Pattern recognition approach to neuromuscular disorders: myopathy and neuromuscular junction

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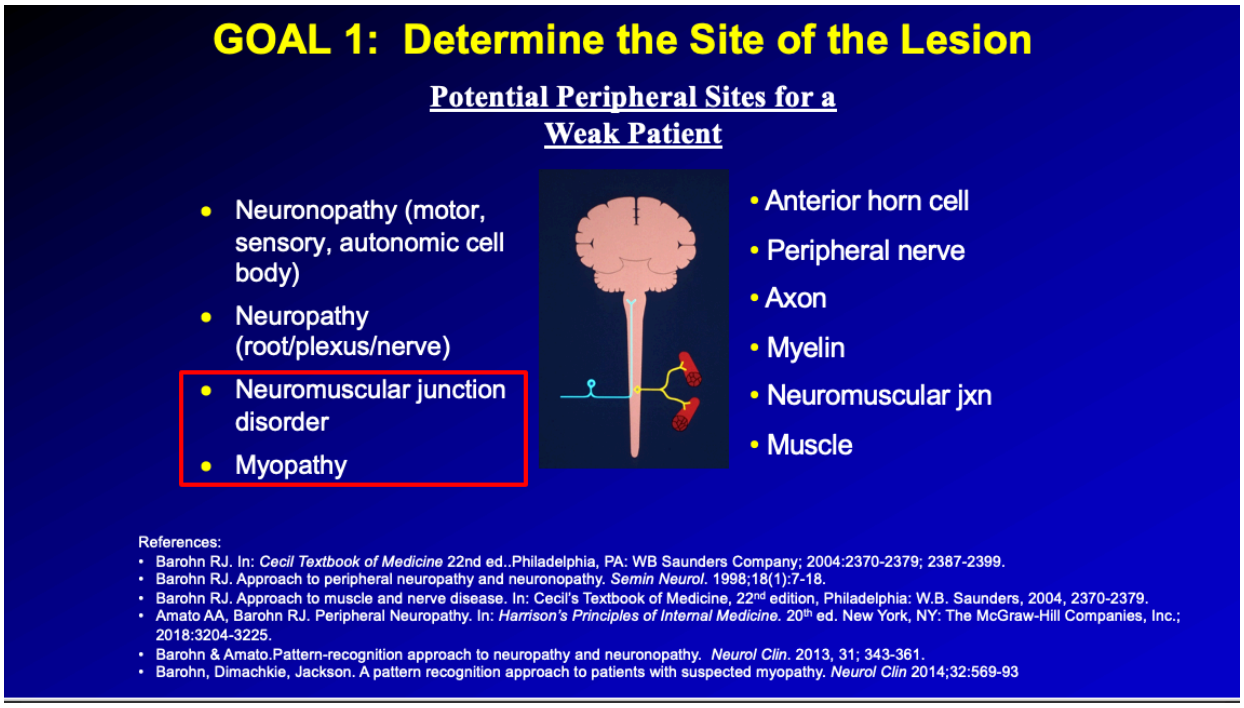
Every neurologist has three goals when they see a patient: 1. To determine the site of the lesion; 2. To determine the cause of the lesion; 3. To determine the specific therapy for the patient's problem and if not a specific therapy, what the best management is (Figure 1).

Figure 1

This discussion will concern the peripheral nervous system components that include neuromuscular junction and skeletal muscle (Figure 2).

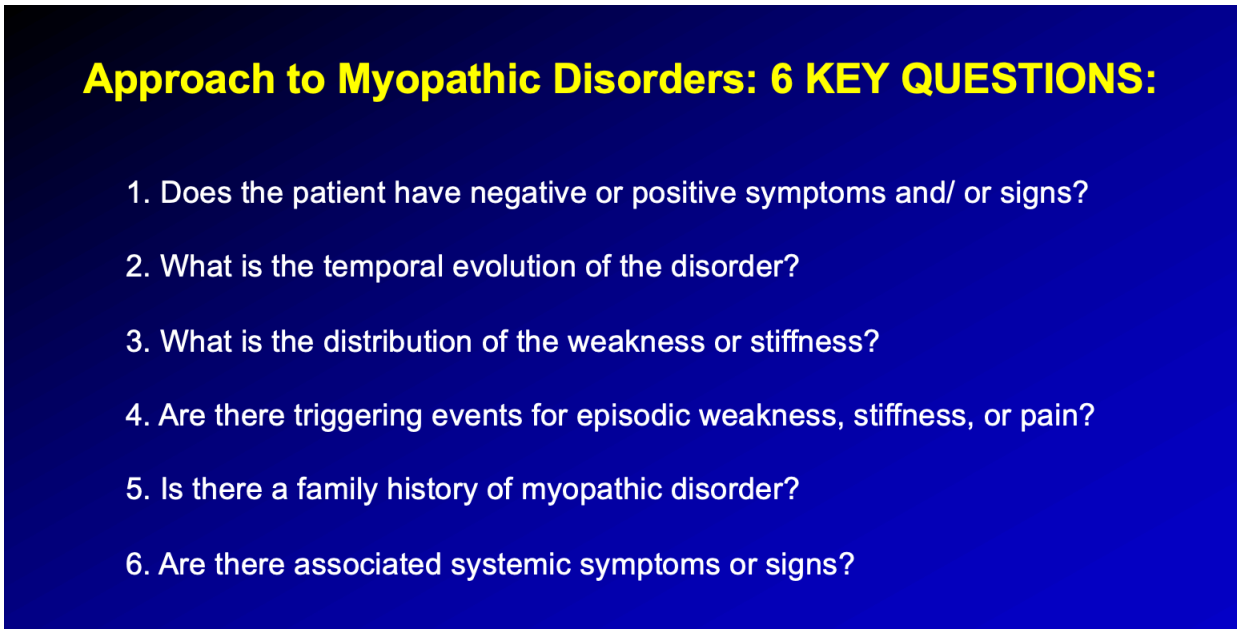
Figure 2



As is true of all areas of neurology, the pattern recognition approach will allow us to make preliminary assessments on the site of the lesion, the cause of the lesion, and what to do for the patient. This of course applies to muscle disorders.

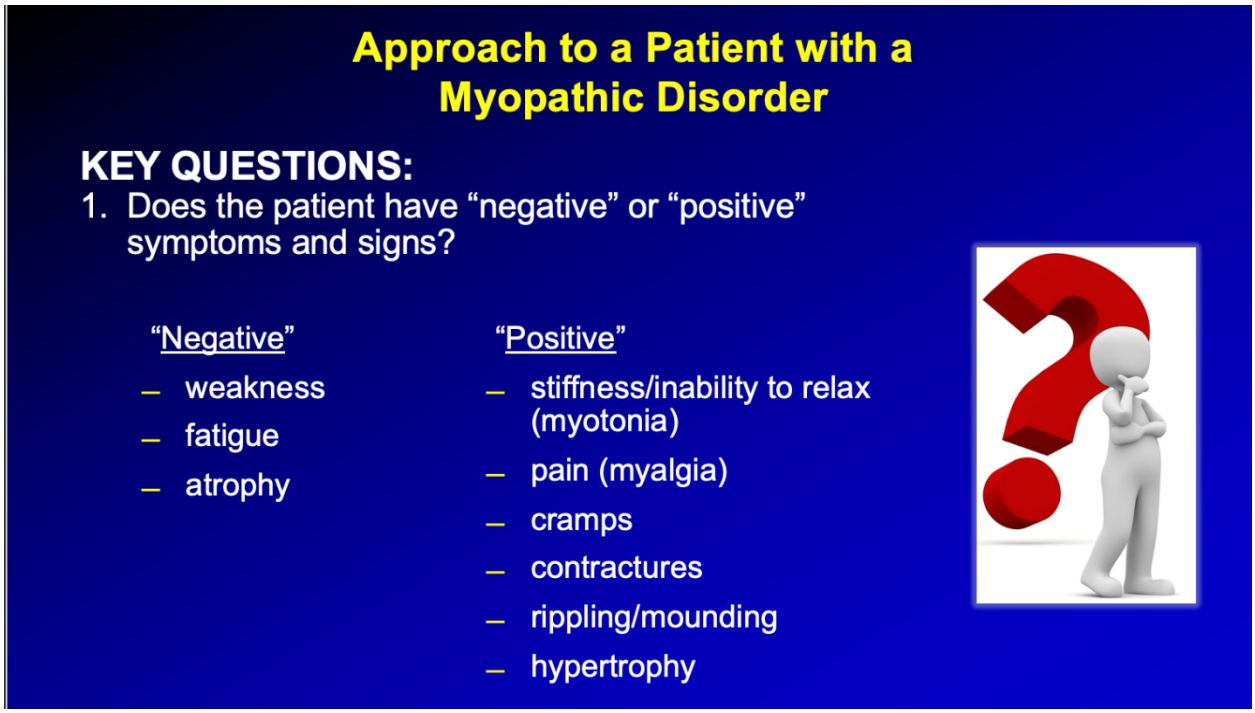
There are six key questions that you should be asking yourself when you take the history and when you do the physical exam (Figure 3). In a patient with a presumed muscle disorder as you gather the answers to these questions you will put the patient into one of the ten muscle presentation patterns. After you do this, you will be in a position to order your initial laboratory tests.

The SIX KEY QUESTIONS for muscle disorders are the following (Figure 3):



Question 1: Does the patient have negative or positive symptoms and/ or signs? (Figure 4)

Figure 4



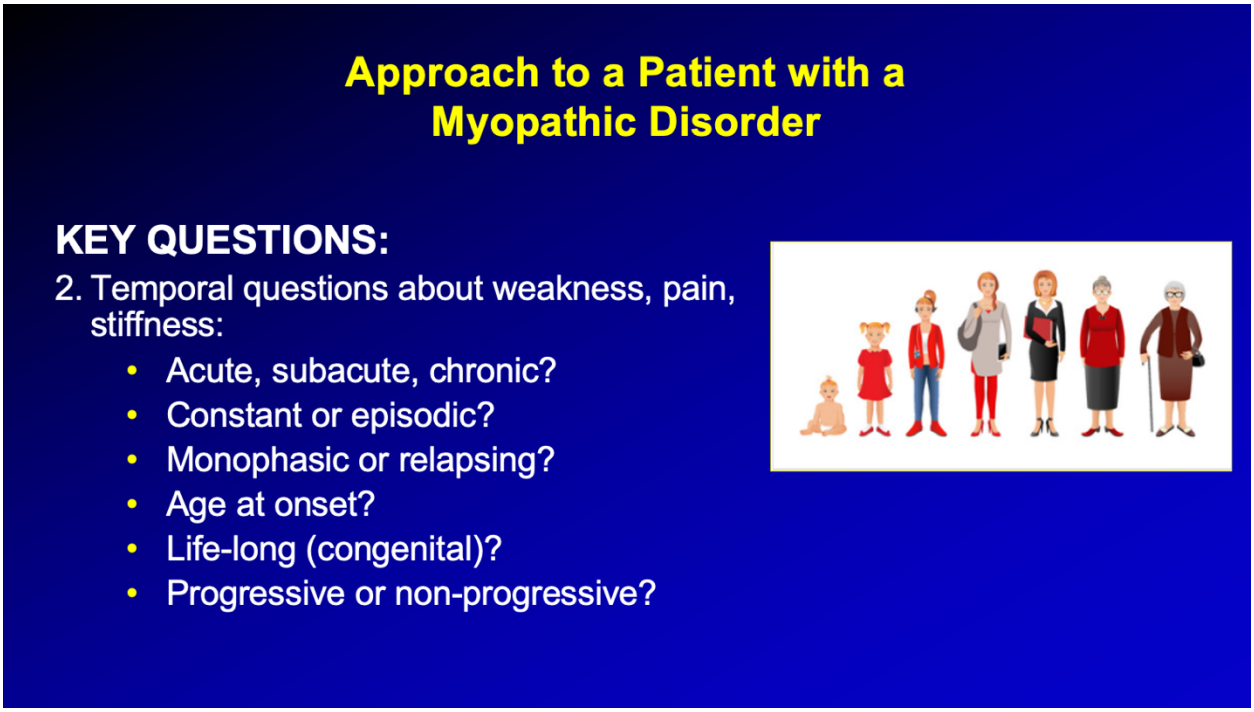
What we mean by negative symptoms/ signs is primarily **weakness**. The patient may state they are weak. On your neurologic exam, you identify that they are weak. Weakness is generally the most prominent symptom and sign of any patient with a muscle disorder. In addition, the patient may complain of fatigue, another negative symptom. However, fatigue is a symptom that is very difficult to demonstrate or quantify as a sign on the neurologic exam. One exception to this is ptosis which can be induced by having the patient maintain up gaze and observing the narrowing of the palpebral fissure. Similarly, double vision (diplopia) can often be elicited by having the patient look in a particular direction of gaze for a period of time. Speech fatigue can be demonstrated by having the patient read out loud and observing slurring of words or a nasal speech after a period of time. Eyelid fatigue, eye motility fatigue, and speech fatigue are hallmarks of neuromuscular junction weakness from disorders such as myasthenia gravis.

Muscle atrophy is a negative sign that should be documented, particularly if it is focal and combined to specific muscle groups. For example, in inclusion body myositis it is common to note atrophy of the flexor forearm muscles and the quadriceps muscles.

