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Diagnostic information for LGMD2B and Miyoshi Myopathy

Clinical Features:

- The typical **age of onset is between 15-30** years of age
- Initial muscle weakness can occur in either:
  - **proximal muscles (LGMD2B)**, particularly quadriceps and hamstrings
  - **distal muscles (Miyoshi Myopathy)**, particularly gastrocnemius
- In cases of gastrocnemius involvement, initial symptom is often inability to stand on tiptoes [1]
- Past history of **steppage gait or inability to stand on tiptoes** indicates distal involvement
- Painful enlarged calves are a typical early symptom[2]
- Regardless of the initial diagnosis, **both distal and proximal muscles are eventually affected**
- **Legs are typically affected before arms**[3]
- **Cardiomyopathy is not generally a major feature** in dysferlinopathy, but can occur in some cases[4]
- Patients often remain **ambulatory until > 30 years** of age[5]. However, the rate of progression is quite variable[6]
- Posterior compartment weakness is not always present, but when it is, it is a clear differentiating factor
- Typically presents with an **autosomal recessive or sporadic** pattern of inheritance
- **Wide inter- and intrafamilial variation**. Different clinical presentations and disease progression can occur in the same family and for the same genotype[7,8]

Laboratory Findings:

- Muscle CT-scan and/or MRI can be used to detect distal muscle involvement
- MRI (especially T2 weighted) can show abnormalities in presymptomatic individuals[9] and in muscles without overt weakness[1]
- Very **high CK levels** (typically > 10 times normal) are found both in symptomatic and presymptomatic patients
- Enzymes normally associated with liver dysfunction can also be elevated[10]
- Muscle biopsies show a **marked dystrophic pattern with necrosis and regeneration** of muscle fibers, and in some cases inflammation[11]
- Patients are sometimes **misdiagnosed with polymyositis** due to inflammatory appearance of biopsies[6]
- Preservation of sensory and motor conduction values[12]
- **Absent or reduced dysferlin protein levels** can be seen using anti-dysferlin antibodies on either a muscle biopsy or via western blot analysis of dysferlin from blood monocytes[13]. **NOTE: reduced dysferlin protein levels can sometimes be a secondary effect of deficiencies of other proteins, especially Calpain-3 (LGMD 2A)[14]**

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Genetics:

- LGMD2B and Miyoshi Myopathy are caused by **mutations in the dysferlin gene**
- Carriers are generally unaffected but can sometimes show relatively mild weakness[15]
- The Dysferlin gene is found on chromosome 2p13.3-p13.1 [16,17] and consists of 55 coding exons [18]
- **Missense, nonsense, small deletions, small insertions, and splice site mutations** have all been described. Most mutations introduce stop codons or premature truncations of the dysferlin protein[19]. See the Leiden database for a list of described mutations. Go to http://www.dmd.nl/ and choose DYSF from the Mutation Databases pull down menu at the top of the screen.
- Gene sequencing at the DNA or RNA level can be done from a blood sample[20]
- There are **no known mutational hot spots** in the dysferlin gene
- Variations in phenotype are not well explained by mutation type
- Due to the large size of the dysferlin gene, and the absence of mutational hot spots, it is generally preferred to **find evidence of deficiency at the protein level** before mutation screening

Dysferlin protein:

- The dysferlin protein has a molecular mass of 235 kDa and is made up of approximately 2080 amino acids[21-22]
- Dysferlin is a **transmembrane protein that is involved in membrane fusion events** and is necessary for **repair of the muscle sarcolemma** following damage[23]
- Dysferlin is **expressed in skeletal muscle, heart, white blood cells (monocytes, macrophages)**, and various other cell types.

Additional information:

- Other clinical diagnoses associated with dysferlin deficiency:
  - **Distal Anterior Compartment Myopathy**[8, 17]
  - Other clinical phenotypes and patterns of muscle involvement can occur [6, 24]
    - **Proximodistal weakness** at presentation
    - **Pseudometabolic myopathy**
    - **HyperCKemia**

- Differential Diagnoses
  - **Polymyositis**[6]
  - Other forms of LGMD

- What clinical/pathological findings most clearly point to a diagnosis of LGMD2B/Miyoshi?
  - **Absent or reduced dysferlin** protein levels in blood monocytes or staining of muscle biopsy
  - Very **high CK levels** (typically > 10X normal)
  - **Distal involvement** is highly suggestive
  - **Recessive or sporadic** pattern of inheritance

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