 3500 live male births.

3. How does Duchenne muscular dystrophy typically progress?
- Duchenne muscular dystrophy becomes clinically evident in early childhood, and most patients are wheelchair-bound by the time they are teenagers. It follows an invariably fatal course, with patients typically succumbing to the disease by early adulthood.

4. How does Becker muscular dystrophy compare to Duchenne muscular dystrophy in terms of severity and prevalence?
- Becker muscular dystrophy is less common and less severe compared to Duchenne muscular dystrophy.

1. What are the similarities and differences in histologic alterations between Duchenne and Becker muscular dystrophy (DMD and BMD)?

- The histologic alterations in skeletal muscles affected by DMD and BMD are similar, but changes are milder in BMD.

2. What are the hallmarks of DMD and BMD, along with other muscular dystrophies?

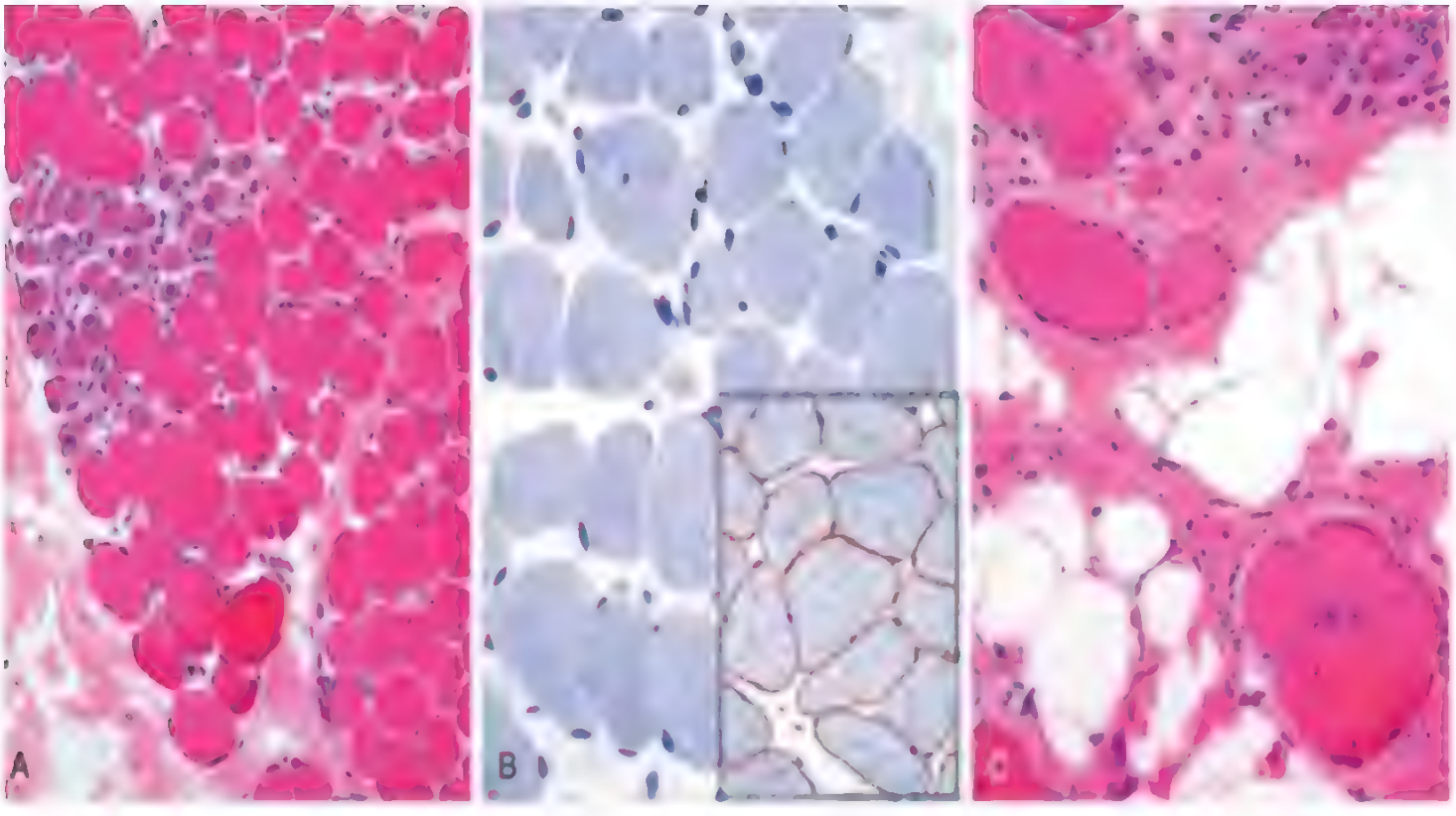
- The hallmarks of DMD, BMD, and other muscular dystrophies are ongoing myofiber necrosis and regeneration, along with progressive replacement of muscle tissue by fibrosis and fat.

3. What are some typical histologic features seen in muscles affected by DMD and BMD?

- Muscles affected by DMD and BMD typically show marked variation in myofiber size and abnormal internally placed nuclei due to ongoing repair processes.

4. Besides skeletal muscles, what other type of muscles are affected by DMD and BMD?

- Both DMD and BMD also affect cardiac muscles, which may show variable degrees of myocyte hypertrophy and interstitial fibrosis.