The main positive symptom is stiffness or inability to relax the muscles. When this symptom occurs in muscle disease, it usually is an indication of myotonia. The next step of course would be to attempt to demonstrate grip or eyelid closure myotonia or percussion myotonia on the neurologic exam. Other positive symptoms include pain and cramping. Positive signs can include mechanical or metabolic contractures, rippling or mounding of the muscles that can be induced with muscle percussion, or muscle hypertrophy or pseudohypertrophy such as enlarged calves.

Question 2: What is the temporal evolution of the disorder? (Figure 5)

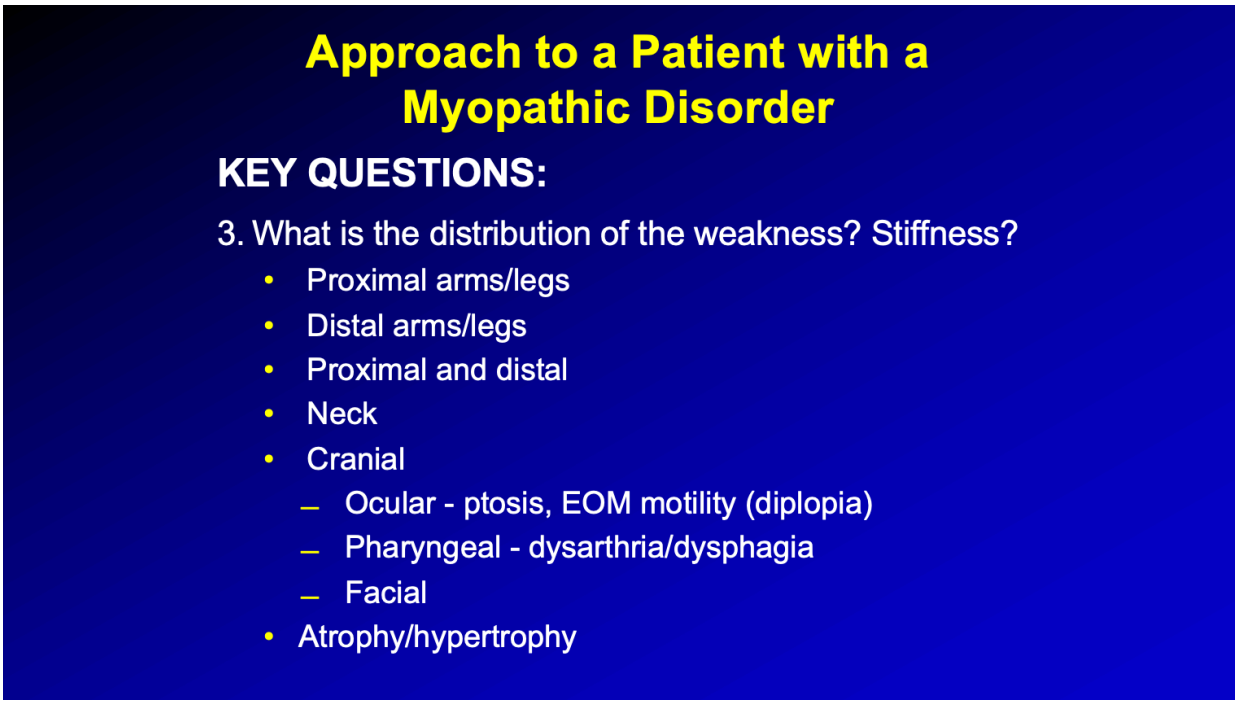
Figure 5



Is the disorder acute, less than 4 weeks? Subacute, 4-8 weeks? Or chronic, more than 8 weeks?
Is the disorder constant or episodic? In other words, do the symptoms and signs come and go?
Is the disorder monophasic or relapsing?
What is the age of onset of the patient when the disorder begins? Does it begin at birth, in the first several years of life, middle age, or late-life adult onset?
If the disorder has existed since childhood, is it congenital? In other words, was it present neonatally or in the first days and weeks of life?
Finally, is it progressive or non-progressive?
Some of the myopathic disorders such as congenital myopathies tend not to be very progressive. Other disorders such as muscular dystrophies and inflammatory myopathies are typically progressive.

Question 3: What is the distribution of the weakness or stiffness? (Figure 6)

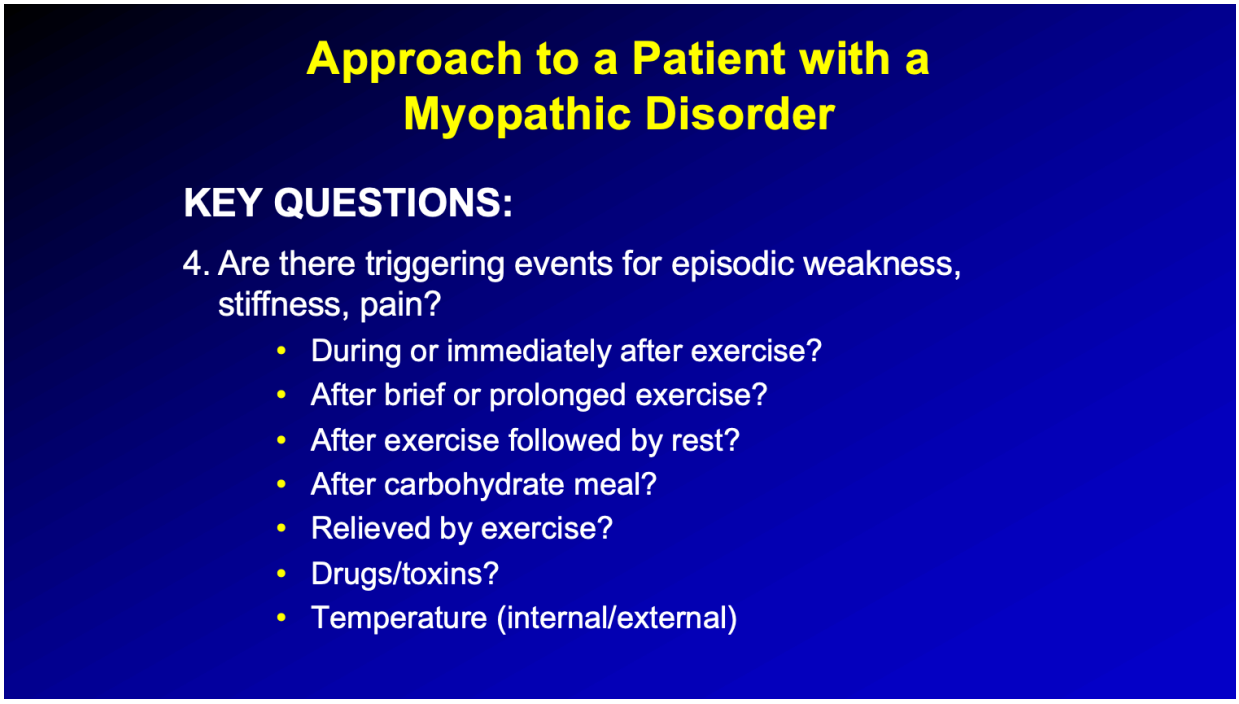
Figure 6



Based on the symptoms and signs, is the weakness primarily in the proximal arms/legs; distal arms/legs; both proximal and distal arms and legs; involve midline cervical or thoracic spine weakness; or involve cranial nerve innervated muscles?
As noted above, the positive finding of muscle stiffness usually denotes myotonia. The distribution of the myotonia can be determined based on symptoms or signs on exam. Most often it is identified in the hand muscles by demonstrating grip myotonia or percussion myotonia of the thenar muscles. But myotonia also can be elicited in the facial muscles, finger extensors, and proximal leg muscles. The distribution of atrophy or hypertrophy should also be documented.

Question 4: Are there triggering events for episodic weakness, stiffness, or pain? (Figure 7)

Figure 7



Triggering events are important in myopathy and they occur more often than in neuropathy.

Is exercise a triggering event and does the weakness occur during or after exercise?

If it is related to exercise, is it following brief exercise which occurs in metabolic glycogen disorders, or after prolonged exercise in metabolic lipid disorders and mitochondrial disorders?

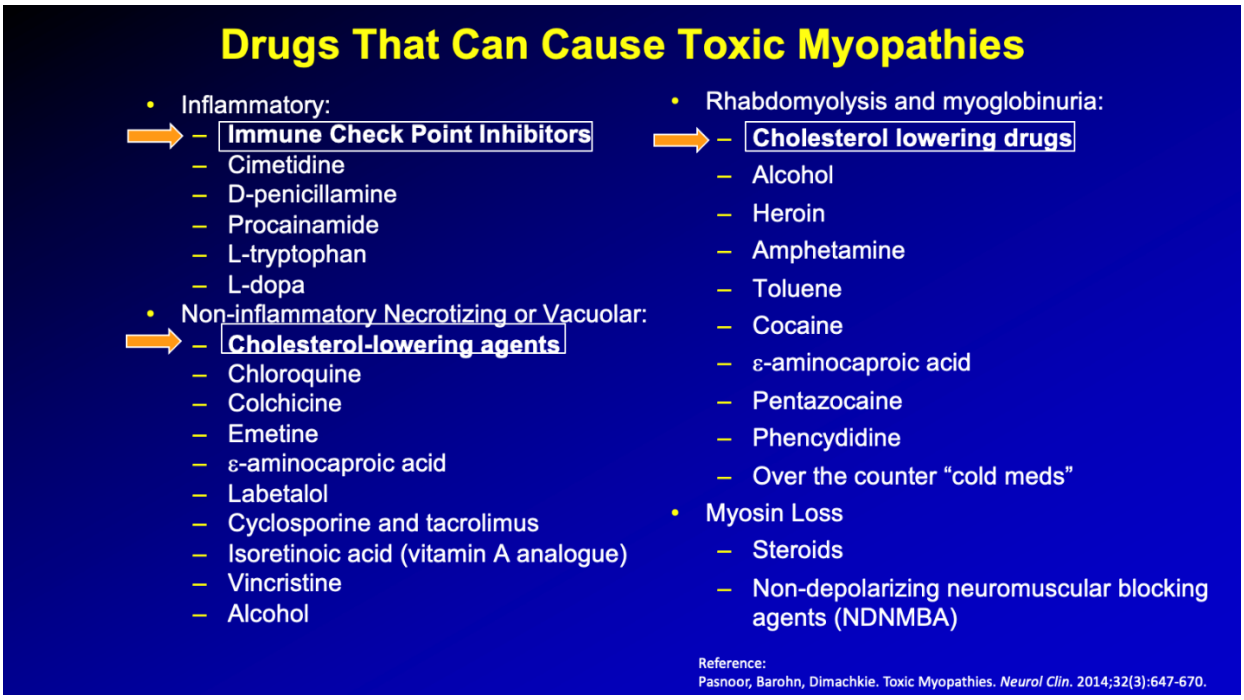
Does the weakness occur after exercise followed by rest? Does it occur after a carbohydrate meal? These are both triggers that can occur in the setting of periodic paralysis.

Are the symptoms relieved by exercise? This has to do more with stiffness. In typical myotonia, exercise makes it better or relieves the symptoms and signs of myotonia. But in paradoxical myotonia, exercise makes the symptoms and signs worse. Therefore, this is called paramyotonia.

Is a triggering event a drug or a toxin? Or was the trigger doing physical activity outside or in a very hot environment, which can occur in some instances of rhabdomyolysis, or does the patient present with an elevated body temperature which can occur in carnitine palmityl transferase (CPT) deficiency?

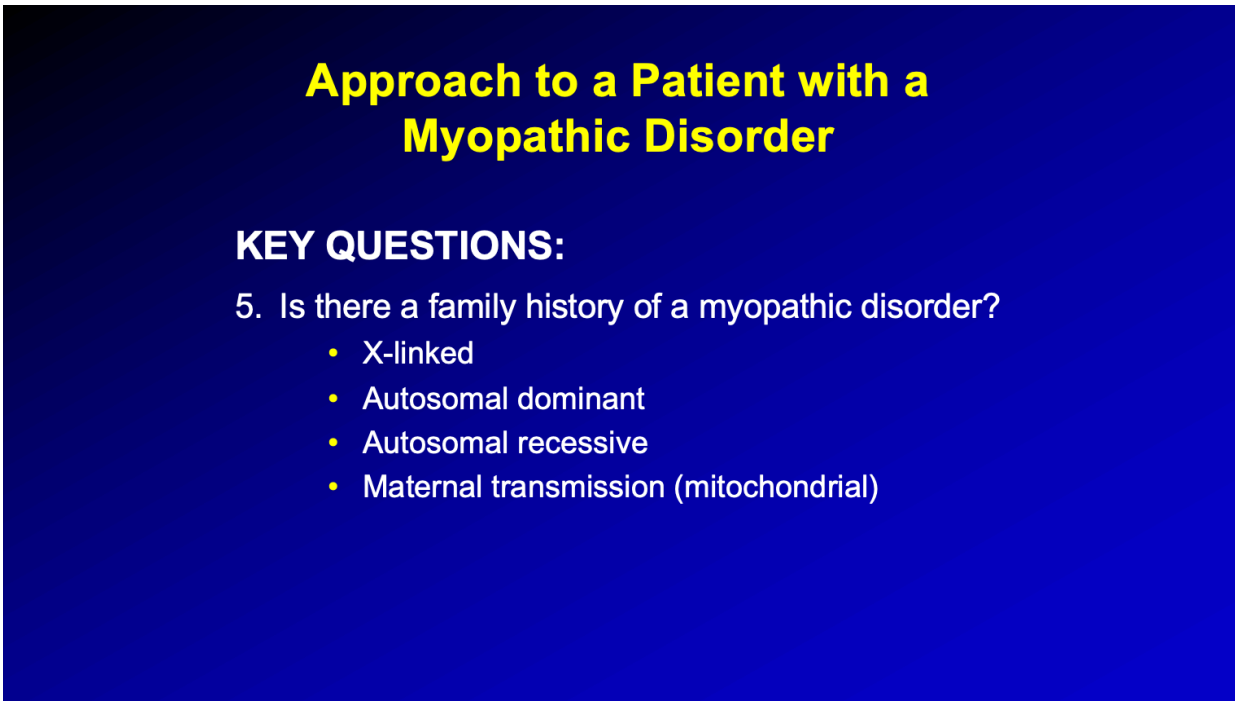
Figure 8 displays some of the drugs that can cause toxic myopathies. The list is extensive. We want to direct your attention to cholesterol-lowering drugs which are used frequently. Cholesterol-lowering drugs can produce more than one myopathic presentation. One is chronic progressive proximal weakness due to statin-associated autoimmune necrotizing myopathy (SANAM) requiring immunosuppressive and immunomodulatory therapy. In those cases, a new class of lipid-lowering drugs, the PSCK9 inhibitors, may be well tolerated. The other is a direct toxic effect leading to acute rhabdomyolysis and myoglobinuria and in milder cases of self-limited toxic necrotizing myopathy which resolves with drug cessation. A new class of agents is immune checkpoint inhibitors used for precision cancer therapy. Some patients exposed to immune checkpoint inhibitors develop weakness due to an inflammatory myopathy, myocarditis, or even a neuromuscular junction disorder as a side effect of the drug. The drugs on this list can cause several types of myopathic disorders including inflammatory myopathies, non-inflammatory necrotizing myopathies, rhabdomyolysis with myoglobinuria, or myosin (thick filament) loss myopathies as occurs in the context of critical illness.

