Evaluation of muscle disorders after patients have been placed in a phenotypic pattern

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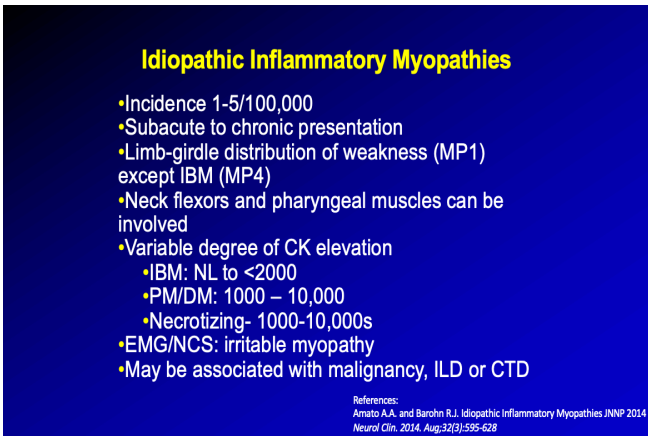
Previously we discussed the pattern recognition approach to myopathy and neuromuscular junction disorders (see Pattern Recognition Approach to Neuromuscular Disorders: Myopathy & Neuromuscular Junction Disorders in the prior issue of the Barohn RRNMF Journal Volume 5 Issue 2 September 2024). That discussion was geared to teach how to approach the patient before ordering laboratory tests and putting patients into one or more of the ten phenotypic clinical patterns. The patterns are based solely on the history and presentation of the patient. In this lecture, a patient has already been placed into one or more of the possible myopathic patterns, specific muscle diseases should be considered as the next step. Therefore, it is time to think about ordering laboratory tests to support or at times confirm the clinical suspicion based on the pattern recognition. We will briefly review a number of myopathies, describe what are the most likely patterns with the condition, and discuss the appropriate laboratory studies, and the possible treatments. The evaluation and approach to neuromuscular junction disorders will be provided in a different lecture.

Inflammatory Myopathies

Figure 1



From a historical perspective, the modern concept of inflammatory myopathies was introduced by Dr. John Walton in a 1954 article in Brain and the book titled Polymyositis authored by him and Dr. Raymond Adams in 1958. In the modern era, a classification of the inflammatory myopathies has been defined in the International Myositis Classification Criteria Project leading to the publication of the criteria by American College of Rheumatology / European Alliance of Associations for Rheumatology.

Idiopathic inflammatory myopathies are relatively rare, about 1 to 5 per 100,000. In most of them, the onset was sub-acute over months. Usually, they present for medical care in less than a year from the onset of symptoms except for inclusion body myositis (IBM) which has a delayed presentation and insidious onset over many years.

The typical pattern is limb-girdle (MP1 pattern). Because MP1 is the most common pattern, in some regards it is the least helpful because it does not distinguish between many different forms of muscle disease. An exception is IBM which presents with the MP4 pattern showing weakness in distal arms and proximal legs.

Figure 2

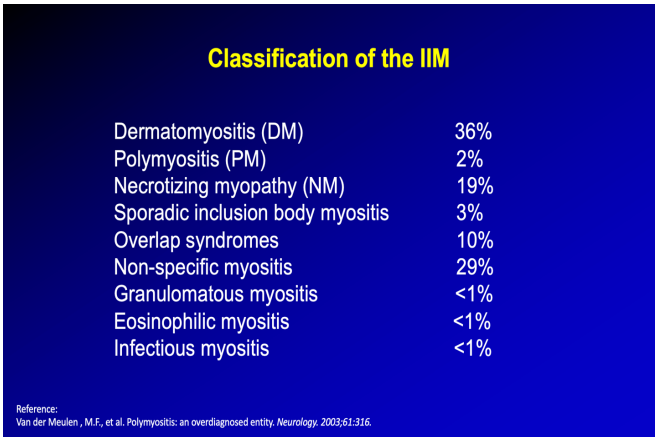
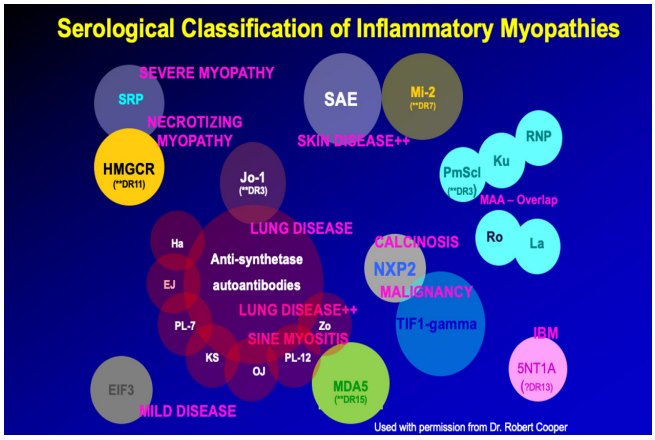


Figure 2 lists a number of different inflammatory myopathies and their frequencies according to a Dutch study. A common misbelief was that polymyositis is a frequent form of idiopathic inflammatory myopathy. But this is not the case. The Dutch study by Van der Meulen et al. showed that polymyositis accounted for only 2% of biopsy proved inflammatory myopathies. The most common inflammatory myopathy diagnosis in adults was dermatomyositis, followed by necrotizing myositis. Surprisingly, in this series, IBM made up only 3%. In our clinics in North America, IBM is more common than that. In the Database Evaluation for Muscle and Nerve Diseases (DEMAND) experience from four clinics, out of 490 inflammatory myopathy patients, 200 were IBM, 188 were polymyositis, and 102 were dermatomyositis.

Regarding laboratory studies, creatine kinase (CK) is very useful and its elevation indicates muscle damage. The magnitude of CK elevation can sometimes provide a clue as to the type of inflammatory myopathy. For example, IBM tends to have CK levels of 500 to 1000 IU/L range, whereas in polymyositis and dermatomyositis it is often over a thousand, and in necrotizing myopathy, it can be much higher. CK may be normal in DM and IBM.

Electromyography (EMG) is also helpful because it can reveal short-duration and small-amplitude motor unit potentials with irritability (denervation potentials in the form of fibrillations or positive sharp wave discharges). The presence of denervation potential suggests an active disease process. But their presence does not distinguish one muscle disease from another.

Figure 3



Some inflammatory myopathies are associated with specific serologic abnormal antibodies (Figure 3).

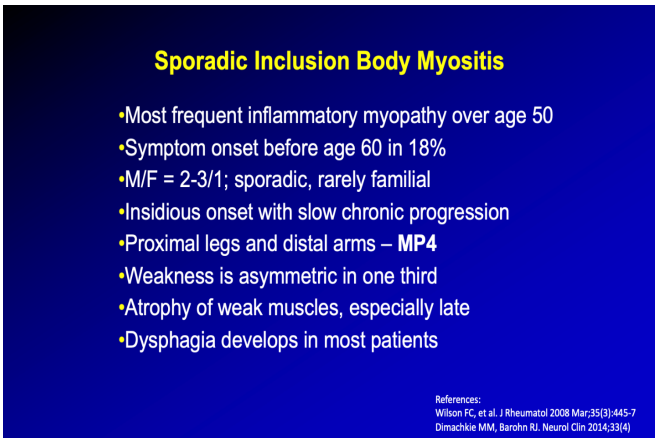
One of the first serologic antibodies that were discovered in inflammatory myopathy patients was the Jo-1 antibody. Subsequently, other tRNA synthetase antibodies were discovered. What is important about the tRNA-synthetase autoantibodies is that they predict a very high likelihood that the patient has concomitant interstitial pulmonary fibrosis. Both the muscle and the lung are targets of the autoimmune attack. The autoimmune attack on the lungs tends to be difficult to reverse with treatment. Therefore, it is important to identify these patients early and treat them aggressively.

Some of these myopathies can be associated with an increased risk for malignancy up to 4 years from disease onset. While malignancies are overall more frequent in dermatomyositis, 2 myositis specific antibodies, Anti-NXP-2 (NXP2) and TIF1-gamma, are predictive of a higher likelihood of having an underlying malignancy. In dermatomyositis, SAE and Mi-2 antibodies are more commonly seen in patients with skin diseases such as calcinosis, severe alopecia, or other forms of breakdown of the skin.

Necrotizing myopathy is associated with SRP antibodies as well as HMGCR antibodies if the patient has been on a statin-lowering agent and sometimes without identifiable statin exposure. Finally, IBM is associated with NT5C1A antibodies in approximately half of the cases (See Figure 5 below and Barohn, Dimachkie, Jackson Neurol Clin 2014 and Dimachkie, Barohn, Amato Neurol Clin 2014).

