# MUSCULAR DYSTROPHIES

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FINAL YEAR PG
DEPARTMENT OF PEDIATRICS

# INTRODUCTION

- *Trophe (Greek):* "Nourishment."
- Dystrophy: Abnormal growth

- Obligatory criteria for muscular dystrophy :
  - Primary myopathy,
  - Genetic basis ,
  - Progressive,
  - Degeneration and death of muscle fibers

- The criteria of muscular dystrophy excludes
  - Neurogenic diseases such as spinal muscular atrophy,
  - Nonhereditary myopathies such as dermatomyositis,
  - Nonprogressive, and non-necrotizing congenital myopathies such as congenital muscle fiber-type disproportion (CMFTD), and
  - Nonprogressive inherited metabolic myopathies.

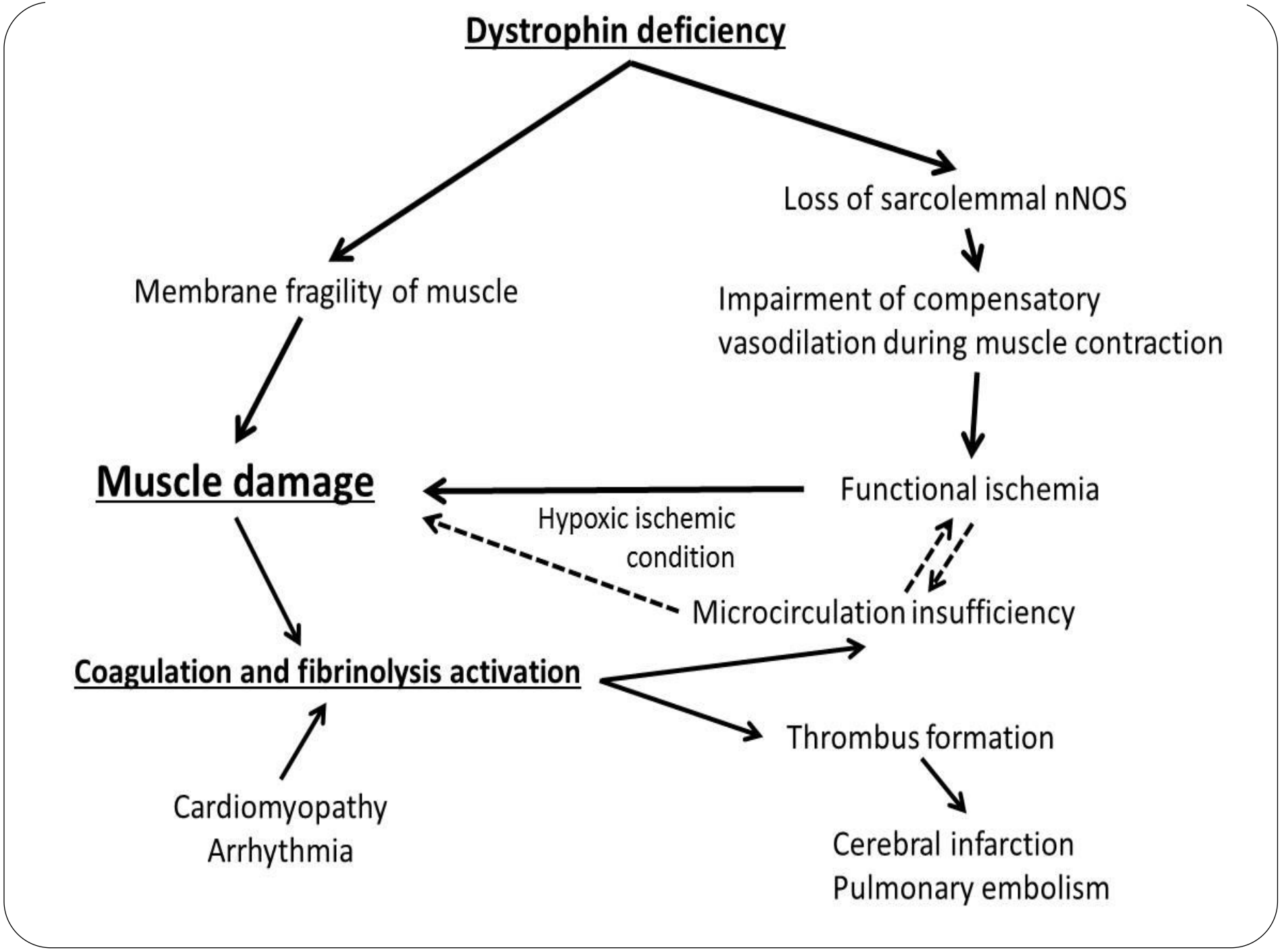
# MUSCULAR DYSTROPHIES: TYPES

- Duchenne muscular dystrophy (DMD)
- Becker muscular dystrophy (BMD)
- Emery-Dreifuss Muscular Dystrophy / scapuloperoneal or scapulohumeral muscular dystrophy.
- Myotonic Muscular Dystrophy
- Limb-Girdle Muscular Dystrophies