Figure 8



Question 5: Is there a family history of myopathic disorder? (Figure 9)

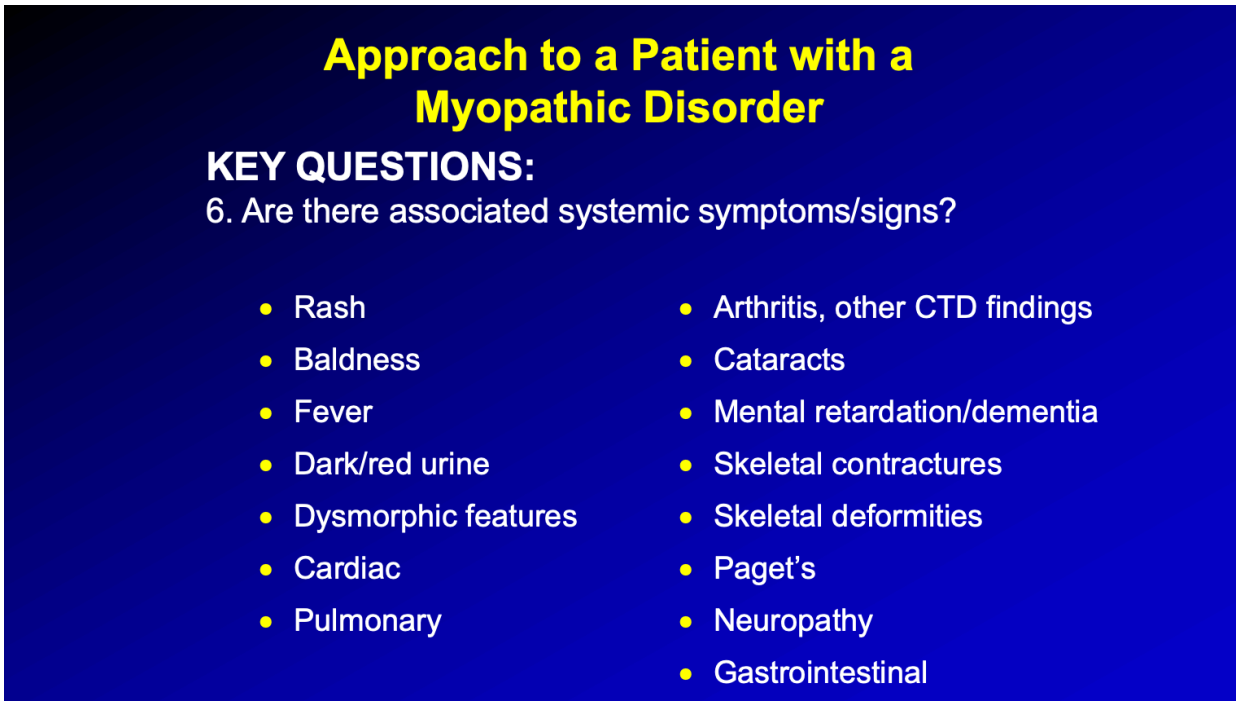
Figure 9



It is necessary to take a detailed family history in all cases of possible myopathies. Based on the family history, is there evidence of an X-linked recessive disorder where only males have the disease, and it is passed through the mother; or an autosomal dominant or autosomal recessive disorder; or maternal transmission to both men and women which is common in mitochondrial disorders?

Question 6: Are there associated systemic symptoms or signs? (Figure 10)

Figure 10



Is there a rash typical of dermatomyositis? Is there frontal baldness which can be seen in myotonic dystrophy? Does the patient have a fever concurrent with muscle symptoms which can be associated with CPT deficiency? Is there dark red urine typical of rhabdomyolysis with myoglobinuria? Does the patient have dysmorphic features of the face which can occur in a number of muscle disorders such as myotonic dystrophy, some congenital muscular dystrophies, and in rare forms of periodic paralysis such as Andersen-Tawil Syndrome? Some myopathies have mechanical muscle contractures as an early manifestation such as Emery-Dreifuss muscular dystrophy or Bethlem myopathy (a collagen-related genetic disorder). Glycogen storage myopathies can have metabolic contractures on exertion. When metabolic contractures occur during an electromyogram there is electrophysiologic silent.

Is there cardiac, pulmonary, and gastrointestinal involvement? Some myopathies have cognitive impairment or learning disabilities such as myotonic dystrophy, congenital muscular dystrophies and some cases of Duchenne muscular dystrophy. Arthritis and other signs of connective tissue disease are seen in dermatomyositis and polymyositis. Cataracts and severe cardiac conduction defects may occur in myotonic dystrophy. Paget's disease is seen in a particular form of inclusion body myopathy with Valosin-associated protein mutations.

The TEN MYOPATHIC PATTERNS (MP) are as follows:

Now we are going to go through the patterns of myopathy presentation. Based on these patterns, you will order certain laboratory tests in order to confirm the suspected diagnosis.

MP1: The limb-girdle pattern. (Figure 11)
This is by far the most common myopathic pattern. It has a broadest differential diagnostic list as evident in Figure 11. They are largely grouped as acquired disorders, most commonly autoimmune versus genetic muscle diseases. Some of this MP1 presentation overlaps with spinal muscular atrophy (SMA) or even neuromuscular junction disorders.

Figure 11

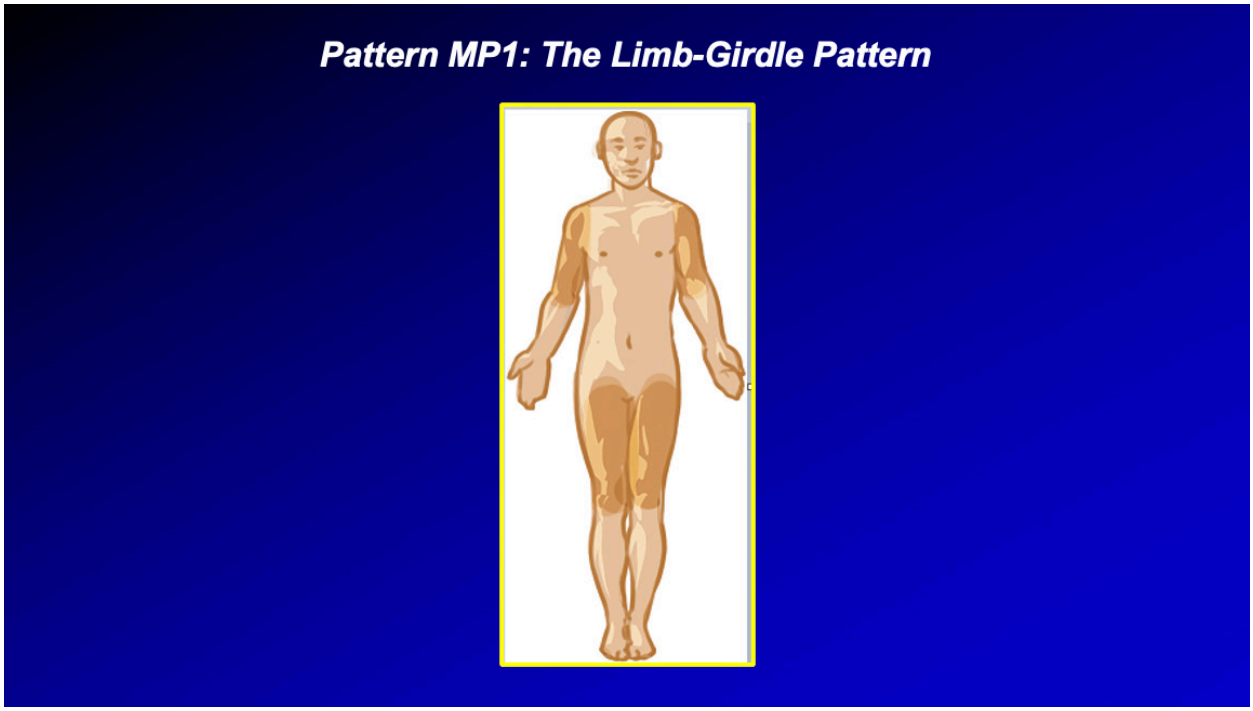
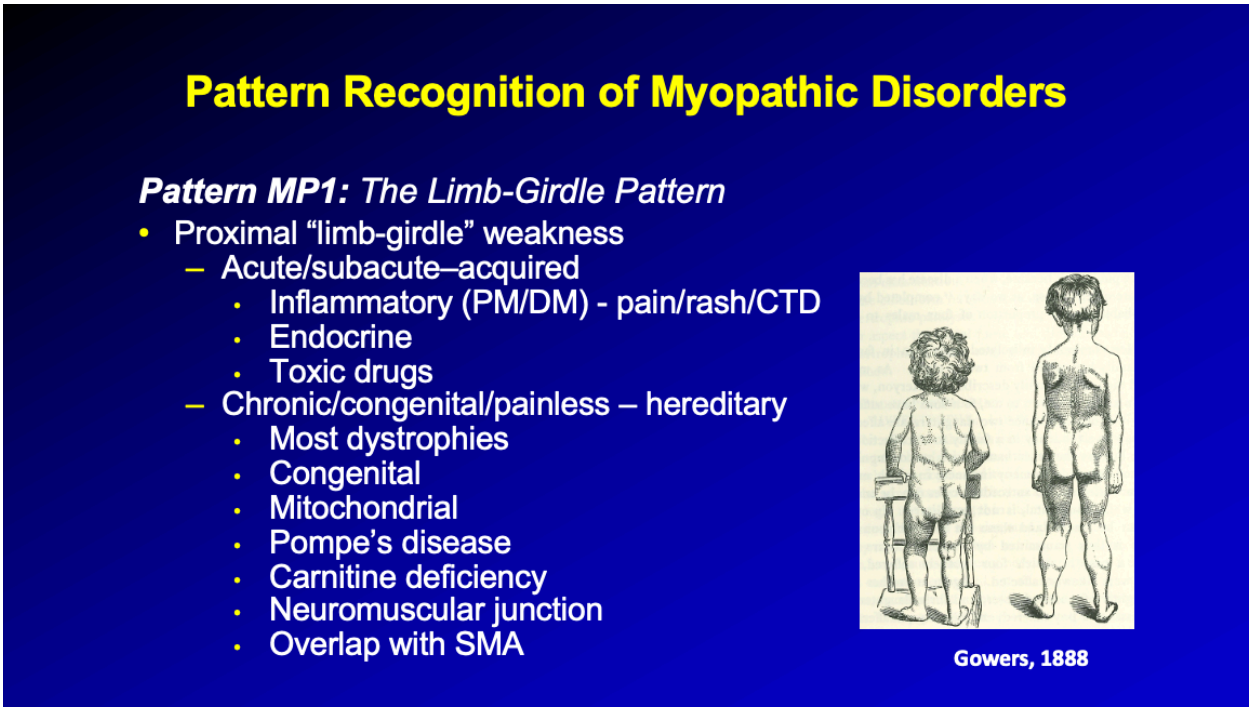


Figure 12



The drawing in Figure 12 comes from Gower's classic textbook A Manual of Diseases of the Nervous System (1888) and shows two brothers of ages 4 and 7 with what later was known as Duchenne muscular dystrophy (DMD). In the textbook, Dr. Gowers referred to the entity as "pseudo-hypertrophic muscular paralysis" because that was the term that Duchenne used in his original classic description from 1868. The drawing also shows calf hypertrophy which is typical of DMD. Figure 13 also comes from Gower's textbook and shows a young boy getting up off the floor and using his arms because he had proximal leg weakness. This observation is now known as Gower's sign. Another figure from the Gower's textbook shows a 14-year-old boy in the later stages of DMD with muscular contraction, wasting, and scoliosis.

