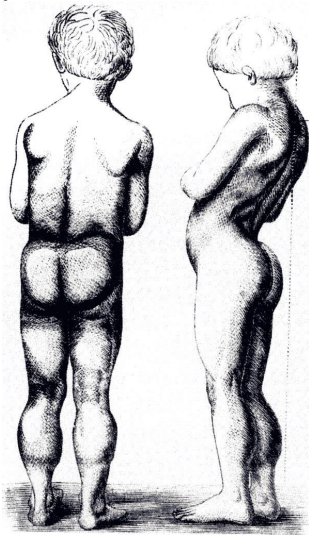


Primer of Duchenne and Becker Muscular Dystrophy

General: Duchenne muscular dystrophy (DMD) is named after Duchenne, and Becker muscular dystrophy (BMD) is named after Becker who recognized a milder form of the disorder. They are X-linked disorders. DMD and BMD are the most common forms of muscular dystrophy, with an estimated incidence of 1:3500 live male births.

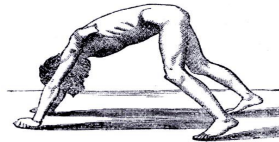
Clinical features: DMD has stereotypic features and course, while BMD has more variable features and course. In DMD, recognition of weakness occurs between ages 2 and 5 years with difficulty walking and later rising from low positions or climbing stairs due to proximal muscle weakness.



Drawing from Duchenne's photographs: calf muscle pseudohypertrophy and hyperlordotic posture.

Boys frequently walk on their toes due to ankle dorsiflexion weakness and subsequent shortening of Achilles tendons. As proximal leg weakness progresses a hyperlordotic posture develops with ambulation. There is greater difficulty straightening their torso after rising from the floor, and arms and hands are used to walk up the thighs (Gower's maneuver). Despite muscle

weakness, calf muscles are large, due to partial replacement of muscle tissue with connective tissue and fat (pseudohypertrophy). Serum CK levels are 10,000 to 20,000.

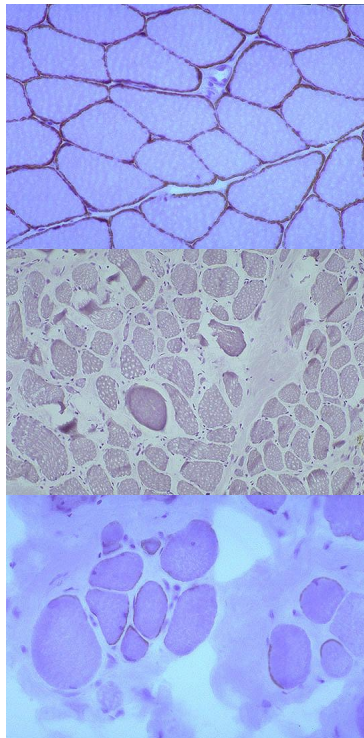


Gower's maneuver.

Ambulation is lost between ages 7 and 13. Arm weakness ensues, and boys become totally dependent for activities of daily living. Death usually occurs by age 20 from pneumonia caused by respiratory failure. There is a mild reduction in cognition. In BMD, symptoms can be recognized at any age, commonly in childhood but later than in DMD, and occasional onset is in adulthood. A cardiomyopathy also occurs, but is more problematic in BMD, probably because they live longer. Genetics: DMD and BMD are allelic forms of an X-linked disorder due to mutations in the DMD gene, which encodes dystrophin. On a genomic scale, this is the largest gene (450 CM), with 79 exons and 8 promoters over 2.2 million base pairs. The gene is highly vulnerable to mutations. Approximately

1/3 of patients have a known maternal family history, 1/3 are *de novo* in the mother, and 1/3 *de novo* in the affected individual. Mutations range from large deletions to point deletions and premature stop codons. In-frame deletions results in BMD and out of frame deletions result in DMD in 90% of cases. Female carriers are usually asymptomatic, but frequently have mildly elevated CK levels, and around 10% have muscle weakness (attributed to skewed X-chromosome inactivation – Lyon hypothesis).

Diagnosis: DMD and BMD due to any mutation in the dystrophin gene can be diagnosed in muscle biopsy tissue using an antibody stain for the protein dystrophin. There is absent staining in DMD and partial staining in BMD.



Normal:
Full staining.

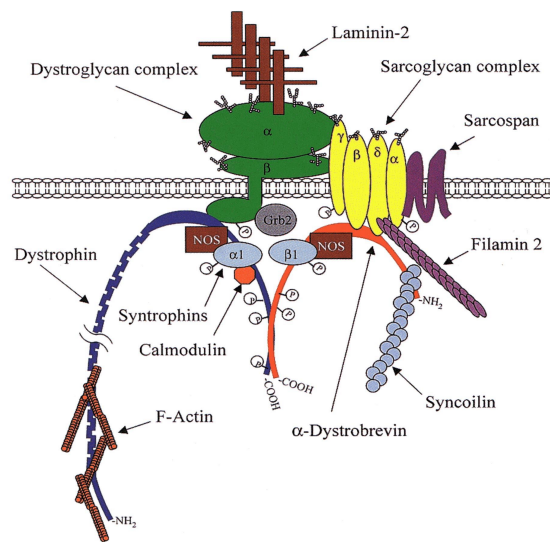
DMD:
Absent staining.

BMD:
Partial staining.

Dystrophin is a subsarcolemal protein that is absent in DMD and patchy in BMD. Large deletions (65% of cases) and duplications (5%) can be identified from extracted DNA from blood by common commercial testing. Recent advances in testing procedures results in the identification of over 95% of all

mutations from blood samples. Patients with negative genetic testing require muscle biopsy for diagnosis, and affected patients have alterations in immunofluorescence or immunoblot analysis.

Pathogenesis: Dystrophin is a protein that links F-actin to the dystrophoglycan protein complex. The complex spans the sarcolemma, and is anchored in the basal lamina. Dystrophin can be considered to be one protein element that “links” the force generated by contractile protein to the basal lamina.



Dystrophin linking F-actin with dystrophglycan complex.

Treatment: There is no curative treatment for DMD or BMD. Corticosteroids (prednisone and deflazacort) have been assessed in controlled trials in DMD showing improved strength and possible prolongation of ambulation, but weakness inexorably progresses. The therapeutic mechanism of corticosteroids is not known. Gentamicin is being studied as an agent that may promote a “read-through” of premature stop condon mutations. There are ongoing attempts to insert the dystrophin gene (whole or portions) into muscle via viral vectors.

Management: Supportive care is the mainstay. Physical therapy can prevent joint contractures (especially Achilles tendons). Occupational therapy assists with adaptive equipment, and all DMD and most BMD will require an electric wheelchair. When patients spend all their time in a wheelchair they slump to one side and frequently develop scoliosis that may require surgical correction. Surgical release of contracted tendons is controversial. Calcium supplementation may help to prevent pathologic fractures. Respiratory therapy can help with nocturnal hypoventilation at late stages, and may prolong survival. If corticosteroids are used, side effects and their management include: counseling for behavioral changes, encouraging limiting food intake to prevent excess weight gain and diabetes mellitus, and calcium for demineralization. There is greater concern for cardiomyopathy with BMD, and yearly cardiac evaluation is appropriate. There may be psychosocial issues that can vary markedly among patients, including school and play issues, and family interactions