- Congenital Muscular Dystrophy
- Facioscapulohumeral Muscular Dystrophy

# **Duchenne muscular dystrophy** (DMD)

- DMD is most common with incidence of 1:3,600 live born
- Mostly inherited as X-linked recessive, but 30% have new mutations such as intragenic deletions (65%) , duplications (7%), or point mutations of nucleotides.

- The defect is in gene at the Xp21.2 locus encoding cytoskeletal protein known as *dystrophin.*
- Dystrophin deficiency at the sarcolemma disrupts the membrane cytoskeleton and leads to loss of other components of the cytoskeleton.

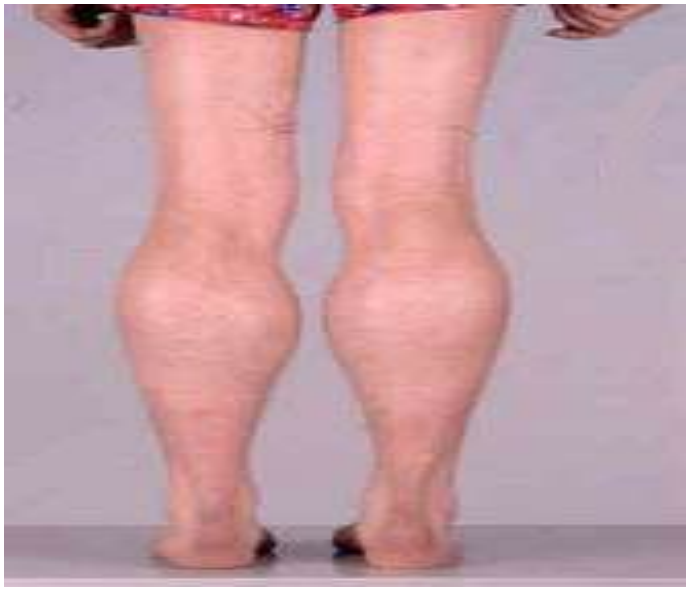

Dystrophin deficiency
Loss of sarcolemmal nNOS
Membrane fragility of muscle
Impairment of compensatory vasodilation during muscle contraction
Muscle damage
Functional ischemia
Hypoxic ischemic condition
Microcirculation insufficiency
Coagulation and fibrinolysis activation
Thrombus formation
Cardiomyopathy
Arrhythmia
Cerebral infarction
Pulmonary embolism