Figure 13

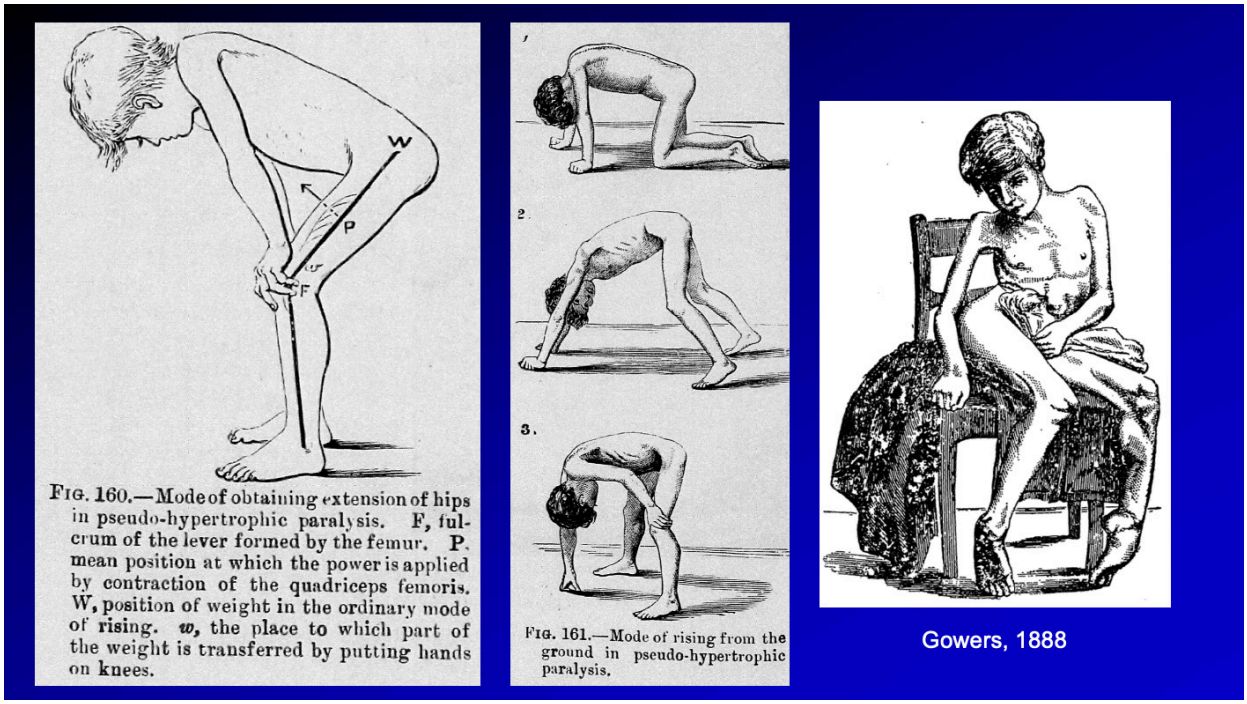


FIG. 160.—Mode of obtaining extension of hips in pseudo-hypertrophic paralysis. F, fulcrum of the lever formed by the femur. P, mean position at which the power is applied by contraction of the quadriceps femoris. W, position of weight in the ordinary mode of rising. *w*, the place to which part of the weight is transferred by putting hands on knees.

FIG. 161.—Mode of rising from the ground in pseudo-hypertrophic paralysis.

The limb-girdle pattern is the most common presentation of myopathies. A patient with an acute or subacute limb-girdle pattern is more likely to have an acquired disorder. A patient with a chronic limb-girdle pattern is more likely to have a hereditary disorder. There are often exceptions to this rule.

MP2: Distal pattern. (Figure 14)

Figure 14

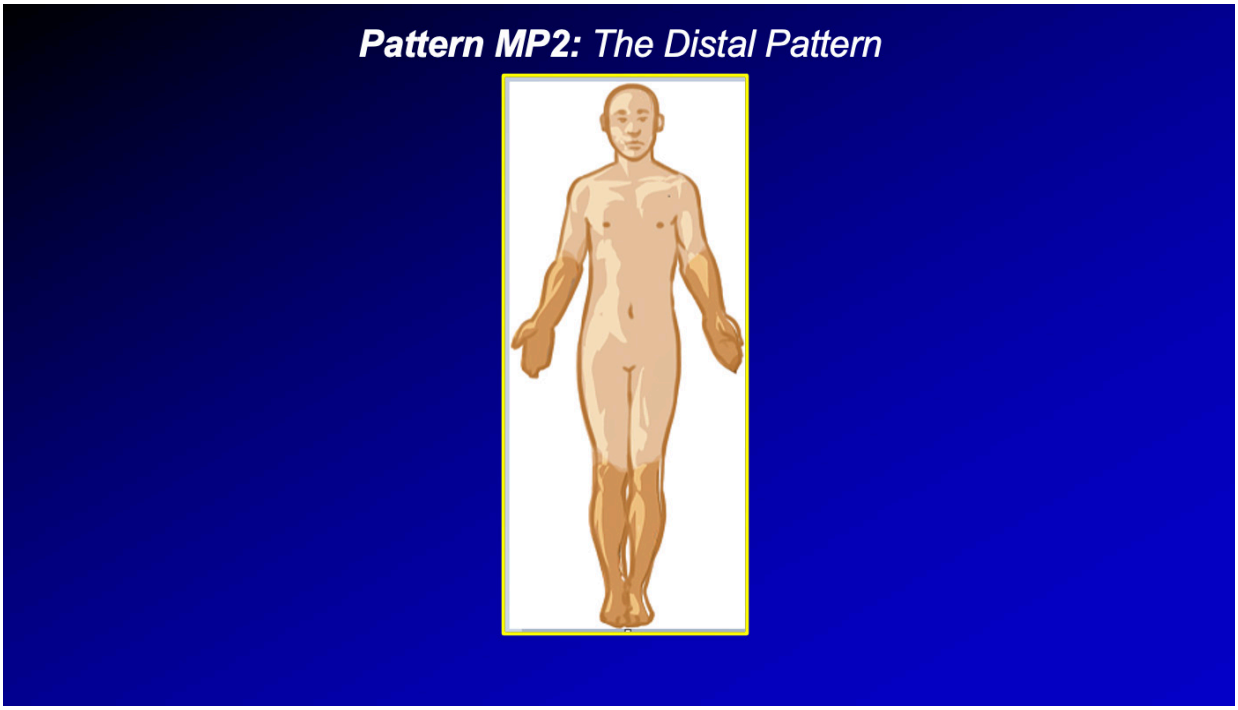
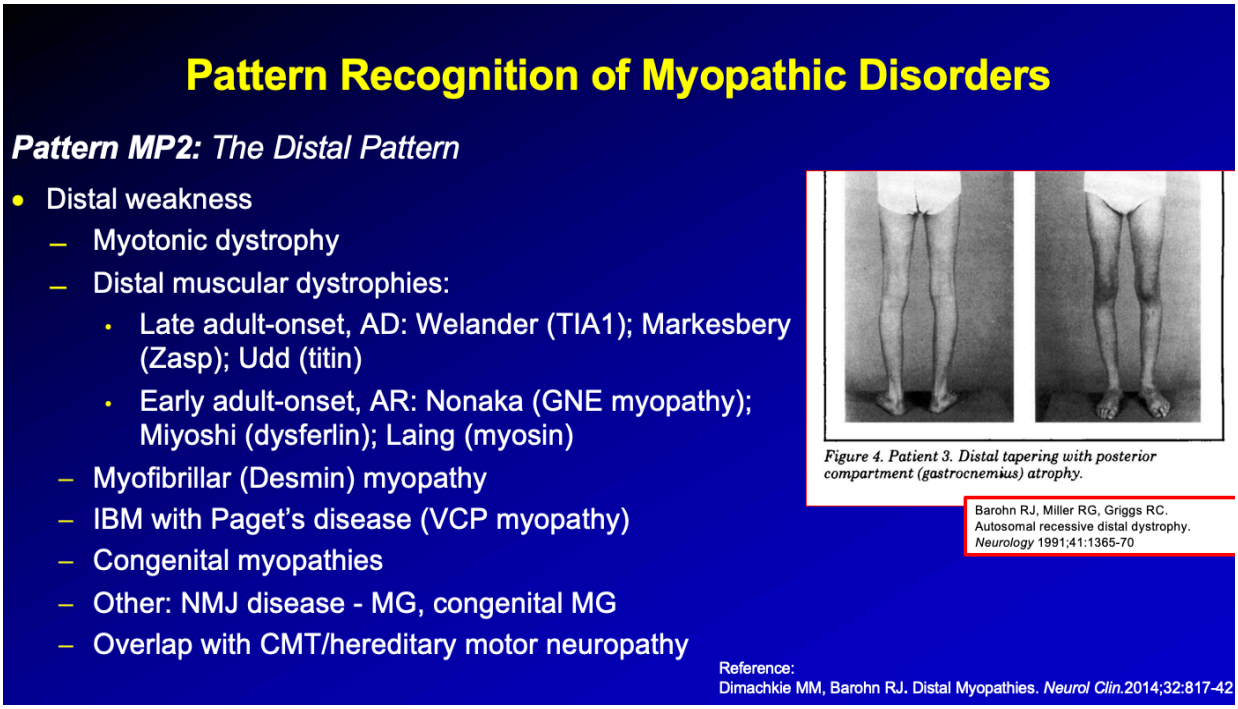


Figure 15



Myopathies with the distal pattern present with distal hand or leg weakness with relatively normal proximal muscle strength, at least initially. The most common muscle disorder that has a distal presentation is myotonic dystrophy which frequently has hand grip weakness and sometimes ankle weakness with very little proximal weakness.

Very rare disorders also come into this distal pattern group, particularly the distal muscular dystrophies. In this group, there are late adult onset distal muscular dystrophies that are autosomal dominant such as Welander (TIA1), Markesbery (Zasp), and Udd (titin) myopathies.

In addition, there are also early adult-onset distal muscular dystrophies that are autosomal recessive such as Nonaka (GNE myopathy), Miyoshi (dysferlin), and Laing (myosin) myopathies.

Other distal myopathies include myofibrillar (desmin) myopathy, hereditary inclusion body myopathy with Paget's disease also known as Valosin-associated protein myopathy. Rarely, nonprogressive congenital myopathies can have a significant distal weakness (nemaline rod, central core, centronuclear myopathy). Myasthenia gravis can have a predominant distal presentation. Usually, this involves finger extension, but ankle dorsiflexion can also be weak. Finally, some of the congenital myasthenia syndromes can have predominant distal weakness. A distal pattern of weakness can also be seen in hereditary motor neuropathy.

MP3: The proximal arm/ distal leg pattern (Scapuloperoneal) (Figure 16)

Figure 16

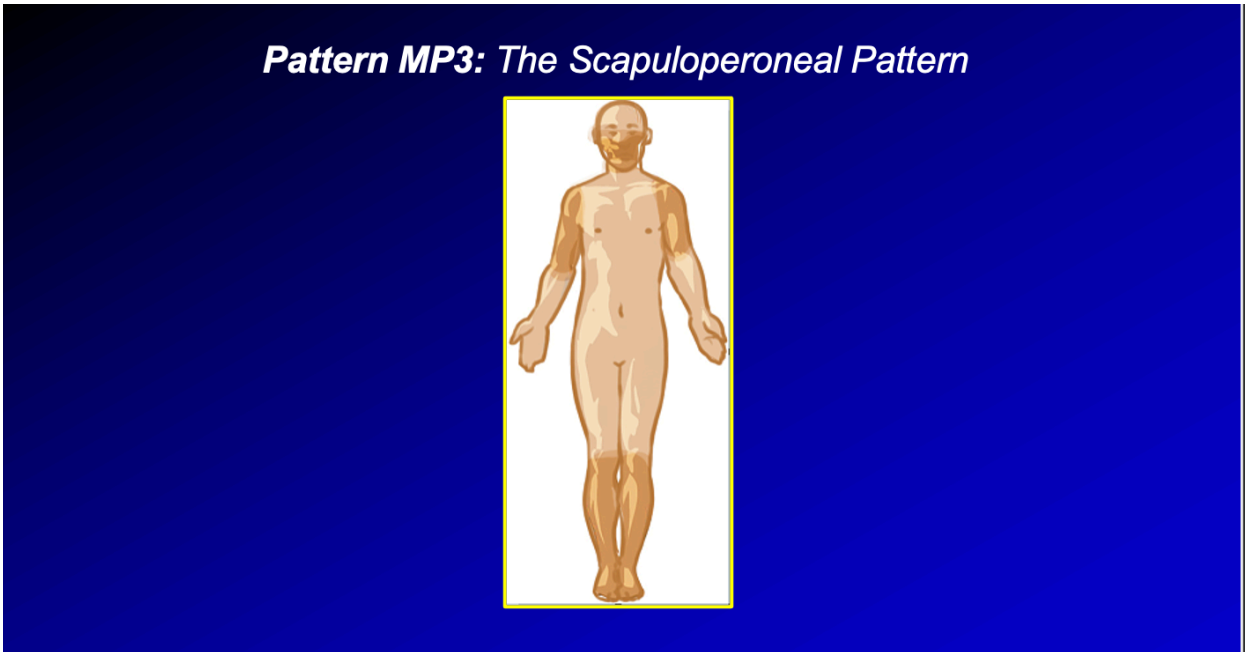
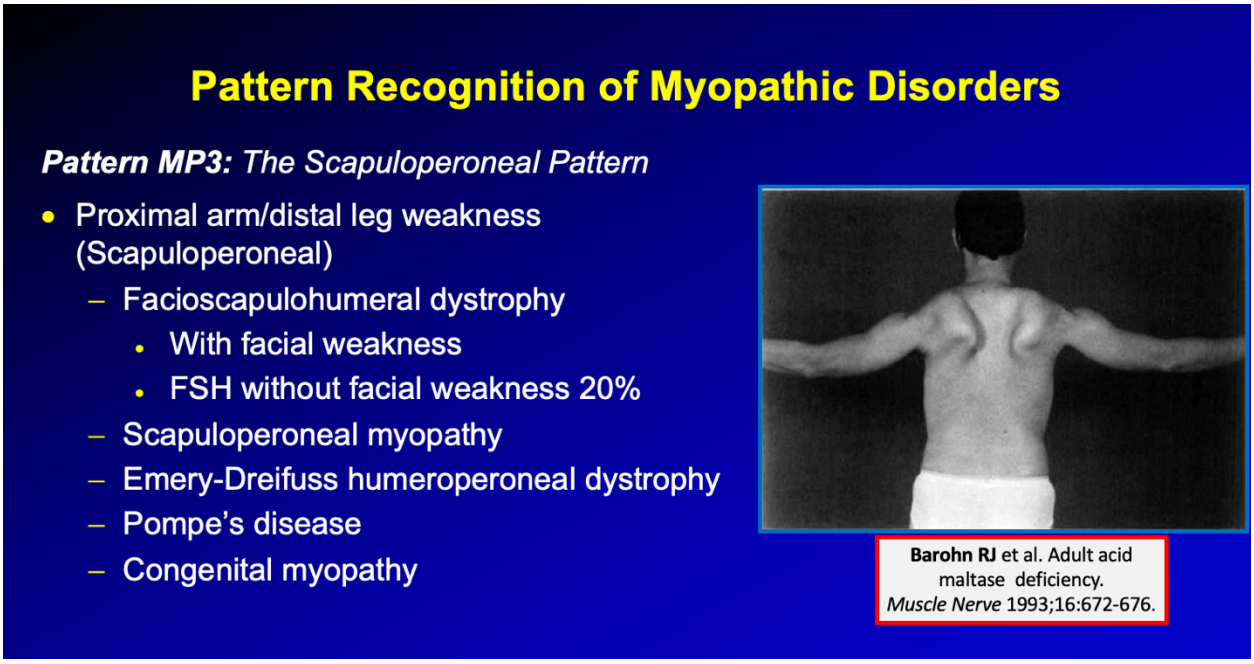