1. What causes Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD)?

- Mutations disrupting the function of the dystrophin gene located on the short arm of the X chromosome (Xp21).

2. Where is the dystrophin gene located?
- The dystrophin gene is located on the short arm of the X chromosome (Xp21).

3. What is dystrophin, and where is it found in the body?
- Dystrophin is a large protein (427 kD in molecular weight) found in skeletal and cardiac muscle, brain, and peripheral nerves.

4. What is the role of the dystrophin-glycoprotein complex?
- It stabilizes the muscle cell during contraction and may be involved in cell signaling through interactions with other proteins.

5. How do defects in the dystrophin-glycoprotein complex affect muscle cells?
- Defects in the dystrophin-glycoprotein complex make muscle cells vulnerable to transient membrane tears during contraction, leading to calcium influx, and may also disrupt intracellular signaling.

6. What is the consequence of myofiber degeneration in DMD and BMD?
- Myofiber degeneration outpaces the capacity for repair over time.

7. Why does cardiomyopathy eventually develop in many patients with DMD and BMD?
- The dystrophin-glycoprotein complex is important for cardiac muscle function, explaining why cardiomyopathy eventually develops in many patients.

1. How large is the dystrophin gene relative to the X chromosome?

- The dystrophin gene spans roughly 2.4 megabases, which is about 1% of the X chromosome.

2. Why is the dystrophin gene prone to sporadic mutations?

- Its large size may make it more prone to sporadic mutations.

3. What are the most common mutations associated with DMD and BMD?

- Deletions are the most common mutations.

4. What is the characteristic finding in muscle biopsy of patients with DMD?

- Patients with DMD usually show complete absence of dystrophin on a muscle biopsy.

5. What type of mutations do patients with BMD often have, and what is the consequence?

- Patients with BMD often have point mutations, resulting in residual but defective forms of dystrophin.

6. How does the severity of the disease correlate with genotype and dystrophin deficiency?

- The severity of the disease correlates with genotype and the extent of dystrophin deficiency.

1. What are some of the first symptoms of Duchenne muscular dystrophy (DMD)?

- Clumsiness and an inability to keep up with peers due to muscle weakness are often the first symptoms.

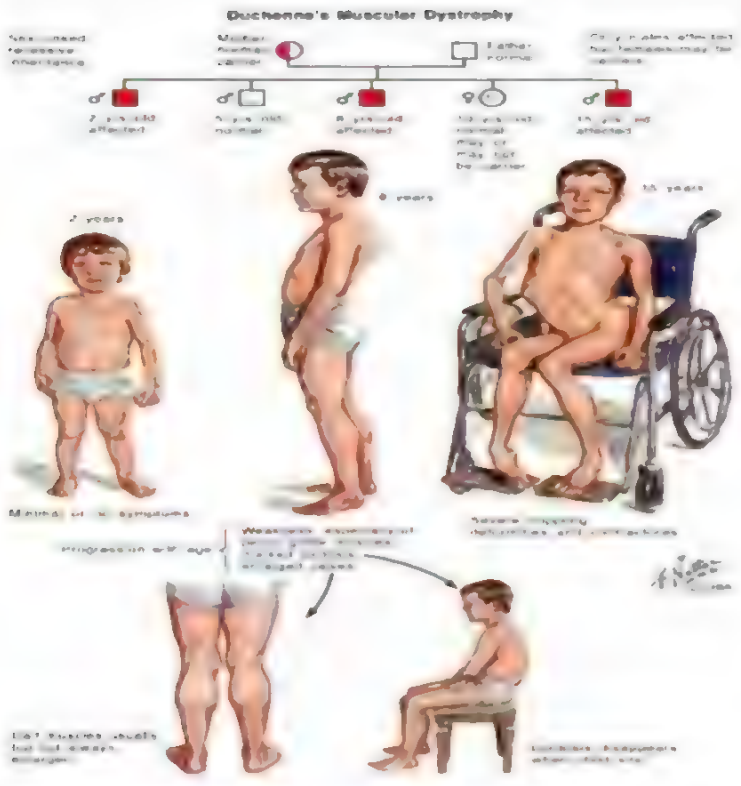
2. Where does the weakness typically begin in DMD?
- The weakness typically begins in the pelvic girdle and then involves the shoulder girdle.

3. What physical finding is characteristic in the early stages of DMD?
- Enlargement of the calves, termed pseudo hypertrophy, is an early physical finding.

4. What initially causes the increased muscle bulk in DMD?
- The increased muscle bulk initially stems from myofiber hypertrophy.

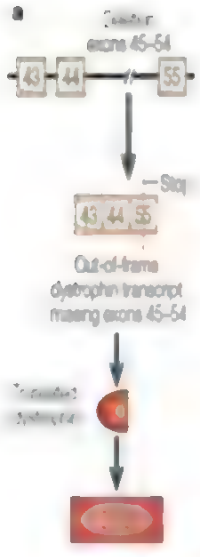
5. What happens to the muscle as myofibers progressively degenerate in DMD?
- As myofibers progressively degenerate,

an increasing part of the muscle is replaced by adipose tissue and endomysial fibrosis.