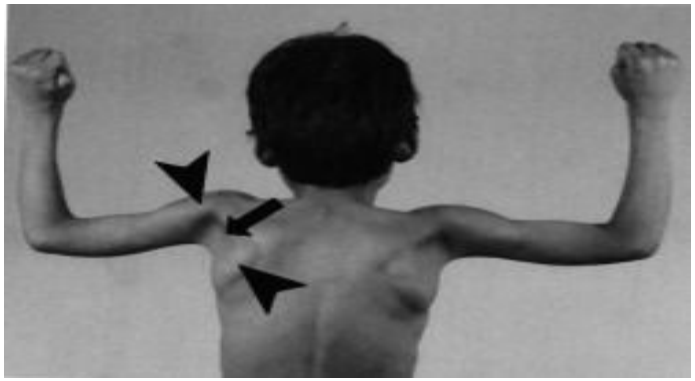
# Clinical Manifestations

- Only males are affected
- Mostly presents after infancy, and Rarely at birth (hypotonia)
- **Symptoms**
  - Delayed walking, falling, toe walking, and trouble in running or walking upstairs
  - Difficulty to stand from sitting position

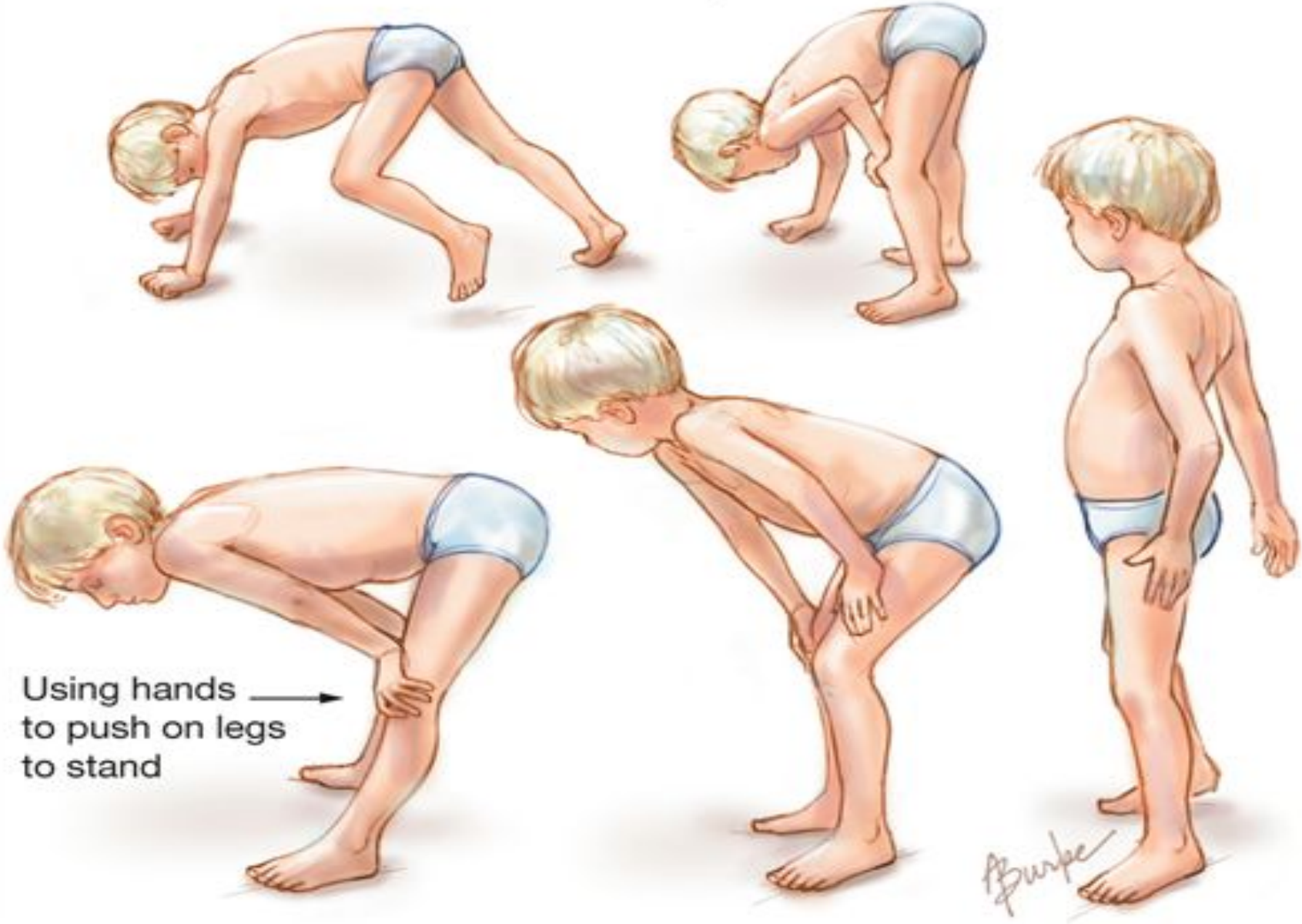
# Clinical Manifestations

- **Signs:**
  - Pseudohypertrophy of calf muscles
  - Gower sign
  - Valley sign
  - Lordotic posture
  - Contractures
  - Scoliosis





## Gowers Sign 3 yr to 5yr



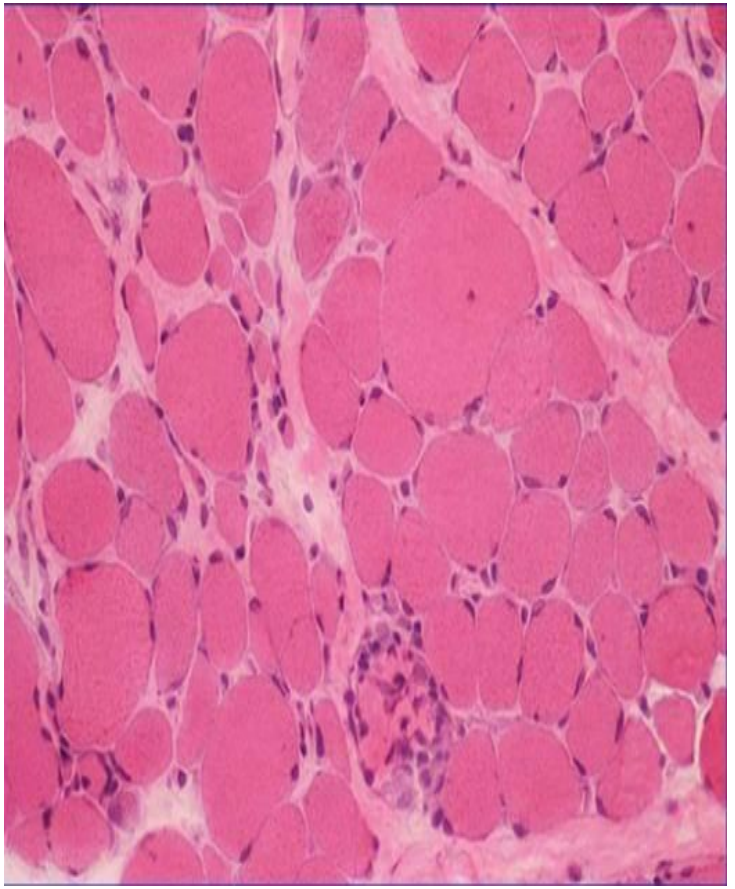
# Clinical Manifestations

- Pharyngeal muscle weakness: Episodes of aspiration, nasal regurgitation of liquids, and an airy or nasal voice quality.
- Respiratory muscle weakness: weak and ineffective cough, frequent pulmonary infections, and decreasing respiratory reserve.
- Anal and urethral sphincter weakness: Incontinence
- Intellectual disability
- Cardiomyopathy

# Laboratory Findings

- Serum CK level: elevated to 15,000-35,000 IU/L (normal <160 IU/L).
- Motor and sensory nerve conduction velocities are normal.
- Polymerase chain reaction (PCR) for the dystrophin gene mutation is confirmatory.
- Specific dystrophin immunocytochemistry performed on muscle biopsy sections detects the 30% of cases that do not show a PCR abnormality.

- **Muscle biopsy** reveals
  - Endomysial connective tissue proliferation
  - Scattered degenerating and regenerating myofibers
  - Foci of mononuclear inflammatory cell infiltrates as a reaction to muscle fiber necrosis
  - Mild architectural changes in still-functional muscle fibers, and many dense fibers.