Figure 17



The MP3 pattern, also called the scapuloperoneal pattern involves scapular stabilizer muscles in the proximal arms and distal leg muscles. The distal leg involvement usually involves the tibialis anterior muscle and produces ankle dorsiflexion weakness. When facial muscles are involved, the disorder is almost always facioscapulohumeral dystrophy (FSHD). We now know through genetic capabilities that 80% of FSHD genetically positive individuals will demonstrate facial weakness, but some do not. There are other rare genetic causes of scapuloperoneal myopathy. Pompe's disease can present with a scapuloperoneal presentation, although most often it presents with an MP1 limb-girdle pattern. Emery-Dreifuss humeroperoneal dystrophy typically has a humeral peroneal pattern with prominent biceps and ankle dorsiflexion weakness, heart block, and mechanical contractures as previously noted. SANAM cases may have scapular winging in association with limb weakness.

Figure 18 shows a drawing from Gower's textbook demonstrating scapular winging due to weakness of the scapular stabilizer muscles.

Figure 18

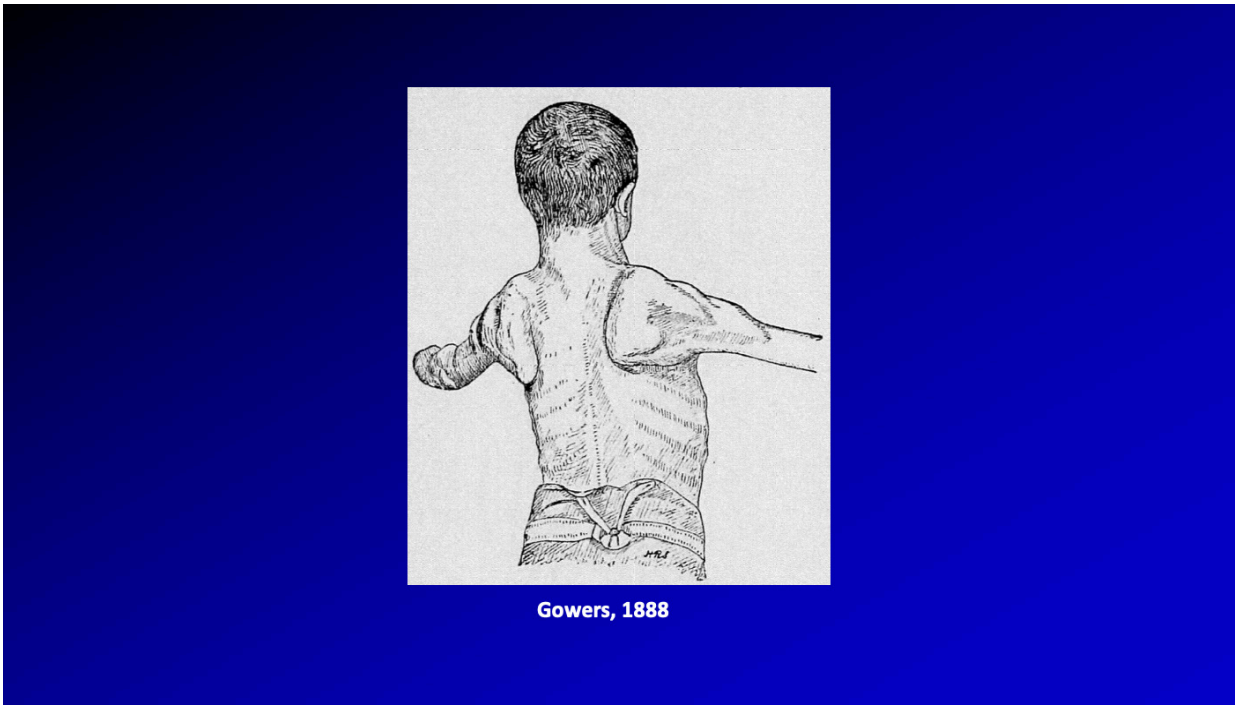


Figure 19 again comes from Gower's textbook and shows a 16 year old boy with orbicularis oculus weakness as well as weakness of the scapular stabilizer muscles and scapular winging that most likely represents a case of FSHD.

Figure 19

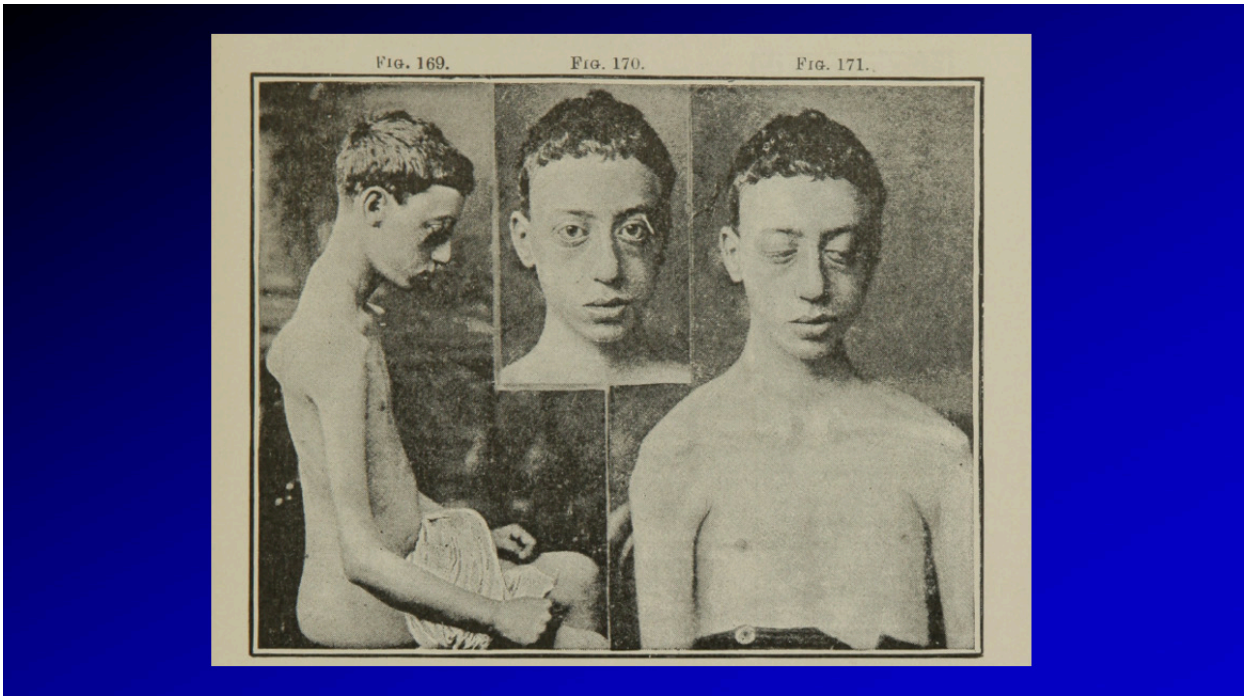
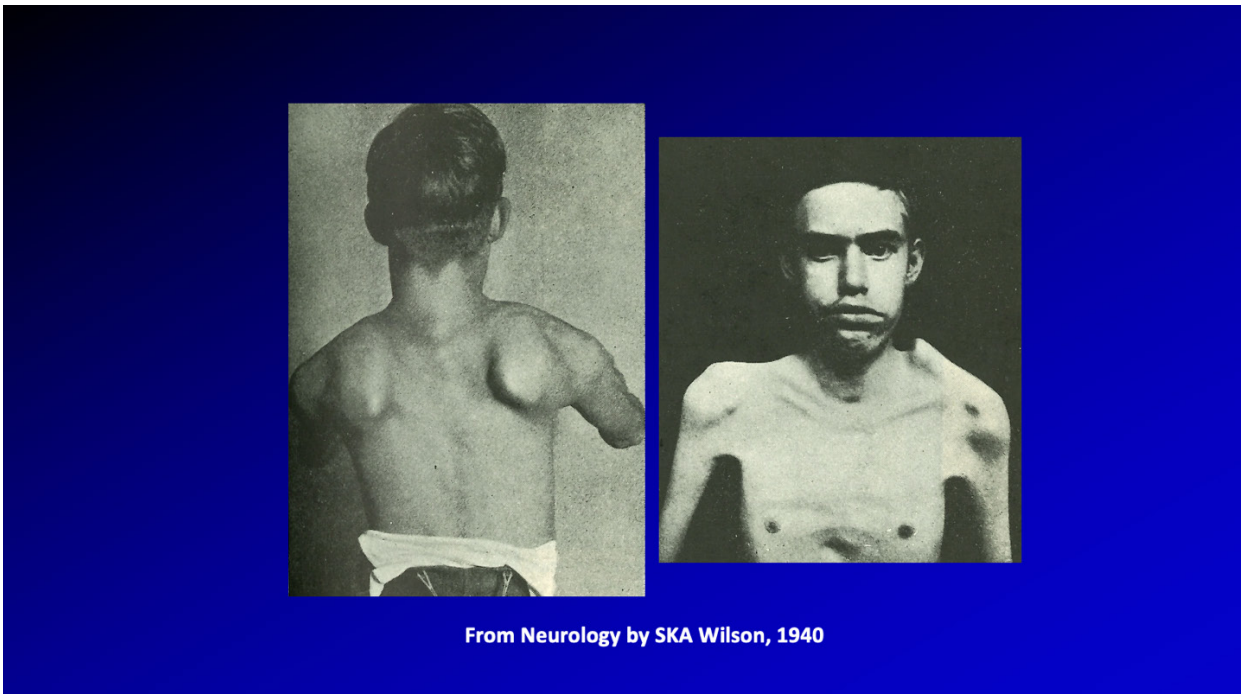


Figure 20 comes from another classic textbook called Neurology by S.A. Kinnier Wilson published in 1940 that shows a young man with FSHD who has scapular winging and facial weakness

Figure 20



MP4: The distal arm/ proximal leg pattern (The IBM Pattern) (Figure 21)