Etiology

- single gene defect
- Xp21.2 region
- absent dystrophin



1. What potential complications related to the heart are associated with Duchenne muscular dystrophy (DMD)?
- Cardiac muscle damage and fibrosis may lead to heart failure and arrhythmias, which may prove fatal.

2. What cognitive impairment may occur in individuals with DMD?
- Cognitive impairment may occur and may be severe enough to be classified as mental retardation.

3. What is the pattern of serum creatine kinase levels in DMD?
- High serum creatine kinase levels are present at birth and persist through the first decade of life but fall as muscle mass is lost as the disease progresses.

4. What are some causes of death in individuals with DMD?
- Death results from respiratory insufficiency, pneumonia, and cardiac decompensation.

5. How does the clinical presentation of Becker muscular dystrophy (BMD) differ from DMD?
- BMD becomes symptomatic later in childhood or adolescence and progresses at a slower and more variable rate.

6. What is the life expectancy for many patients with BMD?
- Many patients live well into adulthood and have a nearly normal lifespan.

7. What may be the dominant clinical feature in BMD?
- Cardiac involvement may be the

dominant clinical feature and may result in death, even in the absence of significant skeletal muscle weakness.

8. What is the current status of treatment for DMD and BMD?
- Treatment is challenging, consisting primarily of supportive care. Definitive therapy requires restoration of dystrophin levels in skeletal and cardiac muscle fibers, with genetic approaches being tested in clinical trials.

1. What type of disease is myotonic dystrophy?
- Myotonic dystrophy is a nucleotide repeat expansion disease.

2. How is myotonic dystrophy inherited?
- It is inherited as an autosomal

dominant trait.

3. What gene is mutated in more than 95% of patients with myotonic dystrophy?
- Mutations occur in the gene that encodes the dystrophia myotonica protein kinase (DMPK).

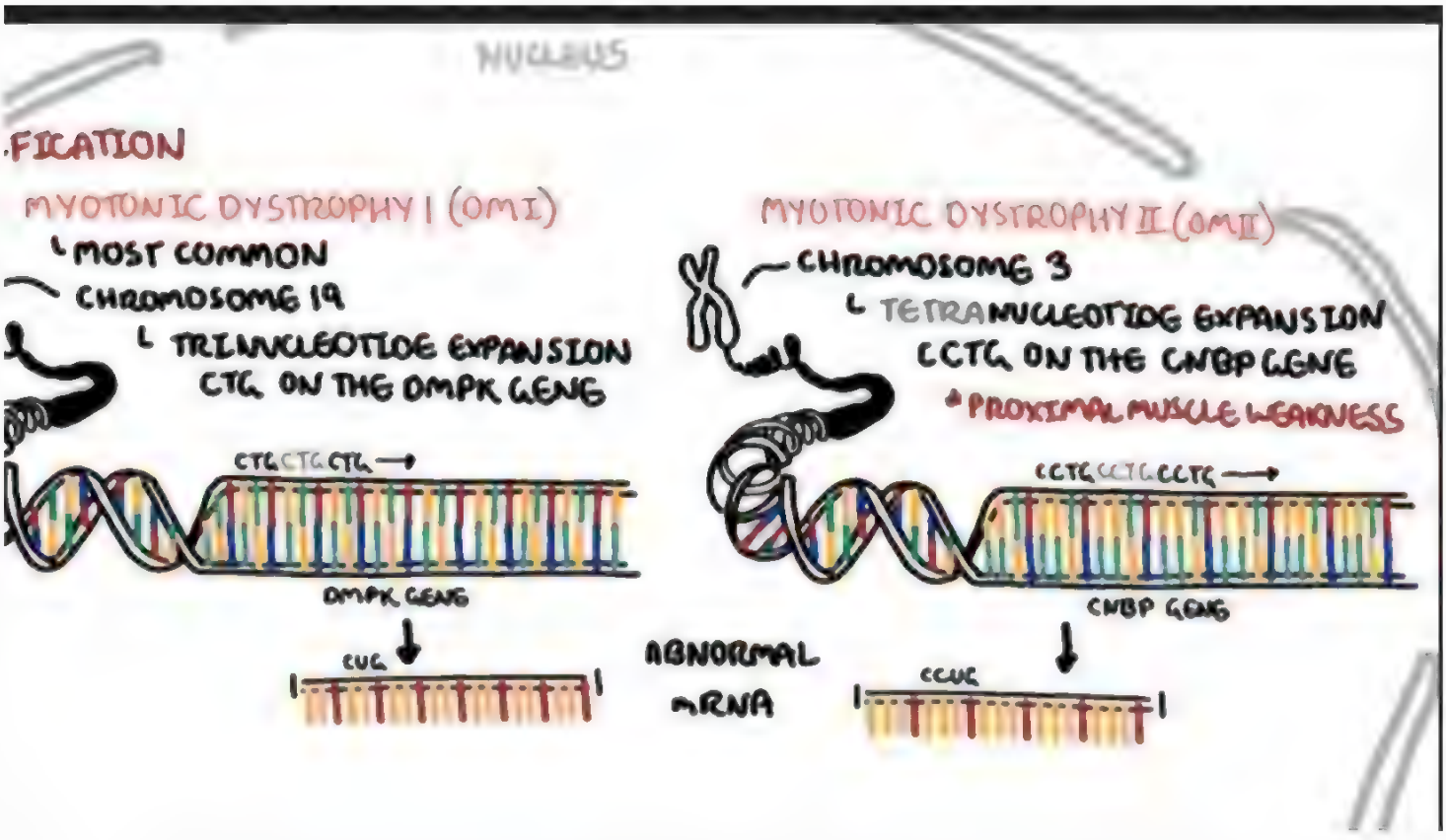
4. What is the normal range of CTG repeats in the gene that encodes DMPK?
- In normal subjects, this gene contains 5 to 37 CTG repeats.