# Management

- AIM: To maintain function, to prevent complications

- SPECIFIC THERAPY: steroids may be beneficial in delaying progression of the disease

  Prednisolone

  Deflazacort

# Management

- SUPPORTIVE THERAPY
  - Adequate nutrition
  - Exposure to sunlight
  - Immunization- influenzae vaccine, pneumococcal vaccine
  - Physiotherapy
  - Orthopaedic surgery for contracture
  - Rx of infections
  - Rx of cardiomyopathy
- MONITORING
  - Pulmonary function test
  - ECG and Echocardiography

# Management

- POTENTIAL TREATMENT UNDER INVESTIGATION
  - IM antisense oligonucleotide drugs that induce exon skipping during mRNA splicing to restore the open reading frame in the DMD gene.
  - Stem cell implantation or activation in muscle was theoretically plausible but has not proved practical.

# Prognosis

- Most patients become confined to a wheelchair by 13yr of age.
- Death occurs usually at about 18-22 yr of age.
- The causes of death are Respiratory failure, heart failure, Pneumonia, or Occasionally aspiration and airway obstruction.

# **Becker muscular dystrophy** (BMD)

- Same gene defect, as DMD
- Onset between 5-15 years
- Milder severity and more protracted course.
- Patients remain ambulatory until late adolescence or early adult life.
- Death often occurs between 30-40 yrs.

## Emery-Dreifuss Muscular Dystrophy / **scapuloperoneal or scapulohumeral muscular dystrophy.**

- Rare, X-linked recessive.
- Slow progressive with Contractures of elbows and ankles developing early, and muscle wasting of scapulohumeroperoneal distribution. Associated with **severe cardiomyopathy.**
- Serum CK value is mildly elevated and muscle biopsy shows Nonspecific myofiber necrosis and endomysial fibrosis.
- Rx is mainly supportive, and may require pacemaker or defibrillator for cardiac problems.

# Myotonic Muscular Dystrophy

- Second most common muscular dystrophy results from the genetic defect - chromosome 19 at the 19q13 locus.
- It has 3 forms. In classic form, Infants can appear almost normal at birth, or facial wasting and hypotonia.
- Characteristic facial features include an inverted V-shaped upper lip, thin cheeks, and scalloped, concave temporal muscles.

- Narrow head with thin and long neck (Swan neck) is present, the **speech** is slurred.
- Progressive wasting of distal muscles with atrophy of Proximal muscles.
- **Gastrointestinal tract** - slow gastric emptying, poor peristalsis, and constipation.
- Encopresis associated with anal sphincter weakness.
- **Cardiac involvement** is usually manifested as heart block in the Purkinje conduction system and arrhythmias.

- **Endocrine abnormalities** involve many gland.
- **Immunologic deficiencies** are common, plasma IgG level is often low.
- **Cataracts** often occur.
- About half of the patients are **intellectually impaired,** but severe mental retardation is unusual.
- Cognitive impairment and mental retardation might result from accumulations of mutant *DMPK* mRNA and aberrant alternative splicing in cerebral cortical neurons.

# Laboratory Findings

- Serum CK and other muscle enzymes are normal or mildly elevated .
- Radiographs of the chest and abdomen and contrast studies of GI motility may be needed.
- Endocrine assessment.

# Diagnosis

- The primary diagnostic test is a DNA analysis.
- The muscle biopsy shows many muscle fibers with central nuclei and selective atrophy of histochemical type I fibers with few degenerating fibers, little or no fibrosis of muscle.
- In the severe neonatal form, the muscle biopsy reveals maturational arrest in various stages of development and disproportion in muscle fibers.

# Treatment

- There is no specific medical treatment.
- Physiotherapy and orthopedic treatment of contractures may be beneficial.
- Myotonia may be diminished, and function may be restored by drugs that raise the depolarization threshold of muscle membranes, such as mexiletine, phenytoin, carbamazepine, procainamide, and quinidine sulfate.