Figure 21

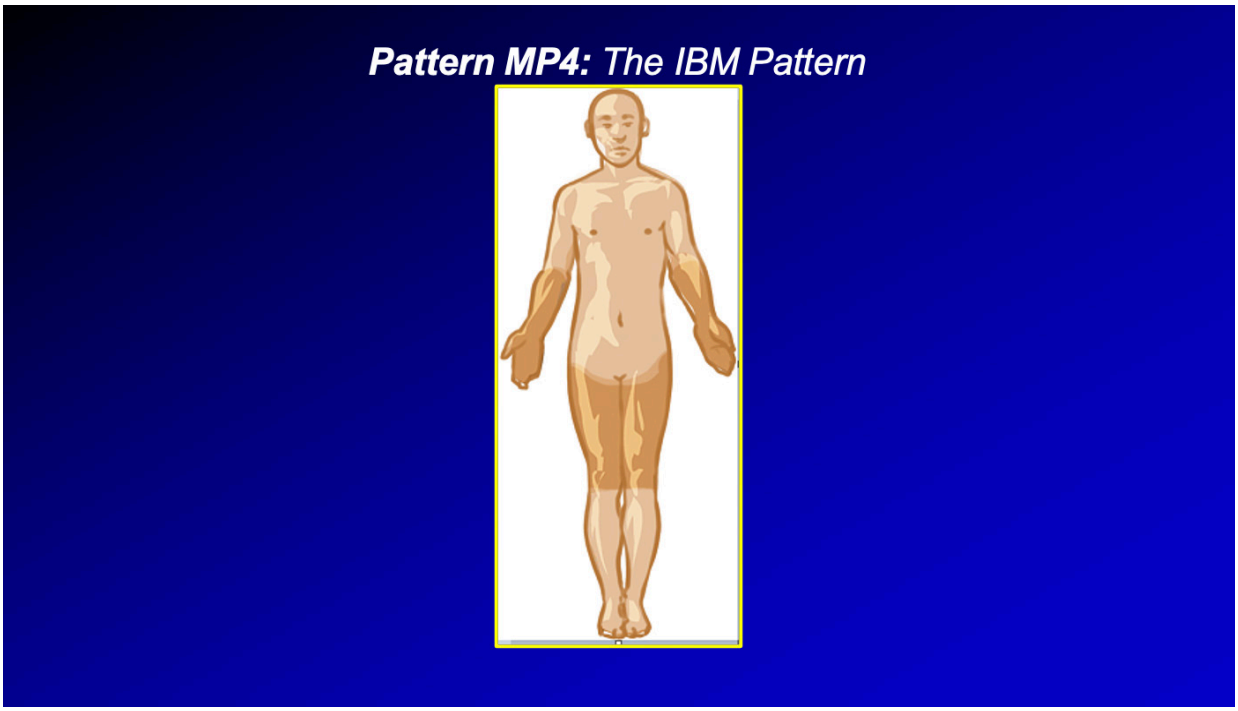
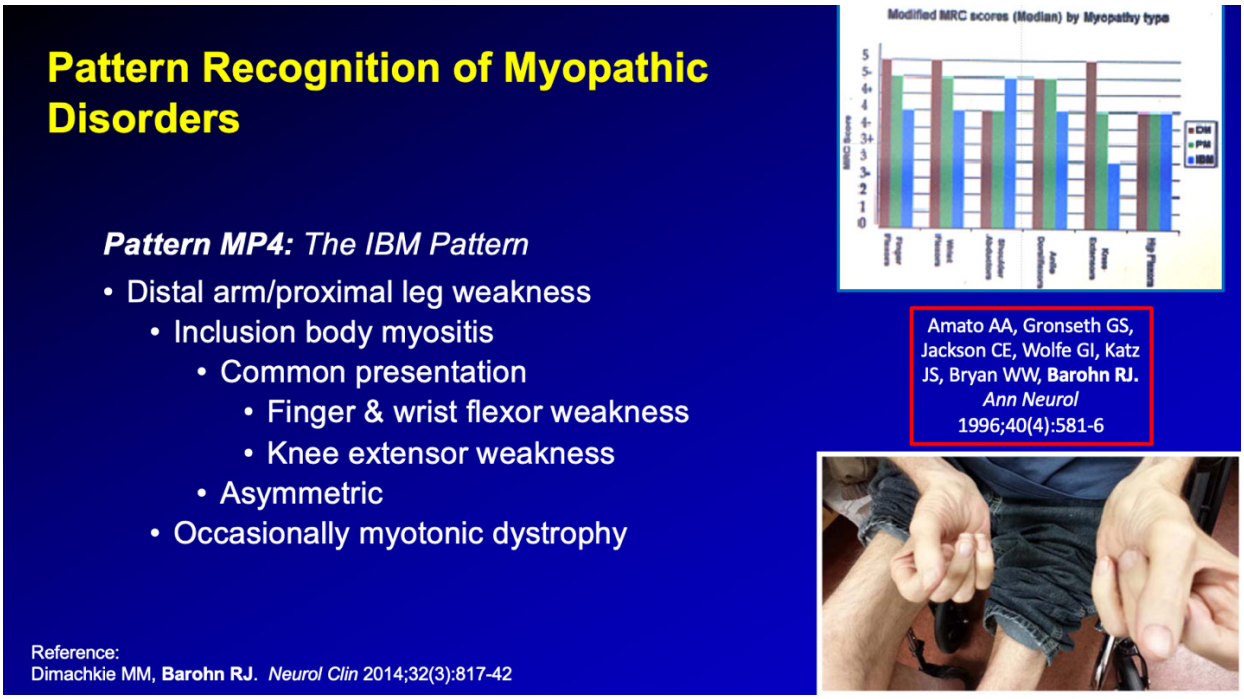


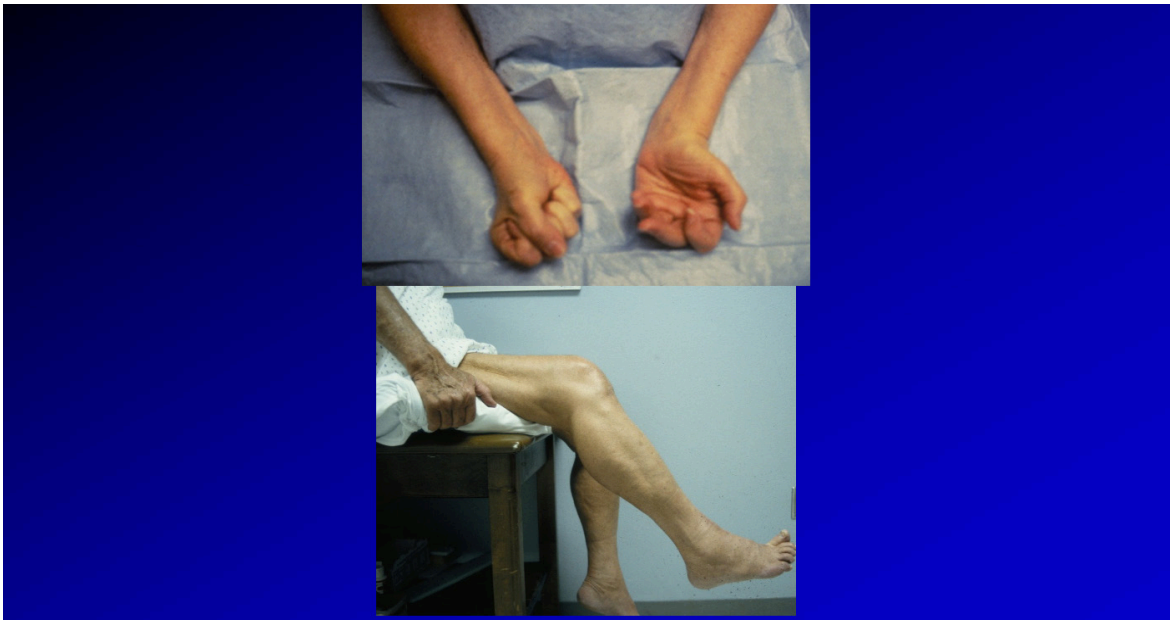
Figure 22



The MP4 pattern is the inverse of the MP3. In the MP4 the distal arm and proximal leg are predominantly involved. This is also called the IBM pattern because IBM is almost always the clinical diagnosis. These patients have prominent finger and wrist flexor weakness and knee extensor weakness. Often, the limb involvement is asymmetric with one side more affected than the other. Patients with IBM almost always have onset of weakness in the sixth decade of life or later. The only other muscle condition that can cause predominant finger flexor and knee extensor weakness is occasional cases of severe myotonic dystrophy. However, usually, there are enough other clinical features to indicate that the diagnosis is myotonic dystrophy and not IBM, for example, younger age of onset and characteristic facial appearance and balding in men and of course myotonia. Other confounders for this pattern are chronic sarcoid myopathy and rarely amyloid myopathy.

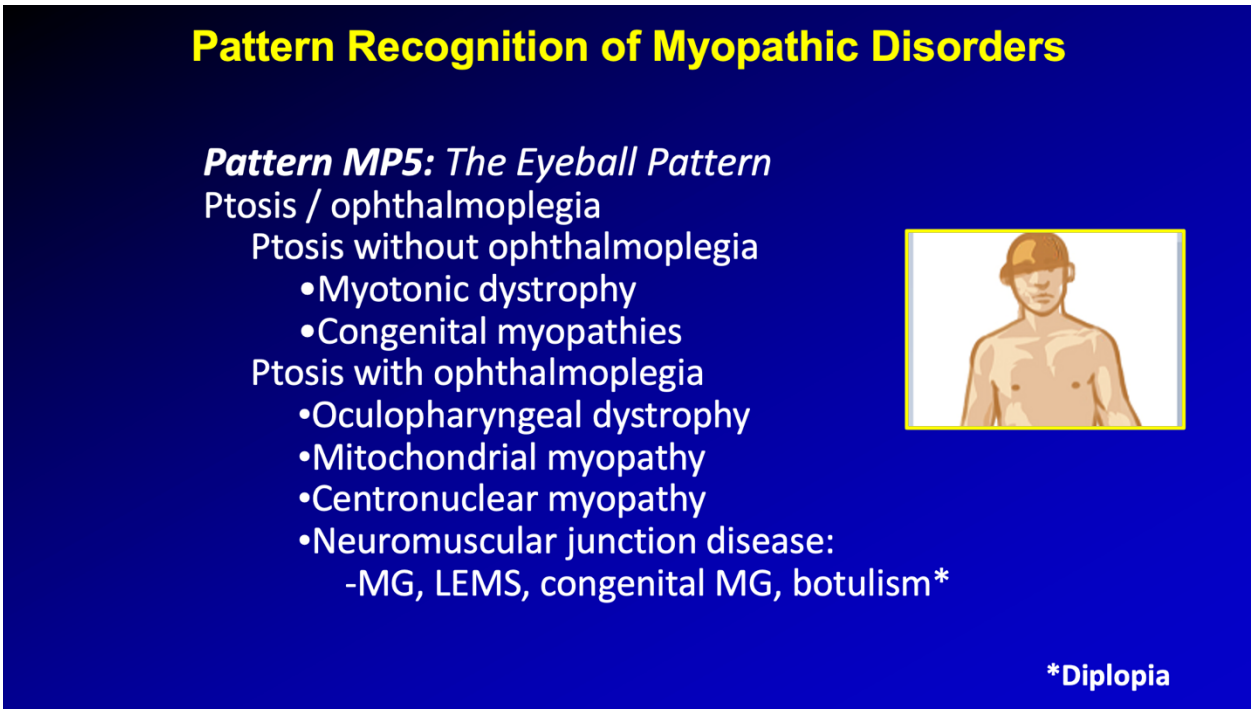
Figure 23 shows an IBM patient with distal forearm atrophy that is asymmetric, and they are having difficulty flexing their fingers.

Figure 23



MP5: The Eyeball Pattern. (Figure 24)

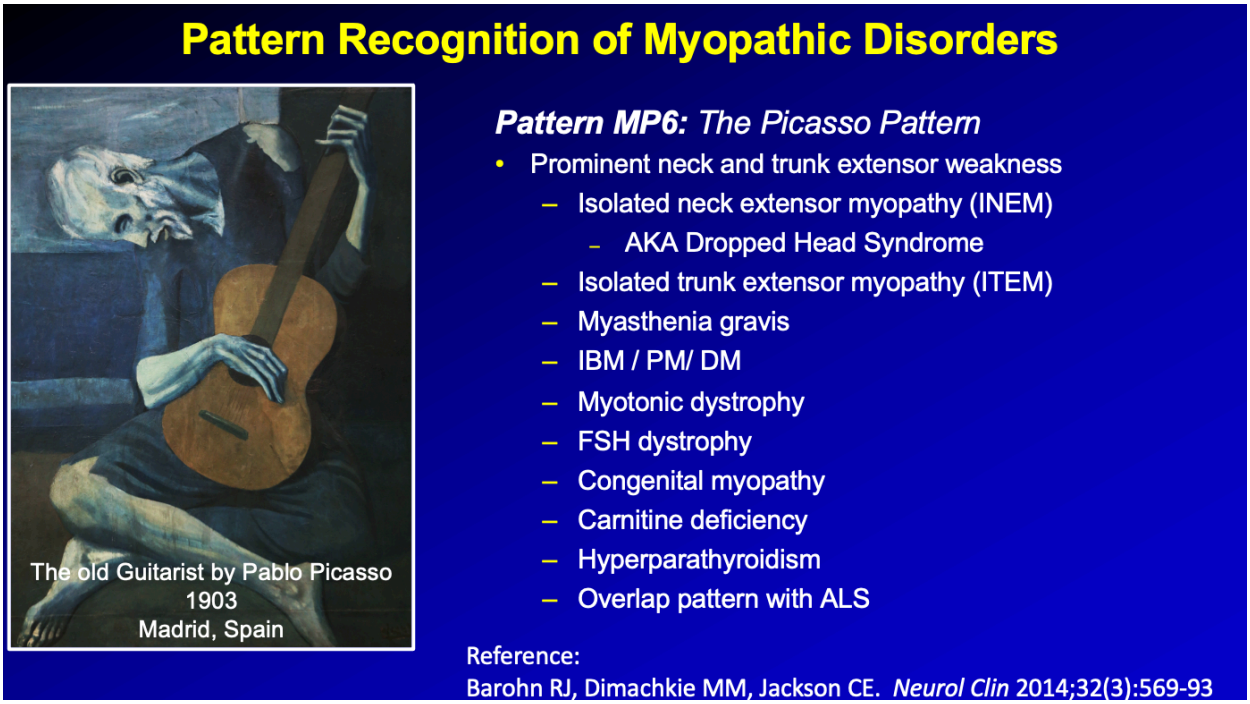
Figure 24



Ptosis without ophthalmoplegia is seen in myotonic dystrophy and congenital myopathies.
Ptosis with ophthalmoplegia is seen in oculopharyngeal dystrophy and mitochondrial myopathy.
It is also seen in X-linked centronuclear myopathies which are often male infants who are very floppy at birth, have ptosis and eye movement abnormalities. One primary difference between neuromuscular junction disorders such as myasthenia gravis versus oculopharyngeal dystrophy or mitochondrial myopathy is that neuromuscular junction disorders often have diplopia because of unequal extraocular muscle involvement. On the other hand, in oculopharyngeal muscular dystrophy (OPMD) and mitochondrial myopathy, even with very limited movement of the eyes there is usually no diplopia because all of the eye muscles are equally affected, though there are exceptions to this rule.