5. What range of CTG repeats do affected patients usually carry?
- Affected patients usually carry 45 to several thousand CTG repeats.

6. How does the disease manifestation change with each passing generation?
- The disease manifestations worsen

with each passing generation due to further trinucleotide repeat expansion.

7. Where is the CTG repeat located in the DMPK mRNA?
- The CTG repeat is located in the 3' untranslated region of the DMPK mRNA.



1. At what age does myotonic dystrophy often manifest with gait abnormalities?
- Myotonic dystrophy often manifests in late childhood with gait abnormalities.

2. What specific weakness is typically observed in late childhood in individuals with myotonic dystrophy?
- Weakness of foot dorsiflexors is observed, leading to gait abnormalities.

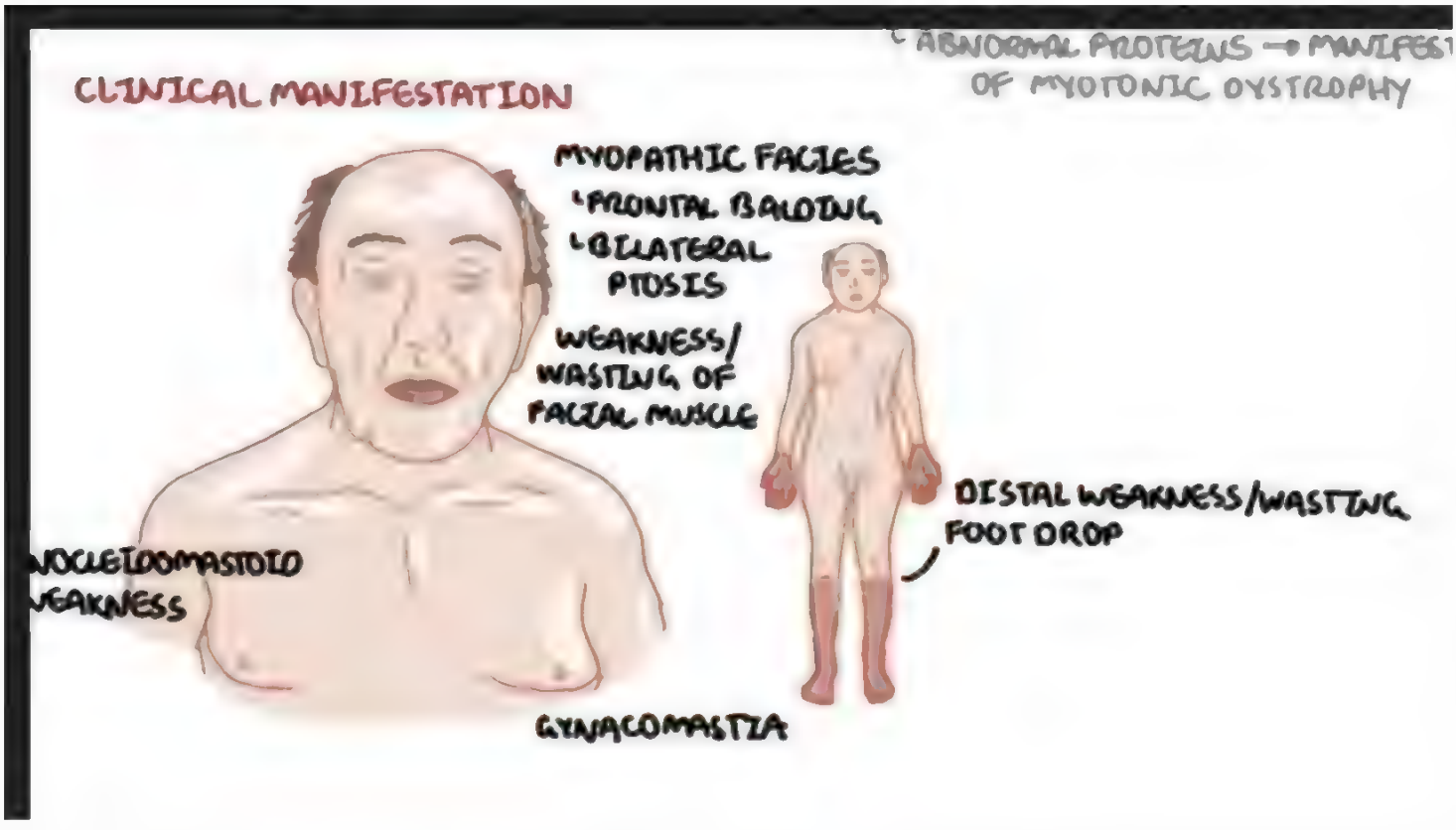
3. What muscles are affected next after weakness of foot dorsiflexors in myotonic dystrophy?
- Subsequent progression involves weakness of the intrinsic muscles of the hands and wrist extensors.