# Limb-Girdle Muscular Dystrophies

- Encompass a group of progressive hereditary myopathies that mainly affect muscles of the hip and shoulder girdles.
- Sixteen genetic forms , defects at a different chromosomal locus and expressing different protein .
- AD and AR inheritance.

**clinical manifestations**

- Delayed until early adult life.
- Weakness of neck flexors and extensors present with Low back pain.
- Confinement to a wheelchair -30 yr of age.

LABORATORY INVESTIGATIONS

- Increased serum CK level.
- The EMG and muscle biopsy show confirmatory evidence of muscular dystrophy, but none of the findings is specific enough to make the definitive diagnosis.
- **Treatment is symptomatic.**

# Congenital Muscular Dystrophy

- Characteristic severe involvement at birth but follow a benign clinical course.
- Autosomal recessive inheritance.
- Contractures or arthrogryposis can be seen at birth and are diffusely hypotonic with thin muscle mass and absent tendon reflexes.
- A minority have severe dysphagia and require gavage or gastrostomy.
- The cerebral malformations occur which vary from
  - Severe dysplasias (holoprosencephaly, lissencephaly) to
  - Milder conditions (agenesis of the corpus callosum, focal heterotopia of the cerebral cortex and subcortical white matter, cerebellar hypoplasia).

- LABORATORY FINDINGS
  - Serum CK level - moderately elevated
  - EMG shows nonspecific myopathic features.
  - Muscle biopsy is essential for the diagnosis.
- DIAGNOSIS:
  - Muscle biopsy is diagnostic
  - An extensive proliferation of endomysial collagen with increased perimysial connective tissue and fat ,myofibrillar splitting,and fibrosis.
- TREATMENT: Supportive

# Facioscapulohumeral Muscular Dystrophy

- Group of diseases with similar clinical manifestations with Autosomal dominant inheritance .
- The frequency is 1:20,000.
- Clinical manifestations are delayed into middle adult life with asymmetry of weakness.
- Earliest and most severe weakness is in facial and shoulder girdle muscles.
- Hearing loss and retinal vasculopathy are associated features, particularly in severe cases.

- **Scapular winging** is prominent.
- Flattening or even concavity of the deltoid contour with wasting and weakness of biceps and triceps brachii muscles.
- Gowers sign and a Trendelenburg gait are present.
- Lumbar lordosis and kyphoscoliosis are common complications of axial muscle involvement with Footdrop in advanced cases.