MP6: Neck and trunk extensor pattern (Dropped head or dropped body syndrome) (Figure 25)

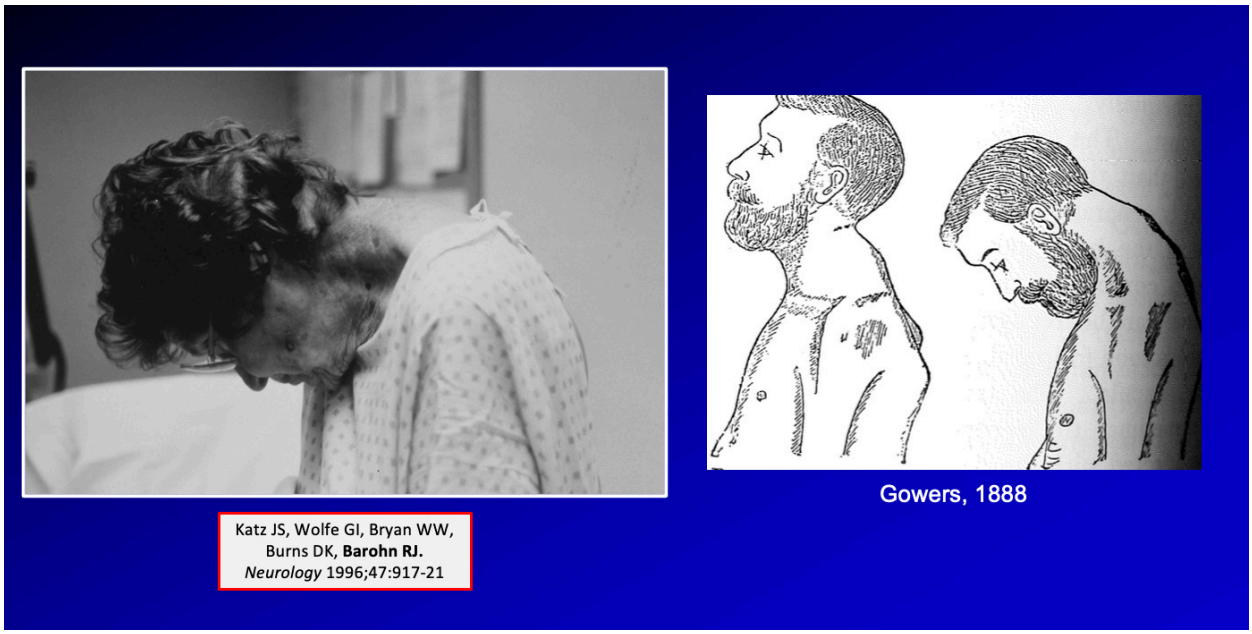
Figure 25



The MP6 pattern is demonstrated in Figure 26 which shows an elderly woman who cannot raise up her head. She has neck extension weakness due to weakness of the cervical paraspinous muscles. This is the MP6 pattern that can have either prominent neck or trunk extensor weakness, and occasionally both. The woman in Figure 26 has isolated neck extensor myopathy. We described a series of these patients in the 1990s however this pattern has been appreciated before and since then. We do not know the cause of this condition that we call isolated neck extensor myopathy (INEM). It is considered to be an idiopathic neck drop in the elderly due to weakness of the cervical paraspinous muscles. It does not respond to treatment with drugs, but it is benign in that it does not progress to other muscles or lead to death. There is a trunk form of this as well which we call isolated trunk extensor myopathy (ITEM). This is also untreatable with medications. There are a number of other muscle conditions that have been reported to be associated with neck drop such as myositis but these patients generally always begin with limb weakness, usually an MP1 pattern. Myasthenia gravis can have predominant neck extensor weakness causing a head drop. Patients often present holding their head up by placing their hand under their chin, they almost always have other features of myasthenia gravis that will lead to the diagnosis such as MP5 eyeball pattern or MP7 bulbar pattern (see below). Myasthenia gravis is of course very amenable to treatment and the head drop can usually be reversed.

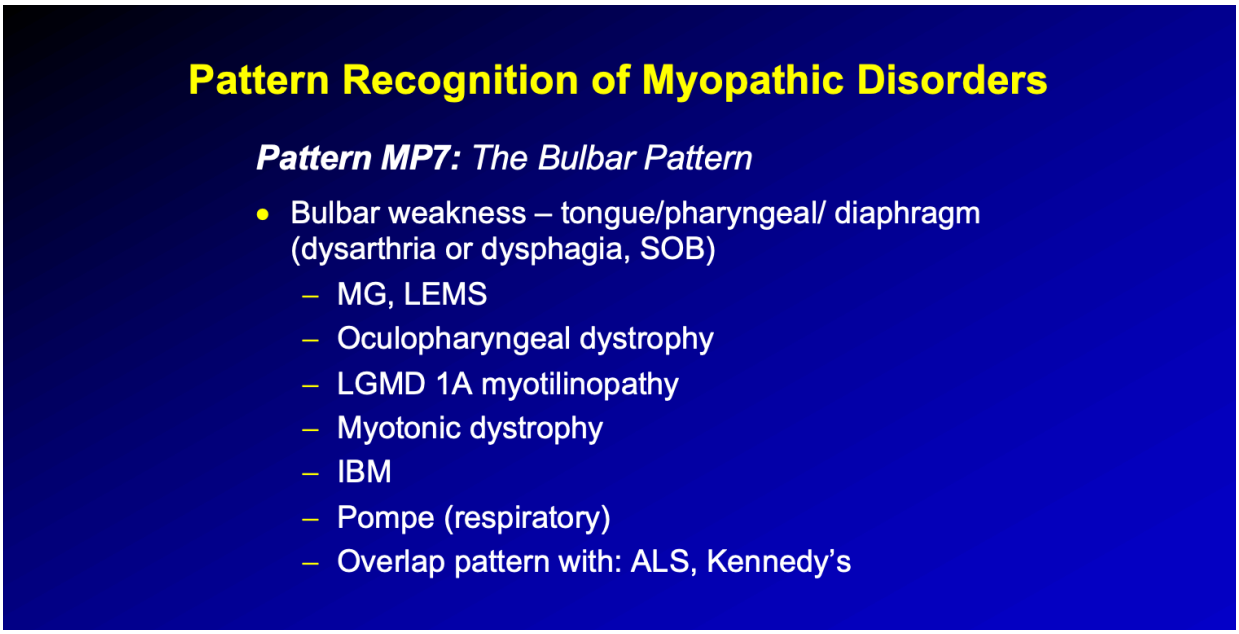
On the other hand, a neuropathic anterior horn cell condition that can cause severe head drop or trunk drop is amyotrophic lateral sclerosis (ALS). This of course is not benign and progresses resulting in death. Therefore, when a patient presents with head drop, usually the big three conditions to consider are INEM which is not treatable but benign, MG which is treatable, and ALS which is non-treatable and progressive. Figure 26 also shows another drawing in Gower's textbook of a man with head drop due to muscle weakness. We do not know the etiology of this middle-aged man's neck muscle weakness, but his probable middle age would suggest that it is not INEM but more likely another neuromuscular cause.

Figure 26



MP7: The bulbar pattern. (Figure 27)

Figure 27



Patients with the bulbar pattern have dysarthria, dysphagia, or shortness of breath due to a myopathic disorder. Myasthenia gravis patients commonly can present with a combination of these bulbar symptoms and signs. Occasionally Lambert-Eaton myasthenic syndrome (LEMS), another neuromuscular junction disorder, can as well but it more often presents with the MP1 pattern, and the bulbar symptoms are either not present or very subtle. The clinical triad of LEMS is proximal weakness, hypo or areflexia and dysautonomia .

Oculopharyngeal muscular dystrophy (OPMD) can present with both eye symptoms as well as dysarthria and dysphagia.

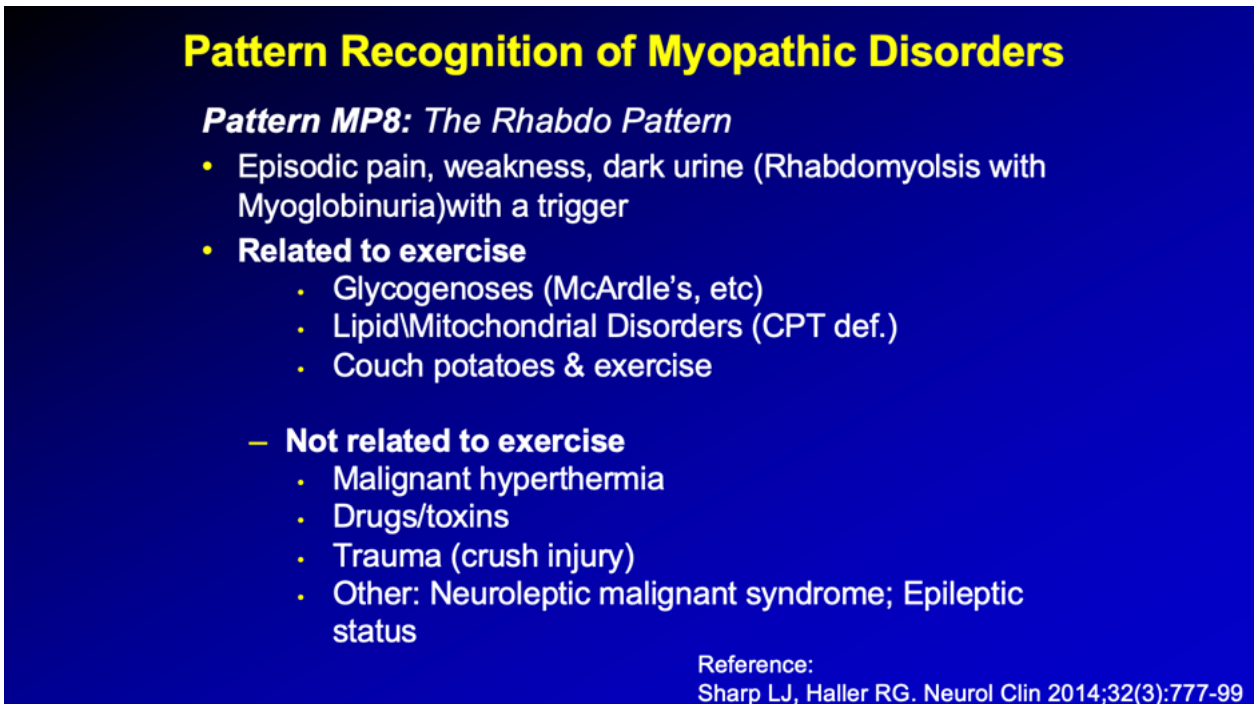
One of the limb-girdle muscular dystrophies (LGMD) with an MP1 pattern can also have prominent dysarthria-autosomal dominant myofibrillar myopathy 3 (previously LGMD 1A) due to myotilin gene defect.

Myotonic dystrophy and IBM both have prominent dysphagia.

Pompe disease is a lysosomal storage disorder that can have a significant diaphragm muscle involvement causing shortness of breath, usually in the context of MP1 or an MP3 pattern as well.