4. Besides muscle weakness, what other symptoms may occur in myotonic dystrophy?
- Atrophy of the facial muscles and ptosis may also occur.

5. What potential complications involving

other organ systems are associated with myotonic dystrophy?

- Other complications include potentially fatal cardiac arrhythmias, cataracts, early frontal balding, endocrinopathies, and testicular atrophy.



Limb-girdle muscular dystrophies (LGMD):

1. Which muscles are preferentially affected by limb-girdle muscular dystrophies?

- Limb-girdle muscular dystrophies

preferentially affect the proximal musculature of the trunk and limbs.

2. What is the genetic basis of limb-girdle muscular dystrophies?
- The genetic basis is heterogeneous.

3. How many dominant and autosomal recessive subtypes of limb-girdle muscular dystrophies are currently recognized?
- There are at least 7 dominant subtypes and 15 autosomal recessive subtypes.

4. What are some components of the dystrophin-glycoprotein complex that can be affected by mutations in limb-girdle muscular dystrophies?
- Mutations can affect components of the dystrophin-glycoprotein complex other than dystrophin. They can also affect proteins involved in vesicle transport and

repair of the cell membrane after injury, cytoskeletal proteins, or posttranslational modification of dystroglycan.

Emery-Dreifuss muscular dystrophy (EMD):

5. What structural proteins found in the nucleus are affected by mutations in Emery-Dreifuss muscular dystrophy?
- Mutations affect structural proteins found in the nucleus.

6. What is the genetic basis of the X-linked and autosomal dominant forms of Emery-Dreifuss muscular dystrophy?
- The X-linked form results from mutations in the gene encoding the protein emerin, whereas the autosomal dominant form is caused by mutations in the gene encoding lamin.

7. Besides compromising the structural integrity of the nucleus, what other role do these proteins play in Emery-Dreifuss muscular dystrophy?
- These proteins may also regulate chromatin structure and thereby affect gene expression patterns.

8. What are the clinical manifestations of Emery-Dreifuss muscular dystrophy?
- Progressive muscle weakness and wasting, contractures of the elbows and ankles, and severe cardiac involvement characterized by cardiomyopathy and arrhythmias that lead to sudden death in up to 40% of patients.

Facioscapulohumeral dystrophy (FSHD):

1. What is the inheritance pattern of facioscapulohumeral dystrophy (FSHD)?
- It is an autosomal dominant form of muscular dystrophy.

2. What genetic changes cause facioscapulohumeral dystrophy (FSHD)?
- It is caused by complex genetic changes that allow the expression of the transcription factor DUX4, which is normally repressed in mature tissues.

3. What is the proposed mechanism behind facioscapulohumeral dystrophy (FSHD)?
- It is thought to be caused by the overexpression of DUX4 target genes.

4. At what age do most patients with facioscapulohumeral dystrophy (FSHD) become symptomatic?

- Most patients become symptomatic by the age of 20 years.

5. Which muscles are typically affected first in facioscapulohumeral dystrophy (FSHD)?
- Weakness usually begins in the facial muscles and the shoulder.

6. What other muscles are affected in facioscapulohumeral dystrophy (FSHD)?
- Weakness may also occur in the lower trunk and the dorsiflexors of the foot.

7. What is the typical life expectancy for most affected individuals with facioscapulohumeral dystrophy (FSHD)?
- Most affected persons have a normal life expectancy.

Acquired Disorders of Skeletal Muscle:

1. What are some common manifestations of acquired disorders of skeletal muscle?
- Muscle weakness, muscle cramping, or muscle pain are common manifestations.

2. What are some examples of acquired disorders of skeletal muscle?
- Examples include inflammatory myopathies, toxic muscle injuries, post-infectious rhabdomyolysis, and muscle infarction in the setting of diabetes.

3. Who is typically affected by these acquired disorders?
- In most instances, these disorders affect adults with acute or subacute onsets.

Inflammatory Myopathies (Polymyositis):

1. What is the underlying mechanism of polymyositis?
- Polymyositis is an autoimmune disorder associated with increased expression of MHC class I molecules on myofibers and predominantly endomysial inflammatory infiltrates containing CD8+ cytotoxic T cells.

2. What is the consequence of the autoimmune attack in polymyositis?
- The autoimmune attack leads to myofiber necrosis and subsequent regeneration.

3. What is the typical treatment for patients with polymyositis?
- Patients with polymyositis are often successfully treated with corticosteroids or other immunosuppressive agents.

Dermatomyositis:

1. What is the most common inflammatory myopathy in children?
- Dermatomyositis is the most common inflammatory myopathy in children, where it may appear as an isolated entity.

2. How does dermatomyositis often manifest in adults?
- In adults, dermatomyositis often manifests as a paraneoplastic disorder.

3. What is believed to be the underlying basis of dermatomyositis?
- In both children and adults, dermatomyositis is believed to have an autoimmune basis.