Inclusion Body Myositis

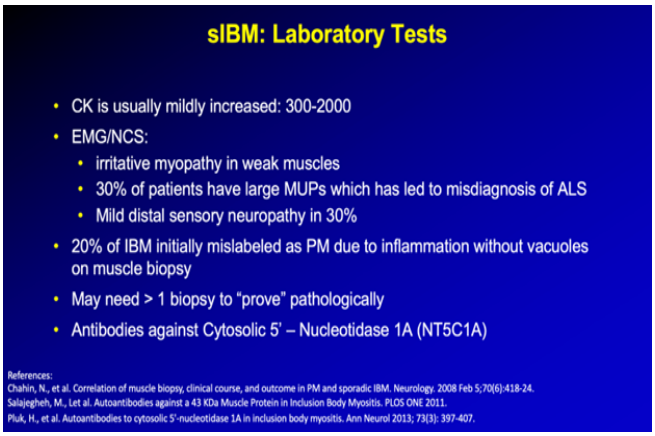
Figure 4



IBM in most series (other than the Dutch study noted above) is the most common inflammatory myopathy in older adults. It is uncommon to occur before age 50. It is more common in men. IBM has a very slow chronic progression, and the average time between onset of weakness and diagnosis is approximately 8 years. These patients may not realize they have a muscle disease for many years. They may think their weakness is simply age-related because it comes on so slowly. IBM has a unique pattern of weakness involving the proximal legs and the distal arms. It is often asymmetric. The muscle involvement is very selective in the proximal legs, the quadriceps muscles (knee extensors) are predominantly involved whereas the hamstrings (knee flexors) are relatively spared. In the arms, the involvement is selective to muscles in the flexor compartment and

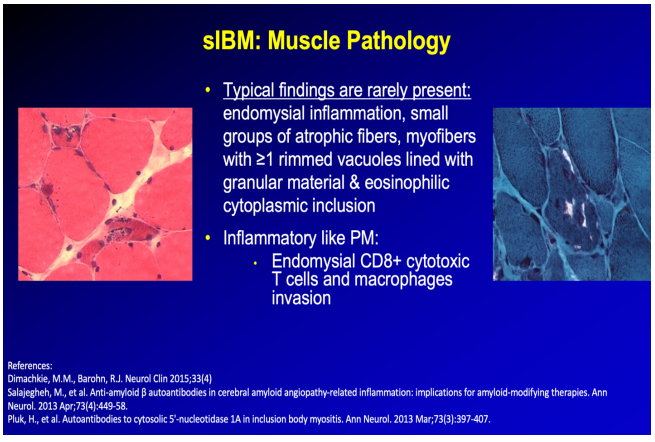
tends to spare the extensor compartment. Therefore, the weakness in the upper extremities involves finger flexors and wrist flexors. Some IBM patients also have dysphagia.

Figure 5



The CK is usually mildly elevated or normal in IBM. Many of these patients will have concomitant neuropathy based on symptoms and signs and electromyographic testing. The needle electromyography (EMG) findings can show long-duration and high-amplitude motor unit potentials which can make the diagnosis confusing and can lead to the misdiagnosis of amyotrophic lateral sclerosis (ALS). However, the pattern of weakness in IBM should make it very clear that it is unlikely to be ALS.

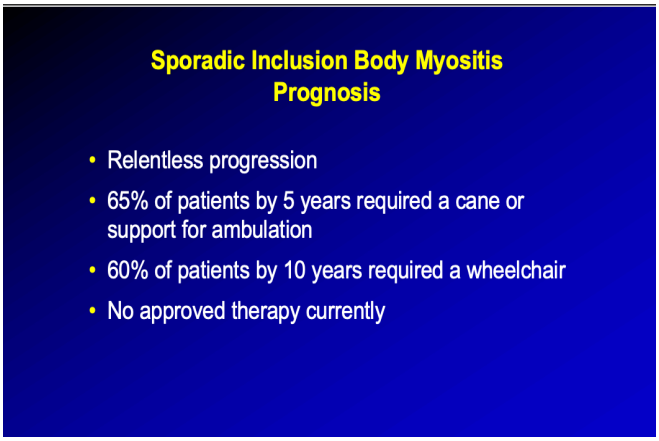
Figure 6



Historically, the standard way to diagnose IBM is via a muscle biopsy. Figure 6 shows the hematoxylin and eosin stain of a biopsied muscle from an IBM patient. There are small atrophic fibers that contain inclusions and small vacuoles. The vacuoles are easier to visualize on the trichrome stain. This type of biopsy finding is characteristic of IBM. However, sometimes the biopsy shows mild inflammation without the characteristic vacuoles. We believe the inflammation is likely a secondary phenomenon as a result of degenerative processes ongoing within muscle fibers. This can therefore lead to the erroneous diagnosis of polymyositis if vacuoles and inclusions are not seen. If the patient is mistakenly diagnosed as polymyositis this can lead to them being put on corticosteroids and other immunosuppressant agents with no clinical benefit. Ultimately, the patient may undergo a second muscle biopsy to search for the characteristic vacuoles leading to the correct diagnosis of IBM. There is a serologic test, the NT5C1A antibody that can be positive in up to 50% of the patients with IBM. However other diseases can be associated with the NT5C1A. For example, patients with Sjogren's syndrome, systemic lupus erythematosus and even some neuromuscular disorders that are non-immune mediated may have a positive NT5C1A antibody titer. Therefore, in the right clinical setting where the patient has asymmetrical proximal leg and distal arm weakness with a slow progression, obtaining a positive serologic antibody test confirms the clinical suspicion and you can probably avoid a muscle biopsy.

This antibody test is now commercially available and should be obtained in any patient where there is a clinical suspicion of IBM based on the pattern recognition. However, the absence of the NT5C1A antibody does not rule out IBM and in this setting a muscle biopsy is necessary to confirm the diagnosis.

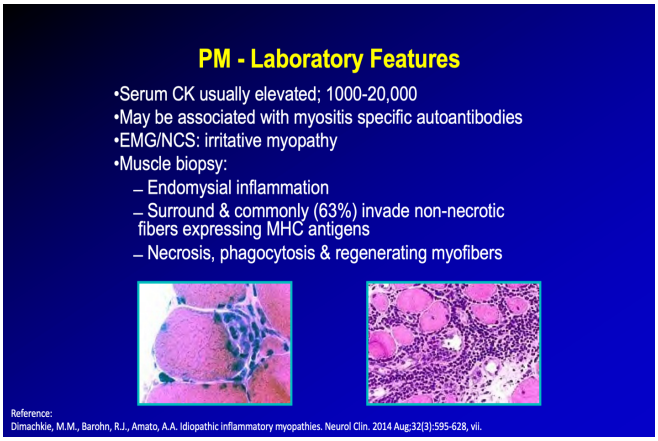
Figure 7



The course of IBM is very slow, relentless, and progressive. About 65% of patients need help with an assistive device for walking after five years and about 60% are in a wheelchair after 10 years.

Unfortunately, there is no effective therapy. A recent phase 2/3 randomized control trial of the drug arimoclomol, a heat shock protein inducer, was negative (See Machado PM, et al. Lancet Neurology 2023;10:900-911).

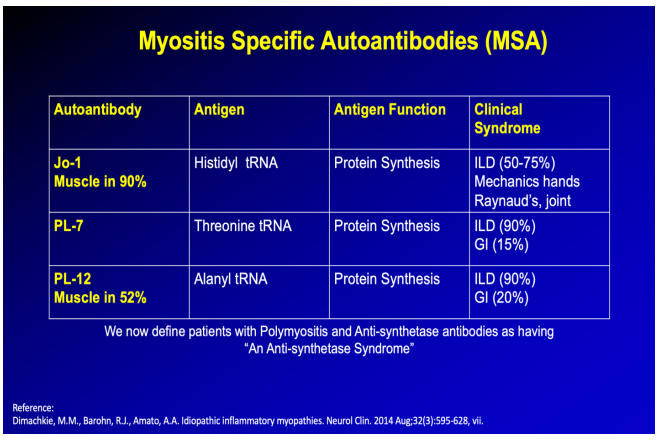
Polymyositis
Figure 8



Polymyositis presents with the classic hallmark MP1 pattern of limb-girdle weakness as previously noted. In addition to limb-girdle weakness, there can be neck flexor weakness and dysphagia. Usually, the facial muscles are not involved. The pathology of polymyositis is different from IBM. There are many inflammatory cells surrounding nonnecrotic muscle fibers that otherwise appear to be healthy (Figure 8).

What used to be called polymyositis has splintered into 4 clinically, pathologically and serologically distinct diseases: necrotizing autoimmune myopathy, overlap syndrome, anti-synthetase syndrome and inclusion body myositis.

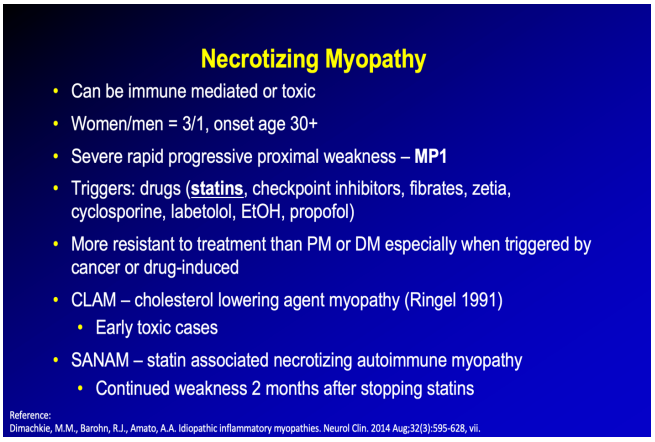
Figure 9



We believe this inflammatory cell invasion of non-necrotic fibers represents a cellular-mediated attack on the muscle fibers.

Some cases of polymyositis are associated with tRNA synthetase antibodies (Figure 9) suggestive of the anti-synthetase syndrome. Polymyositis with these antibodies is now known as anti-synthetase syndrome and is associated with interstitial lung disease. These patients need to be treated aggressively.

