APPROACH TO GENETIC MUSCLE DISORDERS

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Disclosures

No Conflicts of Interest
Objectives

• Discuss the main situations presenting muscular diseases from the simplest to the most difficult

• Present the main genetic muscle diseases

• For each muscle condition: clinical, paraclinical characteristics and genetic diagnosis

• Through decisional trees: orient the diagnosis according to the main clinical sign “from symptom to genetics tests”
Main Aim of Our Lecture

Through practical clinical cases: demonstrate and prove the importance of clinical signs in the guidance of assessments and muscular disorders diagnosis.
Principles-Steps

• Genetic muscular disorders: Huge polymorphism
• Diagnosis difficulties
• Differentiel diagnosis (New born – Neonatal onset forms)
• Approach is based on
  – Semiological analysis
  – Biological tests (CK)
  – Electrophysiological approach (ENMG)
  – Histological aspect (Muscle Biopsy)
  – Genetic tests
• Markers symptoms or Specific symptoms: usefull but diagnosis is based on Bundle of clinical and paraclinical arguments-criteria
Principles-Steps

• To Distinguish: Muscle – Nerve – Anterior Horn
• In Muscle Disorders: Genetic – Acquired

Nosological entities or Frameworks

• Muscular Dystrophies
• Myotonic Muscular Dystrophies
• Congénital Myopathies
• Congenital Muscular Dystrophy
• Metabolic Myopathies

• Inflammatory Myopathies
• Endocrine Myopathies
• Toxic ou Drug Induced Myopathies
Principles-Steps

• In Genetic Muscle Disorders: Search
  – Marker Signs or Diagnosis orientation signs
  – Onset Signs: early, childhood, early adult, adult..
  – Weakness: Proximal, distal, no weakness
  – Myotonia: with weakness – without weakness
  – Paramyotonia
  – Respiratory failure: onset symptom, during evolution
  – Retraction: Rigid Spine, ankle and heel
  – Effort Intolerance
  – Systemic signs...
  – Evolution
1st Situation: Easy!

- Progressive proximal weakness with/no Weasting
- Gowers Sign
- Family history – Cases
- Myotonia
- CK level
- Acute Myolysis
  - Black urine
  - Painful muscle swelling
  - CK level > 10000

Muscle involvement
2nd Situation: So Difficult – Very Difficult

- Neonatal hypotonia
- Cardiac involvement
- Respiratory Involvement
- Axial weakness
- Systemic sign (Endocrine, Ophthalmological signs, CNS and peripheral neuropathy....)
- Symptoms - No Weakness
- Ophthalmoplegia – Ptosis
- Transient signs – Paroxystic signs
- Fatigability and pain at effort

Clinical – Additional tests - Evolution
Laboratory assessment for Genetic Myopathies

- **Confirmation of Muscle Involvement:**
  - CK Level
  - Electroneuromyography
  - Muscle imaging: CT scan or RMN

- **Etiology:**
  - Muscle biopsy
  - Genetic tests (Clinical and Laboratory guidance)

- **Track Complications:** (Depending on muscular disease type)
  - Cardiac
  - Respiratory tests
Muscle Imaging
Expert Laboratory

• Specific patterns:
  – Calpain Myopathy: Selective posterior Involvement
  – Dysferlin Myopathy: Distal anterior/posterior
  – Bethlehem Myopathy

• Non Specific patterns:
  – muscle atrophy (Becker – Duchenne – Some LGMD...)
• Specific patterns:
  – Myofibrillar myopathy
  – RRF – Mitochondrial disease
  – Nemaline Rod-Myopathy
  – Tubular aggregate
  – Glycogen storage
  – Lipid storage
  – Dystrophin Sarcoglycan in ImunoHistocchemistry

• Non Specific patterns:
  – Dystrophic patterns
Childhood Onset Proximal Weaknesses
Duchenne Myopathy

Key Points

- X-linked recessive inheritance
- Typically affects males (30% involve spontaneous new mutations)
- Onset before 5 years of age, 7-12 years: wheelchair dependent
- Proximal muscle weakness, fall frequently
- Contraction of Achilles tendons
- Common: Gowers sign, calf muscle pseudohypertrophy, Lordosis and severe scoliosis
- The central nervous system is also involved in DMD, Mental retardation: 10%
- Acute gastric dilation causing intestinal pseudo-obstruction.
- 20 years: Fatty infiltration of the heart and respiratory infections often lead to death
- Vulnerability to malignant hyperthermia from anesthesia (halothane..)
- Up to 8% of female carriers manifest mild proximal muscle weakness
Duchenne Myopathy
Key Points

- Elevated CK level (> 50–100 times normal)
- Abnormalities on electrocardiography: 90%
  - sinus tachycardia, tall right precordial R waves, and deep narrow Q waves in the left precordial leads
- Dysrhythmias and congestive heart failure (CHF): late in the disease.
- Echocardiogram: dilation and/or hypokinesis of ventricular walls.
- EMG shows myopathic features
- MB:
  - Dystrophic changes
  - Severely reduced or absent dystrophin in muscle biopsy
- Genetic testing: Mutation in Dystrophin gene (chromosome Xp21)
  - 5–10% of DMD cases are caused by point mutations, resulting in premature stop codons.
  - Duplications are evident in another 5% of cases
Becker Myopathy
Key Points

• X-linked recessive - Typically affects males
• milder allelic form of dystrophinopathy
• Onset after 12 years of age
• Proximal muscle weakness and calf muscle pseudohypertrophy (common)
• Elevated CK level (at least fivefold)
• Muscle biopsy evidence of decreased or structurally abnormal dystrophin
• Genetic testing (chromosome Xp21) : frame mutations (translation of semifunctional dystrophin of abnormal size and/or amount)
Late Childhood and Adult onset Proximal Weakness
Sarcoglycanopathy

LGMD 2

• Sarcoglycanopathies: 10% of LGMD
• The clinical, laboratory, and histologic features: quite similar to the dystrophinopathies,
  – severe weakness resembling DMD,
  – a later onset and slower progression similar to BMD.
• Proximal leg and arm muscles are affected early,
• Calf pseudohypertrophy.
• Cardiomyopathy: similar to the dystrophinopathies.
• There are no significant intellectual impairments
Sarcoglycanopathy
LGMD-2

- Serum CK levels are markedly elevated.
- Echocardiogram may reveal cardiomyopathy.
- The proteins of the sarcoglycan complex appear to function as a unit.
- Clinical severity of the sarcoglycanopathies may correlate with:
  - the type of mutation
  - subsequent level of functional protein expression
- Muscle biopsies demonstrate:
  - normal dystrophin
  - all of the sarcoglycans are usually absent or diminished on the sarcolemma, regardless of the primary sarcoglycan mutation