4. Besides muscle involvement, what other manifestations are typically associated

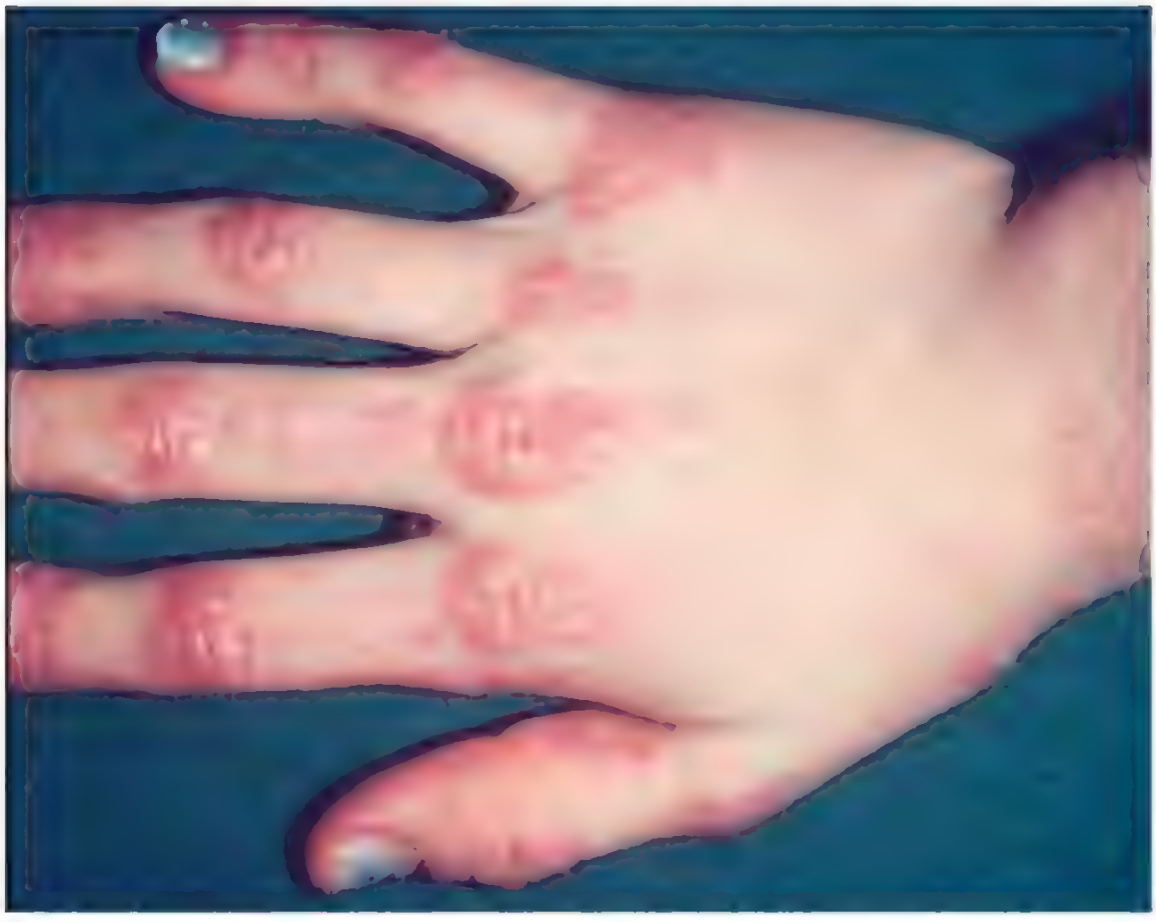
with dermatomyositis?
- The disease is typically associated with skin manifestations, as implied by the name, and may also have systemic manifestations such as interstitial lung disease.

5. What are some microscopic and ultrastructural findings associated with dermatomyositis?
- On microscopic examination and ultrastructural studies, dermatomyositis is associated with perivascular mononuclear cell infiltrates with plasma cells, "dropout" of capillaries, the presence of so-called "tubuloreticular inclusions" in endothelial cells, and myofiber damage.
Dermatomyositis:

1. What is the similarity between dermatomyositis and other autoimmune

diseases like SLE?
- Type 1 interferon-induced gene products are strongly upregulated in affected muscles, similar to some other autoimmune diseases such as systemic lupus erythematosus (SLE).

2. What are some autoantibodies that are relatively specific for dermatomyositis?
- Some patients have autoantibodies against Mi-2 (a nuclear helicase) and p155 and p140, proteins with uncertain functions.



Gottron's papules. Discrete erythematous papules overlying the metacarpal and interphalangeal joints in a patient with juvenile dermatomyositis