Necrotizing Myopathy
Figure 10



In the group of immune-mediated myopathies, necrotizing myopathy is the most recently identified. There are two forms of necrotizing myopathy. One is an acute toxic myopathy which is typically caused by drugs or toxins, and the other is a more chronic immune-mediated necrotizing myopathy. The most common class of drugs to cause acute necrotizing myopathy are the cholesterol-lowering agents. In fact, this was first identified in 1991 and was called cholesterol-lowering agent myopathy (CLAM). Rarely, acute statin induced myopathy can present as a rhabdomyolysis with myoglobinuria (MP8), but more often as a subacute MP1 pattern without rhabdomyolysis (See Barohn, Dimachkie, Jackson Neurol Clin 2014). Usually, once the offending toxic drug is withdrawn the toxic myopathy resolves. However, some patients continued to have progressive myopathy symptoms and signs and persistently elevated CK for 1-2 months after the cholesterol-lowering agent was stopped. We call these cases statin-associated necrotizing autoimmune myopathy

(SANAM) and it is believed that the statin drugs set off an immune-mediated process against muscle fibers. Other drugs or agents that can cause acute toxic myopathy include alcohol, cyclosporine, propofol or immune checkpoint inhibitors (see Figure 8 in Barohn, et al, The Pattern Recognition Approach to Neuromuscular Disorders: Volume 5 Issue 2 September 2024).

Figure 11

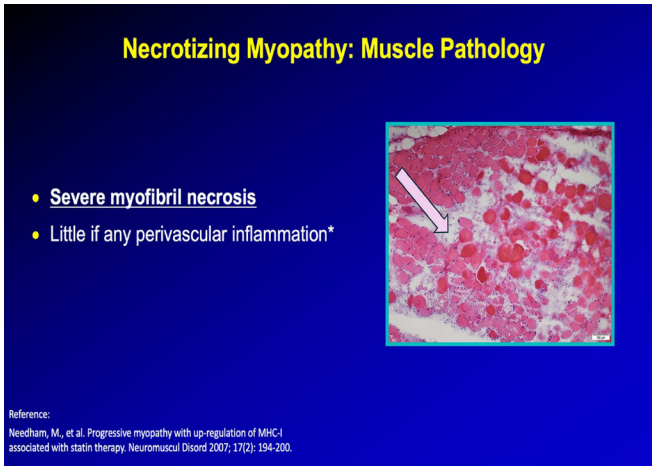


Figure 11 shows the pathology of a severe necrotizing myopathy. There is little inflammation. There is a great deal of muscle fiber necrosis. There are "ghost fibers" that have replaced healthy muscle fibers (See arrow in Figure 11).

Figure 12

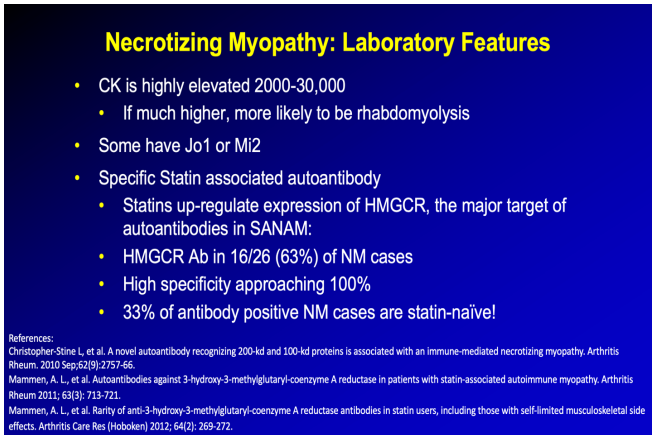
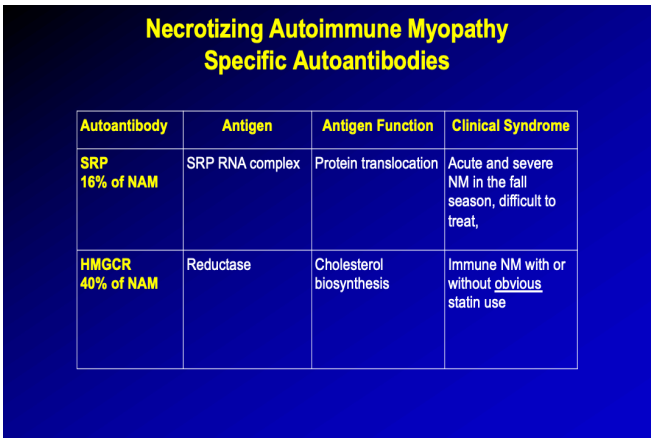


Figure 13

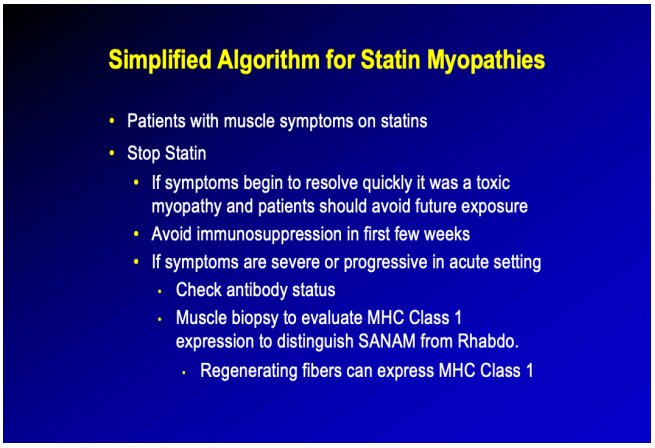


In necrotizing myopathy, CK level tends to be high, at least 1,000 IU/L sometimes over 10,000 IU/L (Figure 12).

HMGCR autoantibody is present in about two thirds of SANAM (Figures 12 and 13). It is speculated that the statins upregulate the expression of HMGCR. However, it has also been demonstrated that about one third of patients with necrotizing myopathy and HMGCR antibodies have never been previously exposed to a statin medication. So clearly in some cases, the statin alone is not the precipitating event for the autoimmune process.

Another antibody associated with necrotizing myopathy is SRP antibodies. These cases tend to be seasonal, often following a flu-like illness.

Figure 14

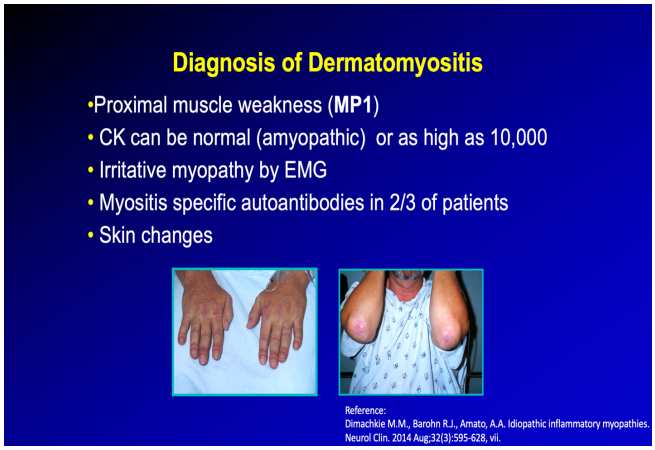


How should you handle a patient who is on statin and has muscle weakness? (Figure 14)

If the patient on a statin presents with muscle cramps and muscle aches without objective weakness the first thing to do is to stop the statin. We would recommend obtaining a serum CK to determine if there is evidence of muscle fiber damage. Usually, these patients present within eight weeks of starting the statin. If the statin is stopped and they improve there is nothing further to do other than get an additional CK if the initial one was elevated. If the statin is stopped and they do not start to get better after 8 weeks, we recommend to test for HMGCR antibody and trend CK levels. If the course continues to worsen, there is a need to consider a muscle biopsy. If the HMGCR antibody is elevated an argument can be made not to perform a muscle biopsy. In either care, immunosuppressive therapy for SANAM should be initiated.

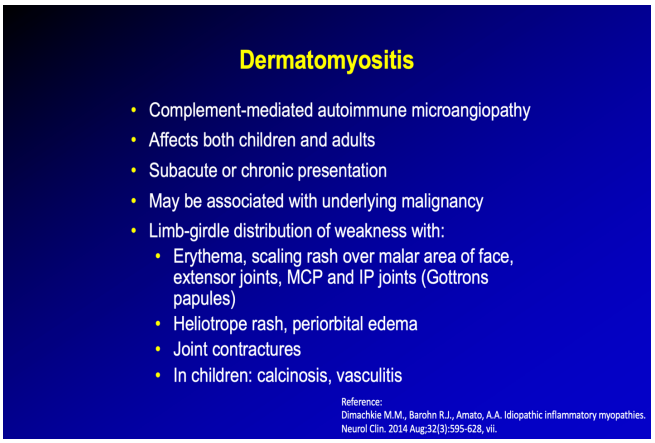
Dermatomyositis

Figure 15



Dermatomyositis has an MP1 pattern of presentation. CK is generally very high but cases with a normal CK and typical skin involvement do occur and have been called amyopathic dermatomyositis. The red skin discoloration usually appears on the extensor surfaces of the fingers, elbows or arms, as well as on the front and back of the neck (Figure 15). The facial rash can appear on the forehead, cheeks, and eyelids. EMG in dermatomyositis shows an irritable myopathy.

Figure 16



Unlike polymyositis, dermatomyositis is an autoimmune muscle disease that can occur in children (Figure 16). Other features of dermatomyositis include calcinosis, vasculitis, and joint contractures.

Before the 1950s and the availability of corticosteroids, children who had dermatomyositis tended to die very often due to ischemic bowel disease because of vasculitis and its widespread nature. Therefore, juvenile dermatomyositis is vasculitis of the muscle rather than myositis. B lymphocytes invade and circle the small capillaries inside of the muscle fascicles. There is immunoglobulin (IgM) and complement deposition around the blood vessels. This leads to entire muscle fascicles that become ischemic.

The blood vessels course through the middle of the fascicle and therefore muscle fibers on the edge of a muscle fascicle become ischemic and become smaller. That leads to the appearance perifascicular atrophy (Figure 17).

