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
• Past history of steppe gait or inability to stand on tiptoes indicates distal involvement
• Painful enlarged calves are a typical early symptom
• Regardless of the initial diagnosis, both distal and proximal muscles are eventually affected
• Legs are typically affected before arms
• Cardiomyopathy is not generally a major feature in dysferlinopathy, but can occur in some cases
• Patients often remain ambulatory until > 30 years of age. However, the rate of progression is quite variable
• 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

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 and in muscles without overt weakness
• 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
• Muscle biopsies show a marked dystrophic pattern with necrosis and regeneration of muscle fibers, and in some cases inflammation
• Patients are sometimes misdiagnosed with polymyositis due to inflammatory appearance of biopsies
• Preservation of sensory and motor conduction values
• 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. NOTE: reduced dysferlin protein levels can sometimes be a secondary effect of deficiencies of other proteins, especially Calpain-3 (LGMD 2A)

Genetics:

- LGMD2B and Miyoshi Myopathy are caused by mutations in the dysferlin gene.
- Carriers are generally unaffected but can sometimes show relatively mild weakness.
- The Dysferlin gene is found on chromosome 2p13.3-2p13.1 and consists of 55 coding exons.
- 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.
- 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.
- 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.
- Dysferlin is a transmembrane protein that is involved in membrane fusion events and is necessary for repair of the muscle sarcolemma following damage.
- 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
  - Other clinical phenotypes and patterns of muscle involvement can occur.
  - Proximodistal weakness at presentation
  - Pseudometabolic myopathy
  - HyperCKemia
- Differential Diagnoses
  - Polymyositis
  - 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