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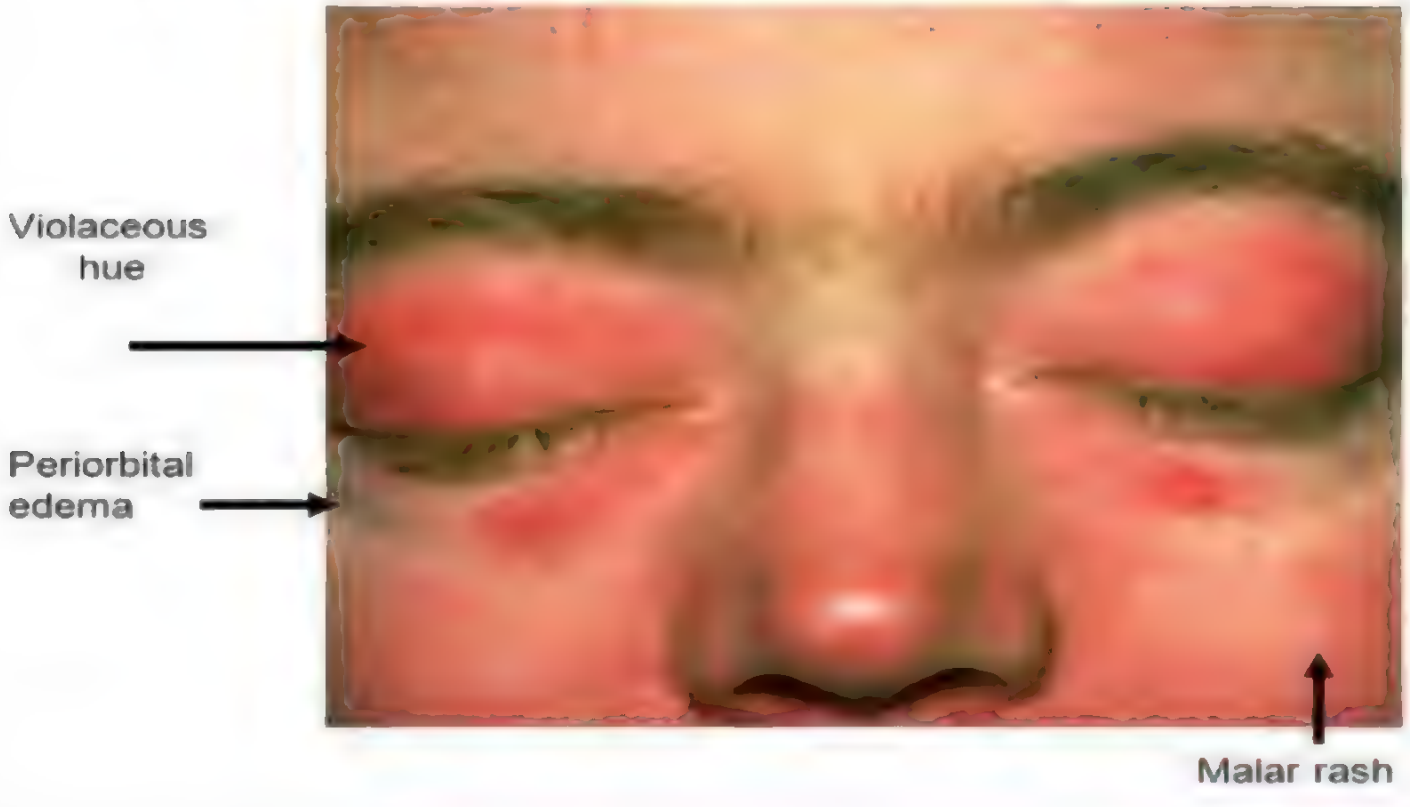
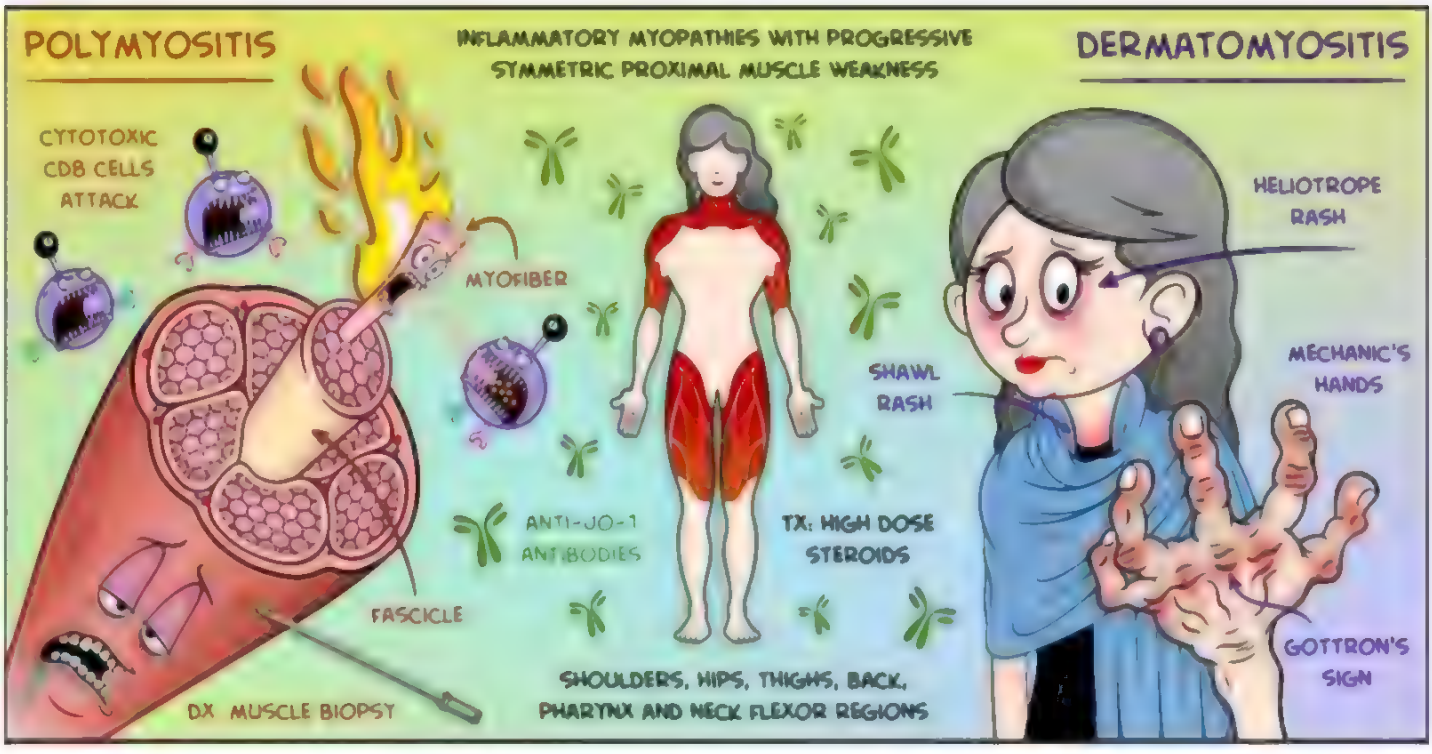
Heliotrope Rash