Figure 17

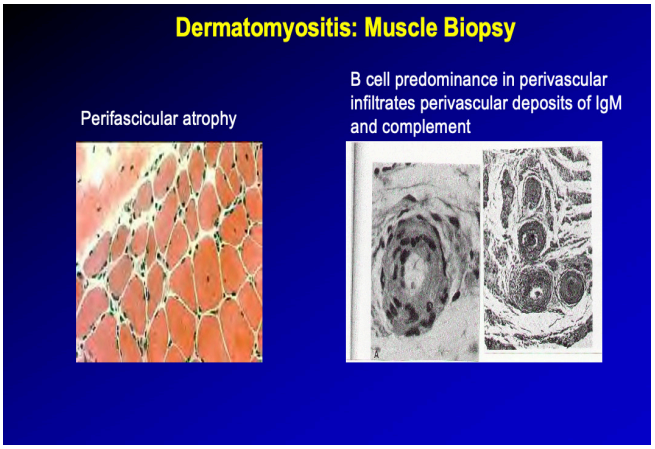


Figure 18

DM Specific Autoantibodies

Autoantibody	Antigen	Antigen Function	Clinical Syndrome
Mi-2	Helicase	Nuclear transcription	Nail fold lesions; higher in Hispanics
Anti-p155(140) TIF1γ	Transcription intermediary factor 1γ	Part of tripartite-motif (TRIM) family, interacts with SMAD 2,3,4; muscle cell regeneration	Cancer in adults; Severe skin disease in children; palmar hyperkeratotic papules, psoriasis like
MDA-5 aka CADM-140 May be weak!!	Type I IF-inducible protein 1, IFIH1	Positive regulator of the IFN response	Severe ILD & cardiopulmonary syndrome, skin ulceration, tender palmar papules
MJ (p140) Up to 40% of DM	NXP-2	Nuclear transcription	JDM with calcinosis
Anti-small ubiquitin-like modifier 1	Small ubiquitin-like modifier 1	post-translational modification; not targeting proteins for degradation	Skin presenting before muscle manifestations; dysphagia common

Figure 18 shows a number of autoantibodies that have been identified in a number of cases of dermatomyositis. Some of these cases predict interstitial lung disease and others can predict severe skin disease.

Cancer and Inflammatory Myopathies

Since many inflammatory myopathies (including IBM) are associated with an increased risk for cancer and are paraneoplastic (Figure 19), what is the standard cancer screening in a patient with inflammatory myopathy? (Figure 20)

We recommend that cancer surveillance screening be performed yearly for the first 5 years after diagnosis of inflammatory myopathy. There are two approaches of cancer surveillance as outlined in Figure 20 or a combination of these approaches can be used.

Figure 19

Cancer Screening in PM/DM/NM

- Risk is highest within the first year of diagnosis
- In those with polymyositis, the risk fell to expected rates 5 years after diagnosis
- In those with dermatomyositis, the risk is always elevated
  - Risk of ovarian, pancreatic, lung cancer remained elevated for up to 5 years
  - Pancreatic and colorectal cancer risks remained elevated past 5 years

Reference:
Hill, C.L. et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet. 2001 Jan 13;357(9250):96-100.

Figure 20

Cancer Screening in DM/PM/NM

- A matter of debate
- Best practice guidelines say to repeat yearly for 1st 5 years after diagnosis
- Approach #1
  - Complete history and physical exam
  - Routine blood and urine tests
  - Fecal occult blood
  - Chest x-ray; mammogram
  - Additional tests in case of specific signs and symptoms

Approach #2: WHOLE BODY CT OR PET

Figure 21 outlines the various immunosuppressive drug therapy options for autoimmune inflammatory myopathy. For polymyositis, dermatomyositis and autoimmune necrotizing myopathy, corticosteroids and intravenous immunoglobulin (IVIG) are often used as first-line immunotherapies. There is now an FDA-approved indication for IVIG in dermatomyositis.

Figure 21

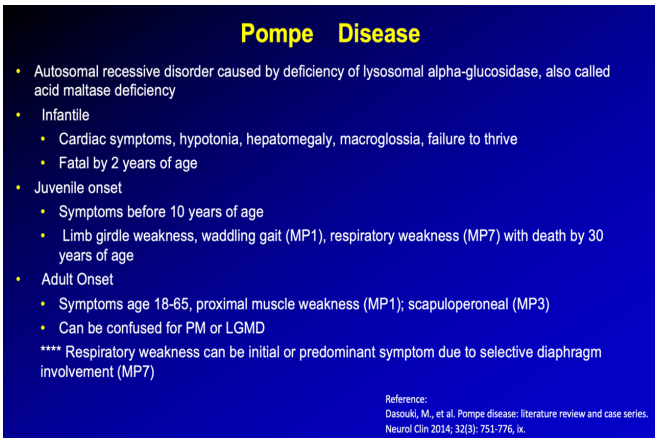
PM/DM/NM Drug Therapy

- 1st Line
  - Prednisone
  - IV methylprednisolone
  - IVIG*
- 2nd Line
  - Methotrexate
  - Azathioprine*
  - Mycophenolate mofetil
- 3rd Line
  - Rituximab*(Oddis)
  - Cyclophosphamide
  - Etanercept* (Amato)
  - Tacrolimus (Oddis)
  - Cyclosporine

*RCT

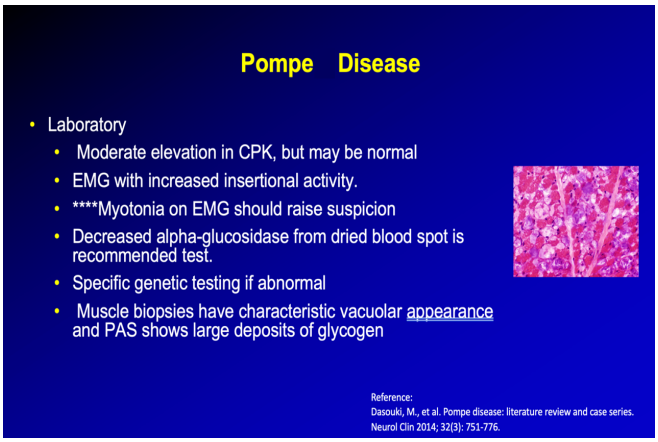
References:
van der Ploeg, et al. Rituximab therapy for myopathy associated with anti-signal recognition particle antibodies: a case series. Arthritis Care Res (Hoboken) 2010; 62(9): 1328-1334.
Amato, A.A., et al. A randomized, pilot trial of etanercept in dermatomyositis. Ann Neurol 2011; 70(3): 427-436.
Dimachkie, M. M., Barohn, R. J., Amato, A. A. Idiopathic inflammatory myopathies. Neurol Clin 2014; 32(3): 595-628, vii.
Baraliakos, X., et al. Efficacy and safety of upadacitinib in patients with active psoriatic arthritis and axial involvement: results from two phase 3 studies. Arthritis Res Ther. 2023 Apr 10;25(1):56.

Pompe's Disease
Figure 22



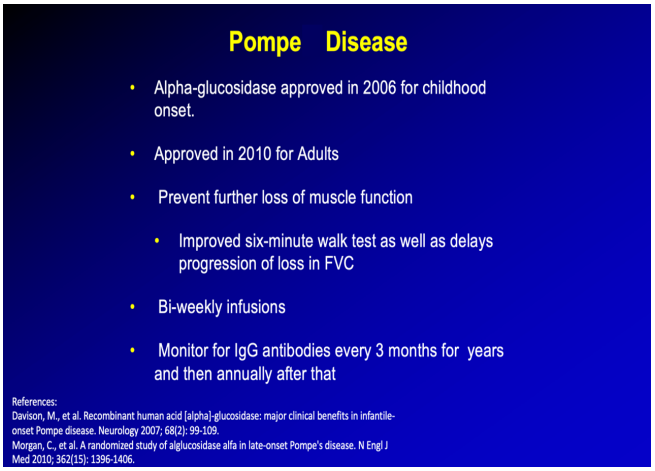
Pompe disease is also known as alpha-glucosidase deficiency or acid maltase deficiency. Pompe disease is an autosomal recessive disorder. It can present at various ages. If it presents in infancy the disease used to be often fatal by 2 years of age without enzyme replacement therapy. Juvenile onset patients used to die of the disease by the second or third decade without enzyme replacement therapy. The late-onset Pompe disease with an adult presentation usually has an MP1 pattern however can also present with an MP3 scapuloperoneal pattern. Because Pompe disease most often has an MP1 presentation it can mistakenly be diagnosed as polymyositis. As also pointed out in the pattern recognition review, Pompe disease patients often have prominent respiratory issues due to diaphragm involvement (MP7).

Figure 23



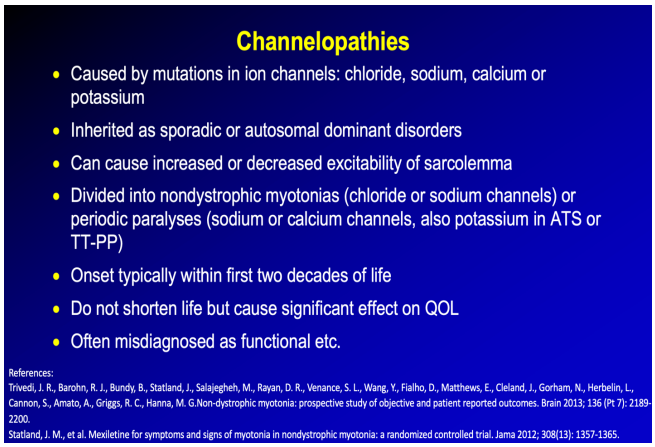
The serum CK is usually mild to moderately elevated. The EMG is interesting because in addition to short-duration small-amplitude motor unit potentials and fibrillation potentials, there can be the presence of myotonic potentials. Figure 23 shows a muscle biopsy showing H&E stained section with vacuolated muscle fibers and loss of muscle fibers and large deposits of glycogen accumulation resulting from a lack of breakdown due to enzyme deficiency.