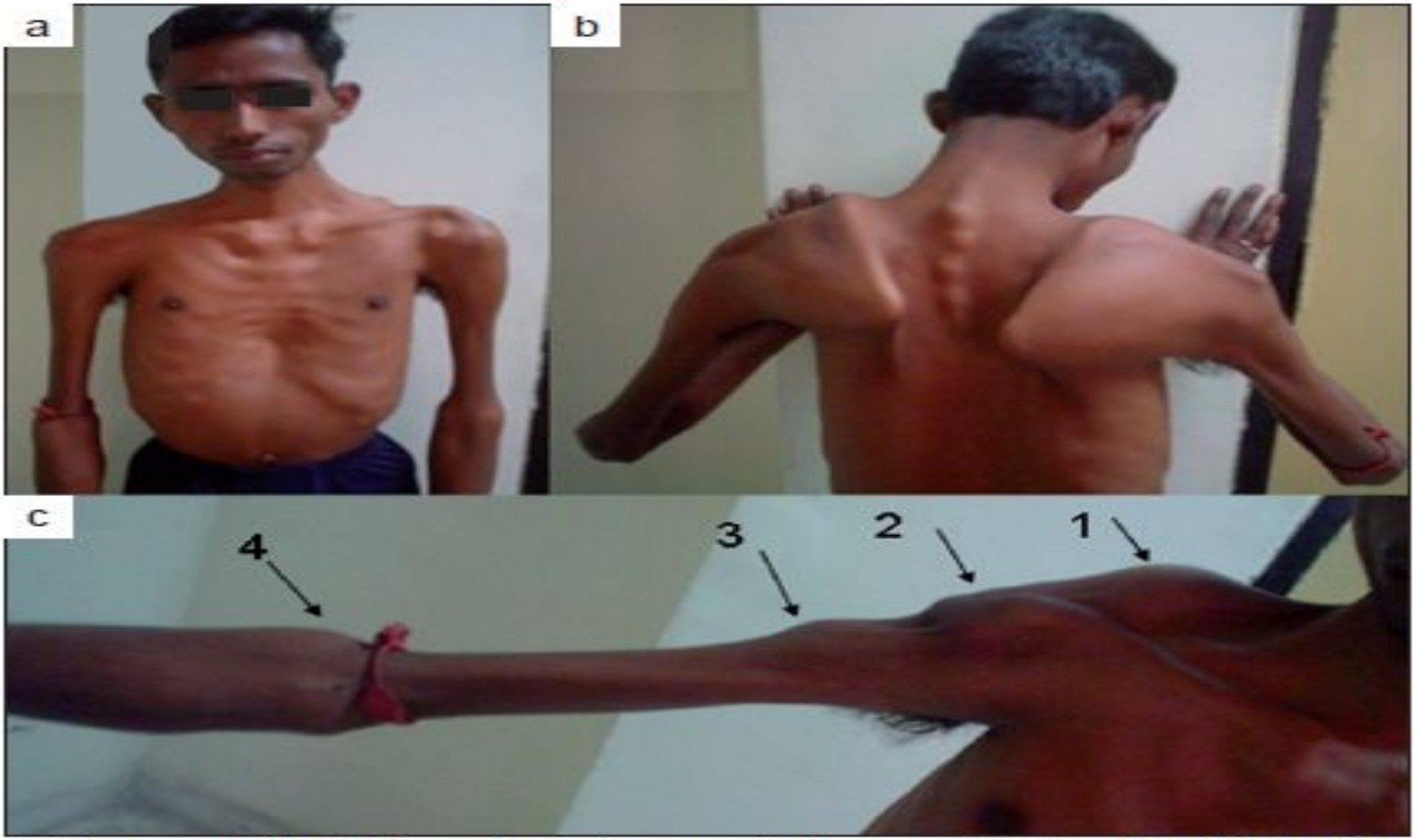



Figure 2: Clinical signs in facio-scapulo-humeral dystrophy: (a) Facial wasting and Popeye sign: wasting of arm muscles with sparing of forearm muscles; (b) scapular winging; (c) Polyhill sign: 1: upward projection of the superior angle of the scapula tenting the wasted trapezius muscle, 2: prominence of laterally projected acromio-clavicular joint, 3: prominent infero-lateral part of the deltoid muscle and 4: prominent muscles of the forearm extensor compartment. (Informed written consent for publication has been obtained from the patient)

- LABORATORY FINDINGS
  - Serum levels of CK and other enzymes vary greatly.
  - EMG reveals nonspecific myopathic muscle potentials.
  - Diagnostic molecular testing in individual cases and within families is indicated for prediction.
- DIAGNOSIS:
  - Muscle biopsy shows extensive proliferation of connective tissue between muscle fibers, extreme variation in fiber size with many hypertrophic as well as atrophic myofibers, and scattered degenerating and regenerating fibers.
  - An “inflammatory” type has extensive lymphocytic infiltrates within muscle fascicles.

# Treatment

- Physiotherapy is of no value in regaining strength.
- Foot drop and scoliosis may be treated by orthopedic measures.
- In selected cases, surgical wiring of the scapulas to the thoracic wall provides improved shoulder stability and abduction of the arm, but brachial plexopathy, frozen shoulder, and scapular fractures are reported complications.
- No effective pharmacologic treatment is available.

# CONCLUSION

- Muscular dystrophies are genetic disorders with defective gene of muscle proteins causing progressive weakness of muscles resulting in wheel-chair confinement and death during the 3$^{rd}$ to 4$^{th}$ decade of life.
- Main treatment focuses on delaying the progression of disease, prevention of complications and supportive therapy to improve quality of life.


THANK YOU