Inclusion Body Myositis:

1. What is the most common inflammatory myopathy in patients older than 60 years of age?

   - Inclusion body myositis is the most common inflammatory myopathy in patients older than 60 years of age.

2. What is the morphologic hallmark of inclusion body myositis?

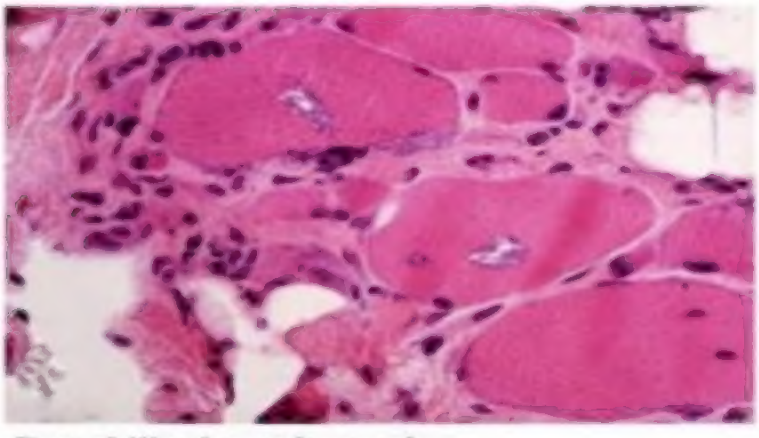
- The presence of rimmed vacuoles that contain aggregates of proteins, including hyperphosphorylated tau, amyloid derived from β-amyloid precursor protein, and TDP-43.

3. What speculation has been made regarding the nature of inclusion body myositis?
- Some speculate that inclusion body myositis is a degenerative disorder of aging due to the accumulation of proteins seen in the brains of patients with neurodegenerative diseases.

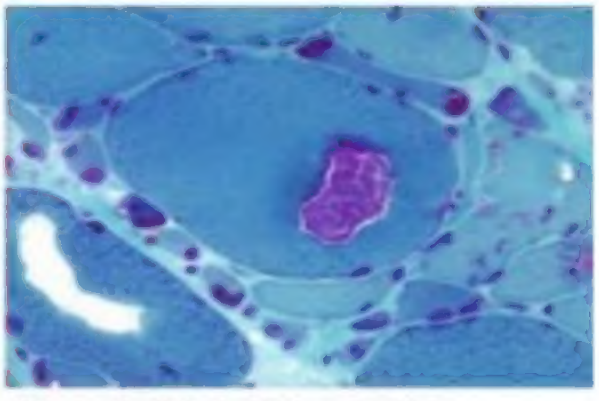
4. Besides the presence of rimmed vacuoles, what other features are typical of inclusion body myositis?
- Other features include myopathic changes, mononuclear cell infiltrates, endomysial fibrosis, and fatty replacement.

5. What is the typical disease course of inclusion body myositis?
- The disease follows a chronic, progressive course and generally does not respond well to immunosuppressive agents, suggesting that inflammation is a secondary event.

Inclusion body myositis



Basophilic rimmed vacuoles



Vacuole filled with granules

Vacuolated muscle fibres infiltrated with CD8/MHC-1complexes. Beta-amyloid deposits and cytochrome oxidase negative fibres may be seen.

Toxic Myopathies:

1. What are some causative insults for toxic myopathies?

- Causative insults include intrinsic factors (e.g., thyroxine) and extrinsic factors (e.g., acute alcohol intoxication, various drugs).

2. What are some examples of drugs that can cause myopathy?
- Examples include statins (e.g., atorvastatin, simvastatin, pravastatin) and others.

3. What is the most common complication of statin use?
- Myopathy is the most common complication of statin use, occurring in approximately 1.5% of users.

4. What are the two forms of statin-associated myopathy that are recognized?
- The two forms are toxicity of the drug itself and statin-induced HMG-CoA

reductase autoantibodies causing an immune-mediated myopathy.