APPROCH 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)
- Approch 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

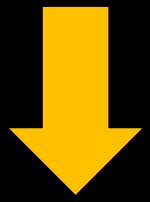
- Inflammatory Myopathies
- Endocrine Myopathies
- Toxic ou Drug Induced Myopathies

Principles-Steps

- In Genetic Muscle Disorders : Search
  - Marker Signs or Diagnosis orientation signs
  - Onset Signs : early, childhood, early adult, adult..
  - Weaknes : Proximal, distal, no weaknes
  - Myotonia : with weaknes – without weaknes
  - Paramyotonia
  - Respiratory failure : onset symtom , 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 weaknes
- Systemic sign (Endocrine, Ophtalmological signs,CNS and peripheral neuropathy….)
- Symtoms - No Weaknes
- Ophtalmoplegia – Ptosis
- Transient signs – Paroxystic signs
- Fatigability and pain at effort

Clinical – Additional tests - Evolution

Laboratory assesement for Genetic Myopathies

- Confirmation of Muscle Involevment :
  - 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 Involevment
  - Dysferlin Myopathy : Distal anterior/posterior
  - Bethleem Myopathy
- Non Specific patterns :
  - muscle atrophy (Becker – Duchenne – Some LGMD…)

Muscle Biopsy
Expert Laboratory

- Specific patterns :
  - Myofibrillar myopathy
  - RRF – Mitochondrial disease
  - Nemaline Rod-Myopathy
  - Tubular agregate
  - Glycogen storage
  - Lipid storage
  - Dystrophin Sarcoglycan in ImunoHistochemestry
- Non Specific patterns :
  - Dystrophic patterns

Childhood Onset Proximal Weaknes

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 Weaknes

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