Figure 24



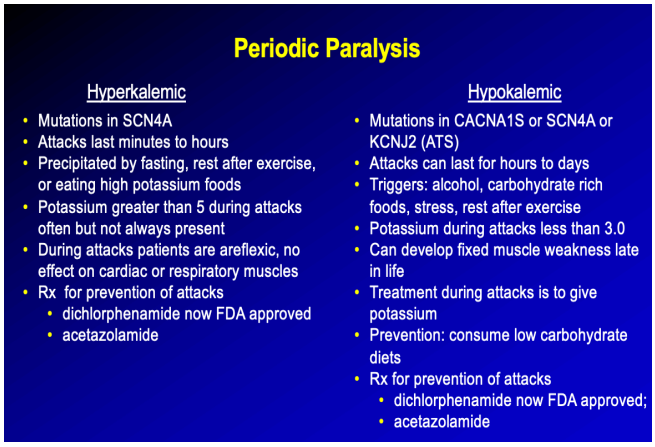
One of the biggest breakthroughs in modern medicine is the introduction of enzyme replacement therapy for Pompe disease. This was the first FDA-approved molecular therapy for a muscle disease. Initially, it was demonstrated that enzyme replacement therapy could dramatically improve infants with Pompe disease and preserve life. It was subsequently shown that chronic enzyme replacement therapy can slow down the progression of juvenile and adult Pompe disease and improve muscle function. Therefore, it is important to recognize Pompe disease early. As the possibility of enzyme replacement therapy was being studied in clinical trials, measuring alpha-glucosidase activity from a phlebotomy sample was developed. This is now a standard procedure for all patients being suspected of Pompe disease. Further genetic testing confirms the diagnosis. Therefore, the combination of an abnormally low alpha-glucosidase level on a blood sample and an abnormal genetic test for Pompe disease can avoid a muscle biopsy and enzyme replacement therapy can be initiated.

Channelopathies
Figure 25



Another group of muscle disorders are the disorders due to muscle channel dysfunction (Figure 25). This group of genetic disorders can be due to mutations in either the chloride, sodium, calcium, or potassium channels. They are inherited disorders that can either increase or decrease the excitability of the muscle fiber membrane. The two most prominent presentations of channelopathies are episodic weakness after exercise or at times unrelated to exercise (MP9), or muscle stiffness and decreased ability to relax (MP10).

Figure 26

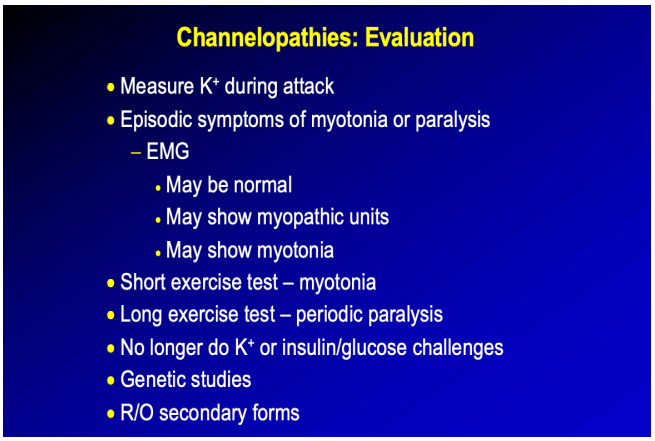


We divide the muscle channelopathies into two groups. One group is the nondystrophic myotonias due to chloride and sodium channel mutations. The other group is the periodic paralysis. These conditions often begin before the first two decades of life and they generally do not cause permanent weakness which is why they are not considered dystrophic. There are exceptions however, as some middle and late age patients with long-standing episodic symptoms of periodic weakness can eventually develop permanent weakness. These conditions do affect the patient's quality of life. These conditions can be difficult to diagnose and sometimes patients can be labeled as being functional or psychogenic.

Periodic paralysis can be further divided into two groups based on the serum level of potassium: hyperkalemic and hypokalemic (Figure 26). The hyperkalemic-associated episodes tend to last a shorter time than the hypokalemic subtype. Hyperkalemic paralysis is typically precipitated by fasting, resting after exercise, or eating high-potassium foods. Hypokalemic paralysis is typically precipitated by alcohol intake, carbohydrate-rich food, stress, and resting after exercise.

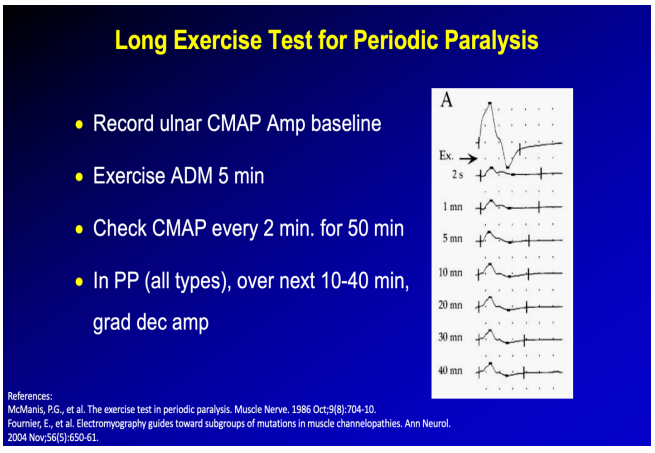
The evaluation of channelopathies is outlined in Figure 27.

Figure 27



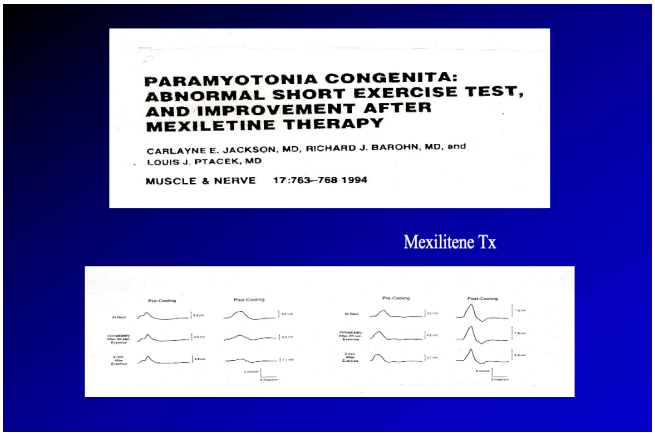
Examining a patient and measuring the potassium level during the paralysis attack is optimal but it is often difficult to have these opportunities. In hyperkalemic paralysis, EMG between attacks may be normal or may show myopathic units or myotonic discharges. However, these are not observed in the hypokalemic group. On nerve conduction studies, the long exercise test for periodic paralysis and the short exercise test for non-dystrophic myotonias can sometimes be useful to differentiate the subtypes (Figure 28).

Figure 28



The short exercise test can sometimes be used to monitor electrophysiologic improvement after treatment initiation for myotonia (Figure 29).

Figure 29

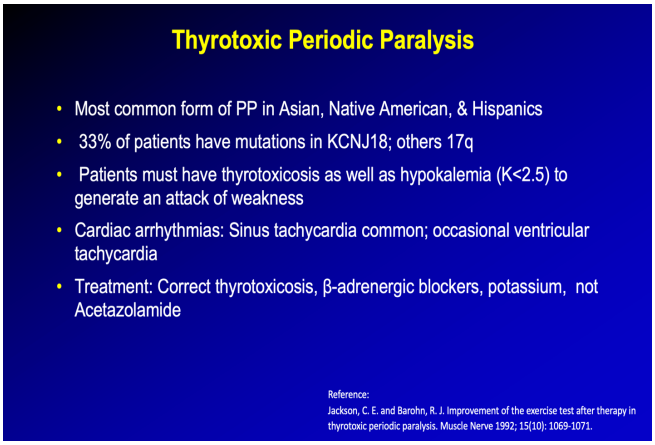


The most efficient and accurate way to diagnose channelopathies is via genetic testing for sodium, calcium, chloride, or potassium channel mutations which are now commercially available. Prior to the advent of genetic testing, an attack could be provoked by administering potassium to produce hyperkalemia and then administering insulin with glucose to produce hypokalemia. However, this is no longer needed with the availability of genetic testing.

Therapy for periodic paralysis is either dichlorphenamide which is now FDA-approved or acetazolamide. Therapy for myotonia is sodium channel-blocking agents. For decades the drug of choice was mexiletine, but more recently ranolazine and lamotrigine have been shown to be effective (See Vivekanandam, et al. Lancet Neurology 2024;10:1004-1012).

Thyrotoxic Periodic Paralysis

Figure 30



There are secondary forms of periodic paralysis. The most common etiology for secondary periodic paralysis is thyrotoxic periodic paralysis.

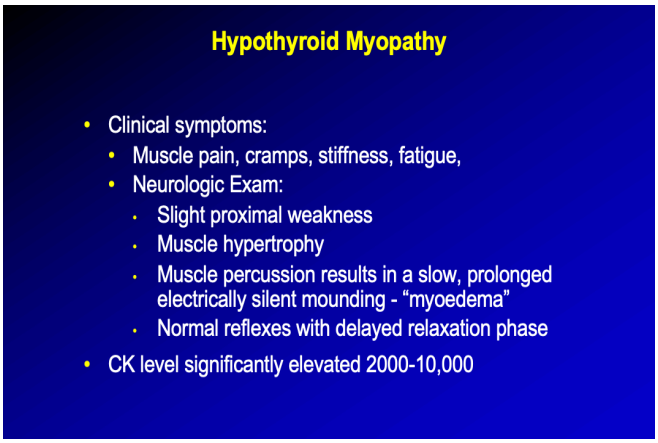
This is the most common form of paralysis in Asians, Native Americans, and Hispanics.

Many of these patients have a concomitant potassium channel defect on chromosome 18 or on chromosome 17. Clinically they have obvious thyrotoxicosis when they present with weakness and hypokalemia.

Acutely the treatment is to correct the hypokalemia, but the long-term treatment is to correct the thyrotoxicosis.

Hypothyroid Myopathy

Figure 31

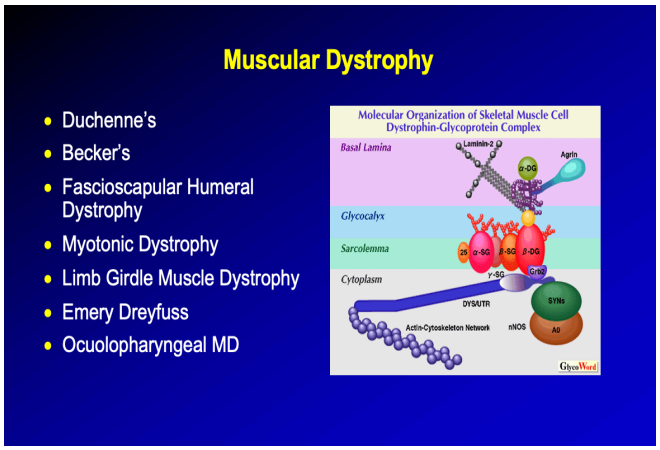


Hypothyroid myopathy patients present with cramps, stiffness, fatigue, and proximal weakness (MP1). Reflexes can exhibit a delayed relaxation phase. Serum CK is often very high. It is important to check thyroid functions in patients with unexplained elevated CK as some of these patients may not have a great deal of symptoms and signs of muscle disease or hypothyroidism.

Muscular Dystrophies

A number of different muscular dystrophies along with a diagram of the molecular organization of a skeletal muscle cell and the dystrophin glycoprotein complex is shown in Figure 32.

Figure 32

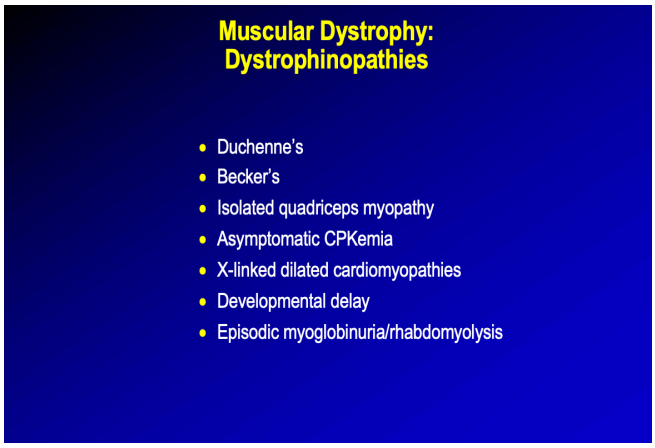


Dystrophinopathies (Duchenne's and Becker's Muscular Dystrophy)

Dystrophinopathies have a number of clinical presentations. The most common presentation is an MP1 pattern of muscle weakness for both Duchenne's and Becker's muscular dystrophy.

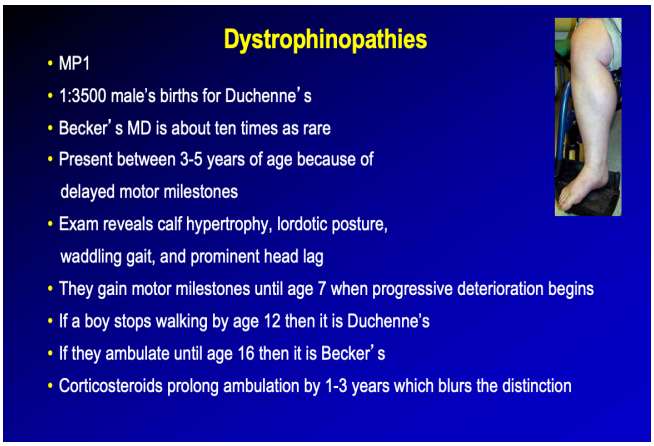
Duchenne and Becker's muscular dystrophy are due to genetic defects in the dystrophin gene and are therefore called dystrophinopathies. Other reported presentations of dystrophinopathies are shown in Figure 33.

Figure 33



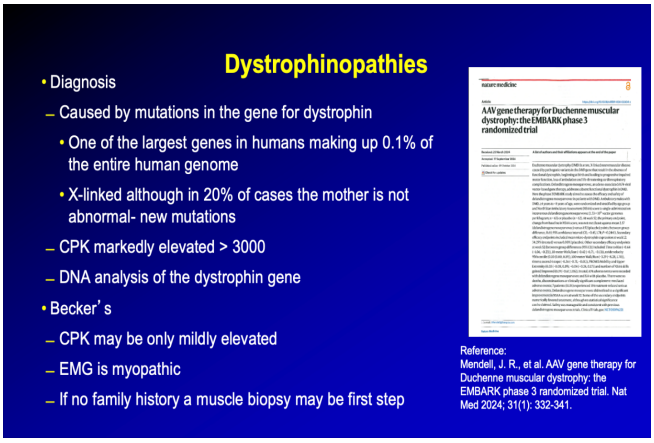
Typical patients with Duchenne muscular dystrophy present between ages 3 and 5 because of delayed motor milestones. There is often the presence of calf hypertrophy (Figure 34).

Figure 34



Boys usually stop walking by age 12 but the use of corticosteroids will prolong ambulation. There is now FDA-approved exon-skipping antisense therapy for dystrophinopathies due to a number of specific deletions in the dystrophin gene. More recently the FDA approved intravenous AAV mediated gene therapy (Elevidys). Therefore, accurate and early genetic diagnosis is important (Figure 35).

Figure 35

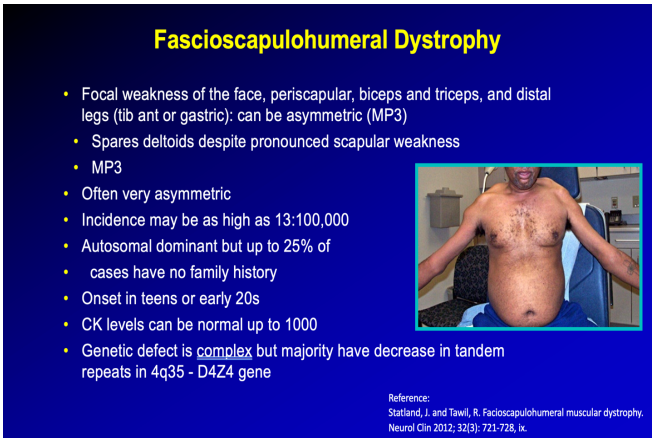


Muscle biopsies will show the absence of dystrophin, but these are no longer needed with a documented dystrophin mutation in the blood (Figure 36).

Figure 36

Facioscapulohumeral Dystrophy (FSHD)

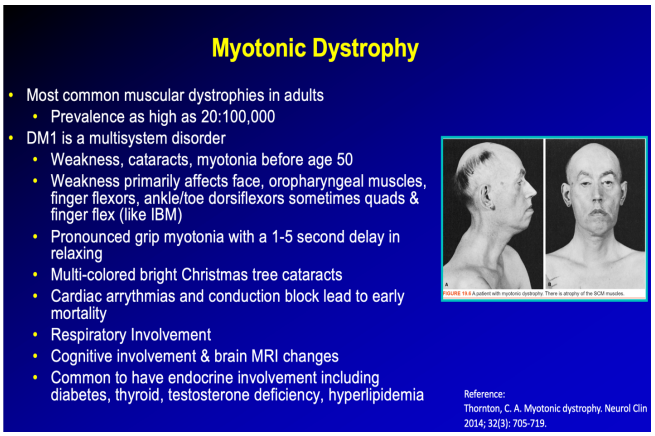
Figure 37



FSHD patients have a scapuloperoneal or MP3 weakness distribution (Figure 37). Patients have weakness of the face, periscapular muscles, biceps, and triceps. In these patients, the deltoid can appear normal with very atrophic biceps and triceps. Scapular winging is prominent and can be observed with either shoulder flexion or abduction. Most patients will provide an autosomal dominant family history but up to 25% will not. The diagnosis is based on demonstrating the genetic defect which is a decrease in the number of tandem repeats in the 4q35-D4Z4 gene.

Myotonic Dystrophy

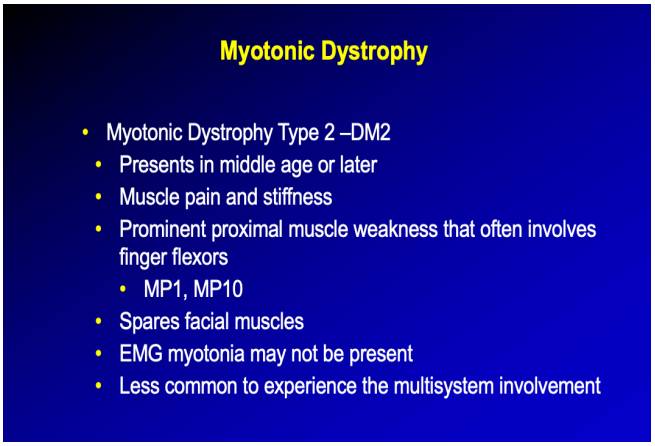
Figure 38



Myotonic dystrophy is probably the most common form of muscular dystrophy in adults. There are two forms of myotonic dystrophy. Myotonic dystrophy type 1 (DM1) is the classic form with multisystem involvement. Along with weakness, they have cataracts. They develop cardiac arrhythmias and conduction blocks which lead to very early mortality, often in the sixth decade. Some of these patients require pacemakers and automatic implantable cardioverter defibrillators. They can have various endocrine disorders, including diabetes, hypothyroidism, and testosterone deficiency. Cognitive impairment is very common.

Myotonic dystrophy can have a number of different presentation patterns including MP1, distal weakness MP2, ocular ptosis MP5, and muscle stiffness (MP10). Rarely, an adult DM1 patient can have severe knee extension weakness combined with severe finger flexor weakness MP4 pattern which is most often seen in IBM. However, the age of the patient and other typical myotonic dystrophy features help distinguish these two diseases.

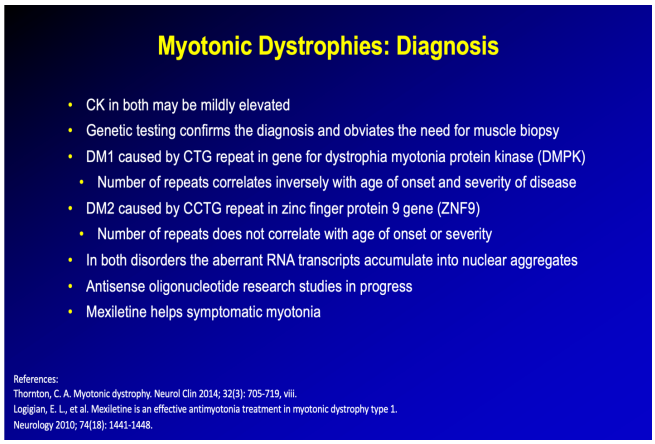
Figure 39



Myotonic dystrophy type 2 (DM2) presents later in life (Figure 39). They do not have all of the features typical for DM1. Most of these patients present with muscle pain and stiffness. On exam, they can have mild or prominent limb-girdle weakness (MP1).

One clue to DM2 is that very often their finger flexors are weak as well, but they do not have facial involvement and they may not have myotonia on exam.

Figure 40



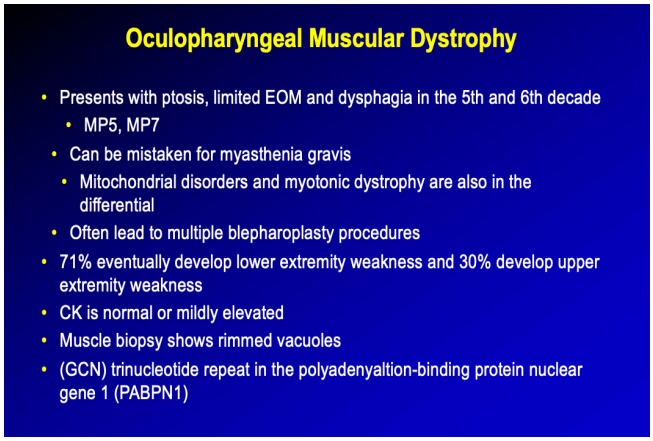
The definitive diagnosis of both types of myotonic dystrophy is via genetic testing of the blood or muscle. Genetic testing confirms the diagnosis. DM1 is caused by CTG repeat expansion of the DMPK gene. DM2 is caused by CCTG repeat expansion of the ZNF9 gene (Figure 40).

In DM1 the number of repeats correlates inversely with the onset age and the severity of the disease. In DM2 the number of repeats does not correlate well with the onset of severity.

Both seem to relate to the increase in RNA transcripts that build up because of these extra repeats and there are several research studies now trying to decrease the amount of RNA with antisense nucleotides. EMG can show classic myotonia but is often more subtle in DM2 and CK may be mildly elevated.

Although not FDA-approved, mexiletine is very helpful to treat their symptoms of muscle stiffness and pain but it does not help weakness.

Oculopharyngeal Muscular Dystrophy
Figure 41



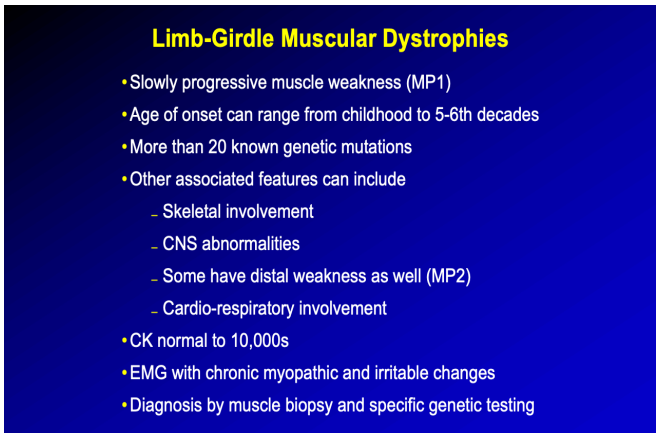
Oculopharyngeal muscular dystrophy (OPMD) is important to recognize because this can be mistaken for myasthenia gravis, as patients will come in with ptosis, extraocular muscle weakness, dysphagia, and often some facial weakness late in the course of the disease (Figure 41).

Therefore, OPMD has features of both MP5 (eyeball pattern) and MP7 (bulbar pattern). One of the clues favoring OPMD rather than MG is that because eye muscle weakness develops slowly throughout the entire lifetime in OPMD, the patient's eyes may not move at all, but they have no double vision. On the other hand, in myasthenia gravis, there may be no obvious deficit in extraocular motility on examination, but the patients complain of diplopia. Muscle biopsies may show the presence of rimmed vacuoles and subtle dystrophic features without inflammation. The definitive test demonstrates the genetic abnormality of a trinucleotide repeat expansion in the PABPN1 gene.

Limb-girdle muscular dystrophy (LGMD) (Figure 42)

Historically, limb-girdle muscular dystrophies were always lumped into one group until genetic mutations were found and there were apparent multiple limb-girdle muscular dystrophies. Most present with an MP1 pattern that is slowly progressive, however, distal presentations can occur (MP2) in some of the LGMDs.

Figure 42



The most common forms of limb-girdle muscular dystrophy are shown in Figure 43.

Figure 43

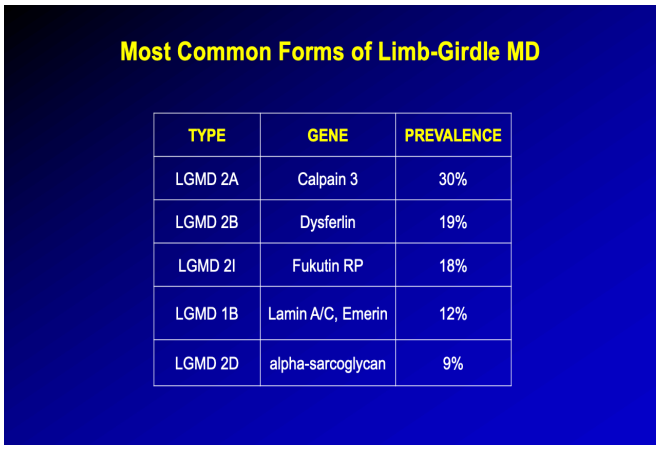
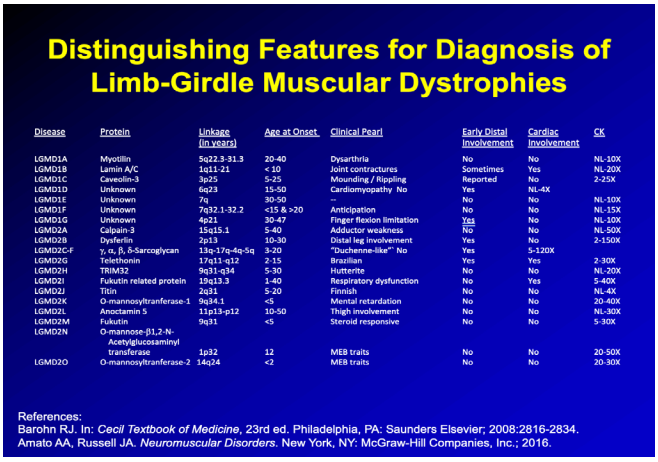


Figure 44 provides more distinguishing features between a number of the LGMDs.

Figure 44



Congenital Muscular Dystrophy

Congenital muscular dystrophies occur within the first year of life and present with prominent hypotonia. Ultimately an MP1 pattern is recognizable. Frequently other organ systems are involved including eyes, lungs, brain, and heart (Figure 45).

Figure 45

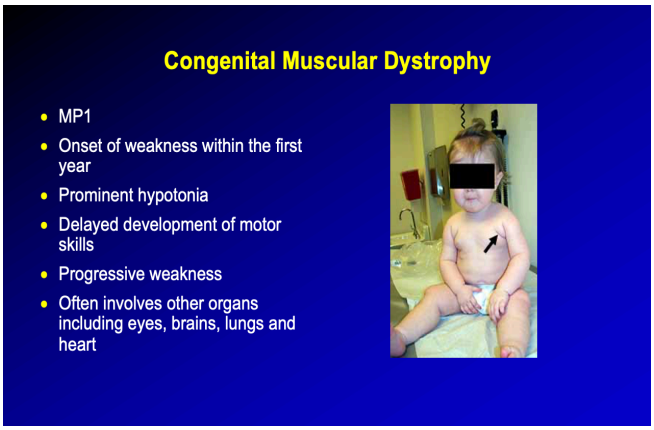


Figure 46 shows a muscle biopsy with dystrophic changes, muscle size variability, and significant replacement of muscle fibers by connective tissue. However, a muscle biopsy is now rarely indicated, and patients are diagnosed with specific genetic testing.

Figure 46

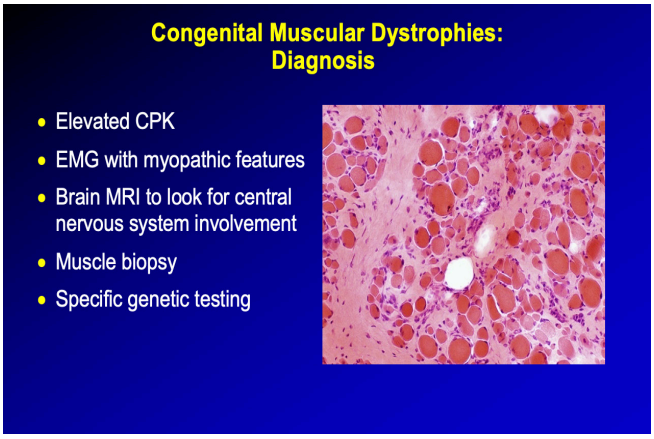


Figure 47 shows a number of different congenital muscular dystrophies with specific genetic abnormalities. While often included on this list, Bethlem myopathy is due to a genetic mutation in collagen genes rather than muscle-specific genes.

Figure 47

Congenital Muscular Dystrophies

	Respiratory	Cardiac	Brain MRI	Course
Merosin	Common	35%	T2 Abnormal	Slowly progressive
Fukuyama	Not seen	Decreased EF	migrational defects	Progressive
Musce-Eye-Brain	Not seen	Not seen	Structural abnormal	Progressive
Walker-Warburg	Not seen	Not common	Structural abnormal	Poor survival
Bethlem	Not seen	some conduction defects	Normal	Progression at 2nd decade
Ullrich	Early resp involvement	Not seen	Normal	Progressive

Congenital Myopathies

There are several congenital myopathies that usually present in childhood with an MP1 pattern. By definition, these tend to be nonprogressive in contradistinction to congenital muscular dystrophies. A number of different molecular genetic defects have now been identified for nemaline rod, congenital myopathy with central nuclei, and congenital myopathy with cores.

Figure 48

Congenital Myopathies

- MP1, occasionally MP2, MP3, MP5
- Early onset hypotonia
- Muscle weakness
- Not progressive by definition
- NI to slightly elevated CPK
- Muscle biopsy with specific pathologic findings

Figure 49

Congenital Myopathies: Nemaline Rod

- 90% are congenital but childhood and adult onset do occur
  - Can be autosomal dominant or recessive
  - 7 identified genes to date
- Weakness and hypotonia
- Cognitive involvement in younger children
- Progressive disorder in kids with death from respiratory involvement
- Adult can present with paraspinous and neck extensor involvement

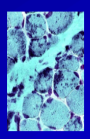


Figure 50

Congenital Myopathies

- Congenital Myopathy with Fiber Size Disproportion
- Autosomal dominant or recessive
- Onset is congenital or childhood
- Diffuse weakness and hypotonia
- 50% are static, 35% improve somewhat and
- 15% worsen

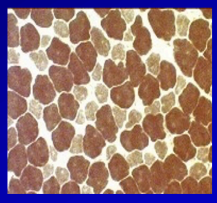


Figure 51

Congenital Myopathies

- Congenital myopathy with central nuclei
  - X-linked (Myotubularin 1) or autosomal dominant or recessive
  - Onset in infancy
  - 50% of mothers will have polyhydramnios
  - Facial and head malformations
  - Hypotonia, muscle and respiratory weakness and ocular (ptosis, EOM)
  - Many die within the first 6 months
  - Longer survivors require respiratory support

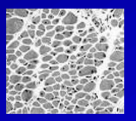
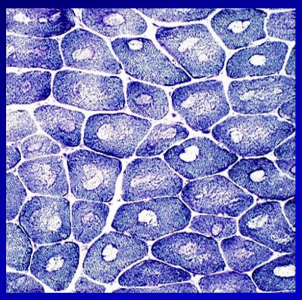


Figure 52

Congenital Myopathies: CORES

- Ryanodine receptor syndromes
- Central core myopathy
- Congenital or childhood onset
- Autosomal dominant or recessive
- Hypotonia
- Congenital hip dislocation and reduced fetal movements
- Slowly or not progressive
- Malignant hyperthermia
- Usually Limb Girdle
- MP1



Metabolic Myopathies

The last group of disorders we will consider in this lecture are the metabolic myopathies. We have already discussed Pompe disease which is included in this group and is considered a static metabolic myopathy. Another group of metabolic myopathies with static presentation

are the mitochondrial myopathies which can be associated with not only an MP1 presentation but also the eyeball presentation and ptosis with ophthalmoplegia (MP5). Other metabolic myopathies are episodic and present with rhabdomyolysis and myoglobinuria, MP8 pattern (Figure 53). These can also be considered dynamic disorders. Metabolic myopathies that have exercise intolerance and rhabdomyoma provoked by intense exercise under 10 minutes are usually glycogen disorders. On the other hand, dynamic metabolic myopathies in which symptoms are provoked by low-intensity exercise lasting longer than 10 minutes are usually lipid disorders.

Figure 53

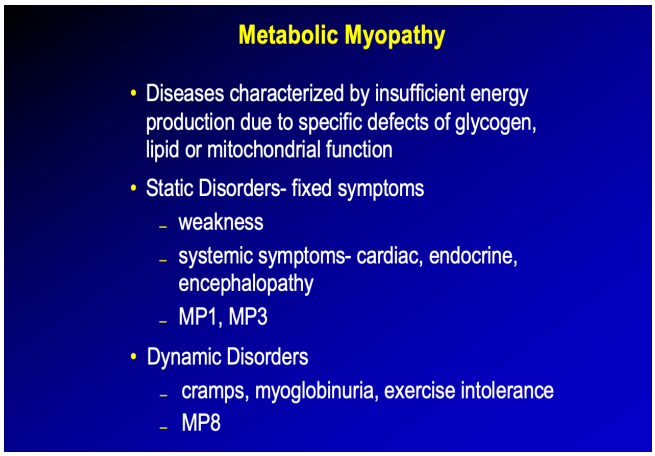


Figure 54

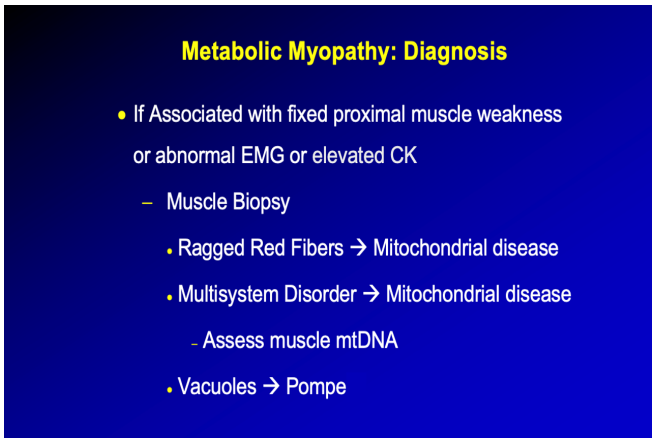


Figure 55

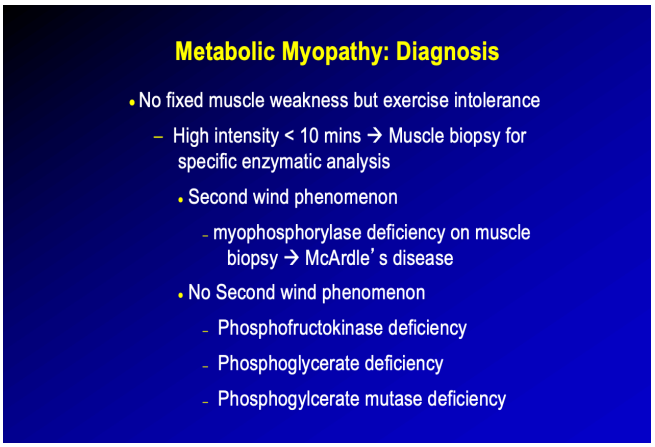
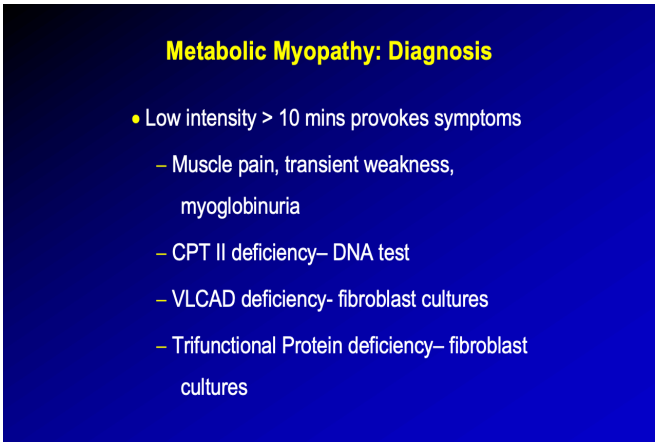


Figure 56



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