MP8: The Rhabdo pattern. (Figure 28)

Figure 28



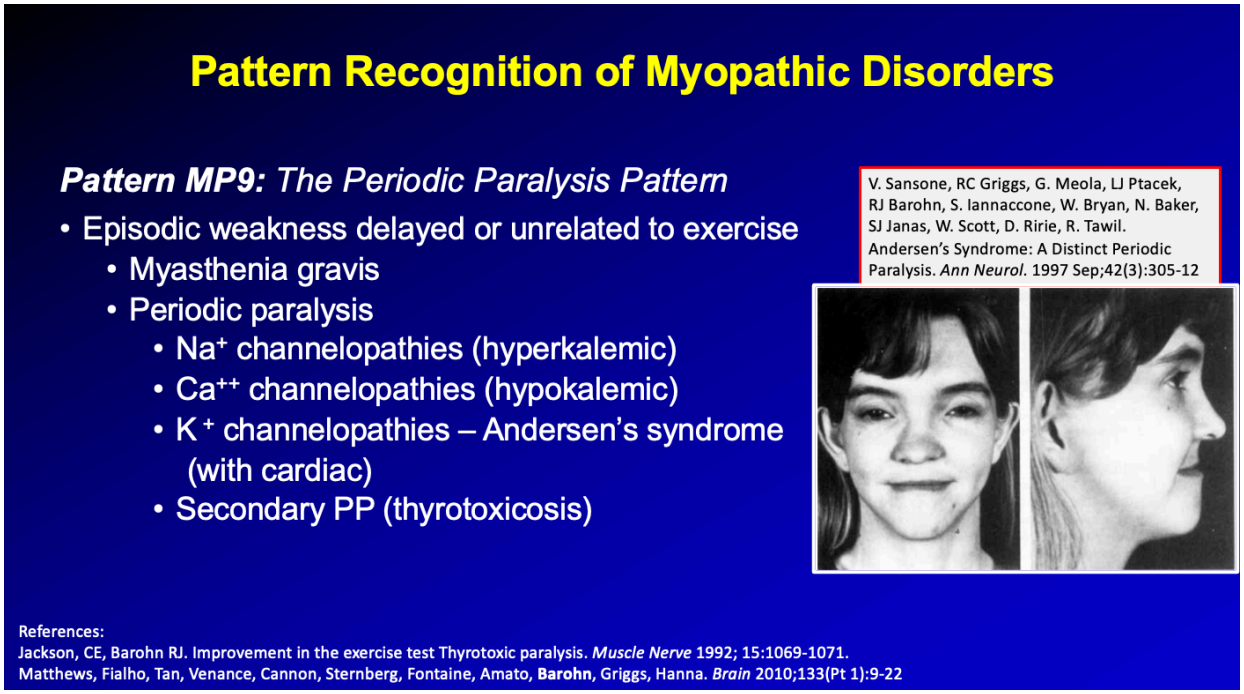
MP8 or the "rhabdo pattern", has episodic pain, weakness, and dark colored urine. There is always a trigger setting off the episode of rhabdomyolysis and myoglobinuria. When the trigger is exercise you need to consider whether it is from brief exercise, in which case there is usually an underlying glycogen disorder such as McArdle's disease. On the other hand, if the trigger is prolonged exercise, the underlying disorder is more likely to be a lipid metabolic disorder such as CPT deficiency or a mitochondrial disorder. Some of these patients who have exercise as a trigger do not have an underlying metabolic myopathy and they have simply been inactive for a prolonged period of time and are suddenly put under extraordinary conditions of exercise that can result in muscle injury. We often see the phenomenon in military recruits who are required to do intense exercise that they have never been exposed to and this can set off rhabdomyolysis and myoglobinuria. When delayed in onset by 1-2 days after exercise, this suggests delayed onset muscle soreness (DOMS).

When these patients are worked up, frequently you will not find an underlying glycolytic, lipid, or mitochondrial disorder. They have simply extended their ability to exercise beyond their capacity. We sometimes have also called this the "couch potato syndrome".

Other triggers that are not exercise-related include anesthesia-associated malignant hyperthermia, drugs/ toxins, trauma, neuroleptic malignant syndrome, and status epilepticus.

MP9: The episodic pattern. (Figure 29)

Figure 29

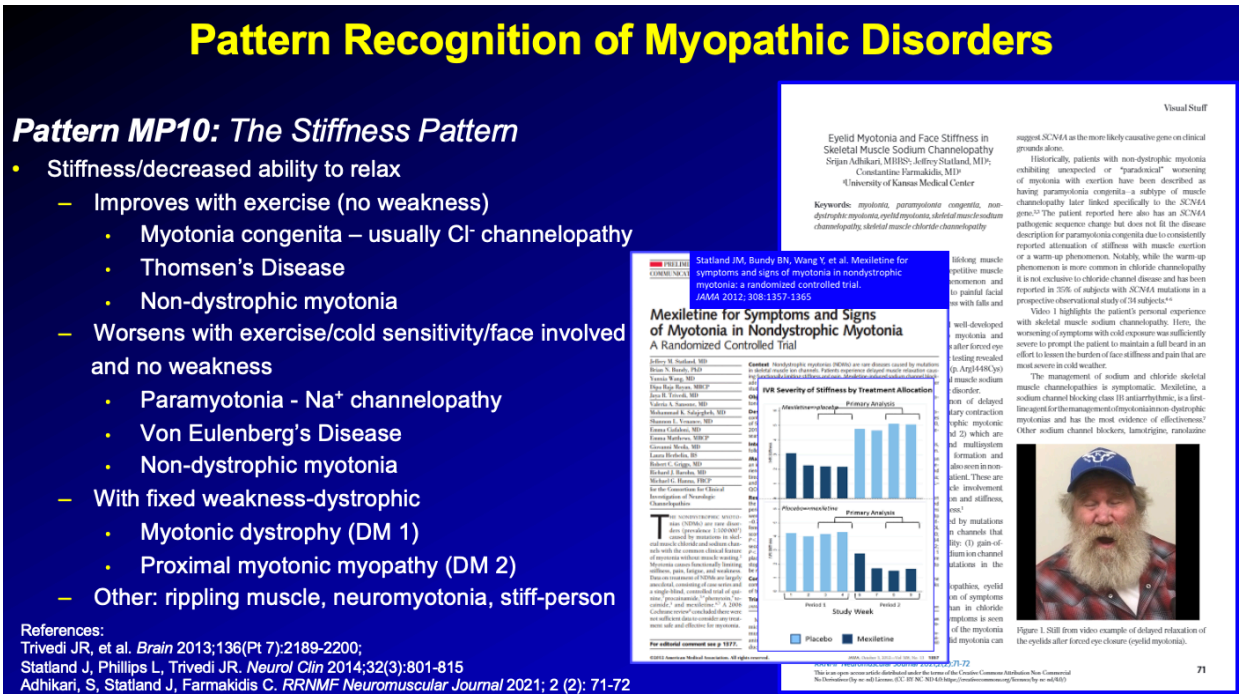


MP9 is the periodic paralysis pattern in which there is episodic weakness that is delayed or unrelated to exercise. There is no associated rhabdomyolysis or myoglobinuria, no pain, and no underlying metabolic disorder. MP9 is usually caused by muscle channelopathies. We also include neuromuscular junction disorders in this pattern because we are often taught that myasthenia gravis weakness is set off by exercise. However, for those who are experienced clinicians who take care of myasthenia gravis patients, we find that frequently you cannot get that history from the patient. Myasthenia gravis patients can have weakness unrelated to exercise nevertheless because it does occur at times, we include it in the MP9 pattern.

The main purpose of discussing the MP9 pattern is to remind you about periodic paralysis. This can be due to a sodium channelopathy that is usually hyperkalemic, a calcium channelopathy that is usually hypokalemic, or a potassium channelopathy which is the rare Andersen's syndrome. There are also secondary causes of periodic paralysis and the most common is thyrotoxicosis.

MP10: The stiffness pattern. (Figure 30)

Figure 30



Video link: https://www.youtube.com/watch?v=lyl0dPKrd2w

MP10 is the "stiffness or decreased ability to relax pattern". This is layman's terminology for myotonia. If stiffness improves with exercise and the patient is not weak, the underlying disorder is usually chloride channelopathy also known as myotonia congenita. This is one of the forms of non-dystrophic myotonia.

On the other hand, if the stiffness worsens with exercise, and is extremely cold-sensitive, particularly involving the face, and there is no weakness the underlying disorder is usually a sodium channelopathy. Sodium channelopathies are another form of non-dystrophic myotonias that are also called paramyotonia or paradoxical myotonia. The term paradoxical is used because other myotonias get better with exercise whereas paradoxical myotonia gets worse with exercise.

When there is fixed weakness with a myotonic disorder, the underlying diagnosis is usually myotonic dystrophy. Autosomal recessive chloride channelopathy present with myotonia and proximal weakness. The most common myotonic dystrophy is DM1 in which there is a significant amount of distal weakness, facial weakness, and other systemic involvement. Proximal myotonic myopathy is also known as DM2 and in these patients, the weakness is predominantly in a limb-girdle MP1 pattern but there are also varying degrees of myotonia which sometimes can be subtle. DM2 patients often also complain of myalgias.

Interestingly, no matter what type of myotonia or paramyotonia the patient may have, sodium channel-blocking drugs such as mexiletine dramatically improve myotonia symptoms and signs. The use of mexiletine for myotonic disorders is off-label and not FDA-approved .

EXCEPTIONS TO MYOPATHIC PATTERNS

There are exceptions to the pattern recognition approach of myopathic disorders. Two are noteworthy. Some dystrophinopathies present not with MP1 limb-girdle weakness but instead, present an MP8 pattern and have episodic pain and dark red urine. Patients with these dystrophinopathies usually have Becker muscular dystrophy (BMD) rather than early-onset DMD which always has an MP1 pattern.

Another exception is McArdle's disease which typically presents with the MP8 rhabdomyolysis pattern. However, we and others have noted that there are patients who present late in life with an MP1 limb-girdle pattern who have McArdle's disease and who cannot provide a good history for exercise and tolerance and rhabdomyolysis. (Figure 31).

Figure 31

Exceptions to Pattern Recognition Approach to Myopathic Disorders

1. Dystrophinopathies with episodic pain, dark/red urine (MP8, NOT MP1!)

2. Late-life McArdle's disease with fixed limb-girdle weakness; not episodic (MP1, NOT MP8!)

Figure 32

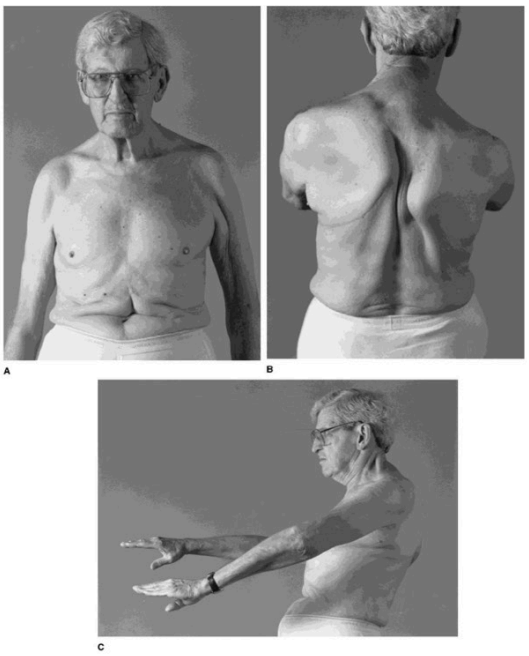


FIGURE 1. Muscle atrophy and weakness of shoulder girdle and proximal upper limb musculature. Note the prominent skin crease in the left upper arm (A) and the marked scapular winging (B). Asymmetric weakness of shoulder girdle musculature is evident, with poorer shoulder flexion on the left side (C).


CASE OF THE MONTH

ABSTRACT: McArdle's disease or myophosphorylase deficiency is one of the most common muscle glycogenoses and typically presents in childhood or adolescence with exercise intolerance, myalgia, myoglobinuria, and cramps in exercising muscle. We describe an elderly man who developed asymmetric proximal arm weakness at age 72. He had no history of exercise-induced cramps, myalgias, or myoglobinuria. Creatine kinase levels were elevated, serum lactate did not rise on ischemic exercise testing, and muscle biopsy showed a vacuolar myopathy with absent myophosphorylase activity. This unusual case demonstrates that McArdle's disease may present with fixed, asymmetric proximal weakness at an advanced age and should be considered in this clinical setting, especially when a history of poor exercise tolerance can be elicited.

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McARDLE'S DISEASE PRESENTING WITH ASYMMETRIC, LATE-ONSET ARM WEAKNESS

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McArdle's disease (glycogenosis type V) is an autosomal recessive muscle disorder due to myophosphorylase deficiency.[1] Myophosphorylase initiates the breakdown of glycogen to liberate glucose-1-phosphate.[2] The gene for myophosphorylase has been cloned, sequenced, and localized to chromosome 11q13.[3,4,5] Genetic mutations include single base substitutions causing missense or nonsense mutations and base-pair or codon deletions.[5,20–22] The R49X nonsense mutation in exon 1 accounts for the most common mutant allele in patients from North America and northern Europe.[5,20,23] McArdle's disease classically is associated with lifelong exercise intolerance. It typically presents in the first two decades of life with easy fatigability, painful muscle contractures referred to as cramps, and myoglobinuria induced by vigorous exercise.[3,5,13–15] The disease is known to present later in life in the form of symmetric, slowly progressive, limb weakness with a lesser degree of exercise intolerance. We describe a very late presentation of McArdle's disease in an elderly man who at age 73 developed asymmetric atrophy and weakness in the upper extremities.

CASE REPORT

An 83-year-old man of Swedish–Finnish heritage developed proximal left arm weakness at age 73 followed by right arm weakness at age 80. There was no pain or sensory loss, and his legs were not involved. As an adolescent, he was physically active and played sports, and later served in the U.S. Navy during World War II. After the war, he worked as a business executive until his retirement. On close questioning, he recalled experiencing fatigue and feeling short-winded after brief, vigorous exertion or when beginning lower intensity exercise such as walking briskly or serving as a golf caddy. For instance, while playing baseball, he could never run beyond second base to stretch a long hit into a triple or home run. After 10 to 15 min of moderate exertion, however, there was a second-wind phenomenon and his dyspnea would disappear. He could subsequently complete four rounds of golf in a day or walk briskly for several hours without any fatigue. There was no history of muscle cramping, myalgias, or pigmenturia. Family history was negative for neuromuscular disease.

On examination, he had marked atrophy of the supraspinatus, infraspinatus, biceps, and triceps

Abbreviations: ADP, adenosine diphosphate; AMP, adenosine monophosphate; EMG, electromyography; FSH, facioscapulohumeral; PAS, periodic acid-Schiff
Key words: late-onset; McArdle's disease; myophosphorylase; weakness
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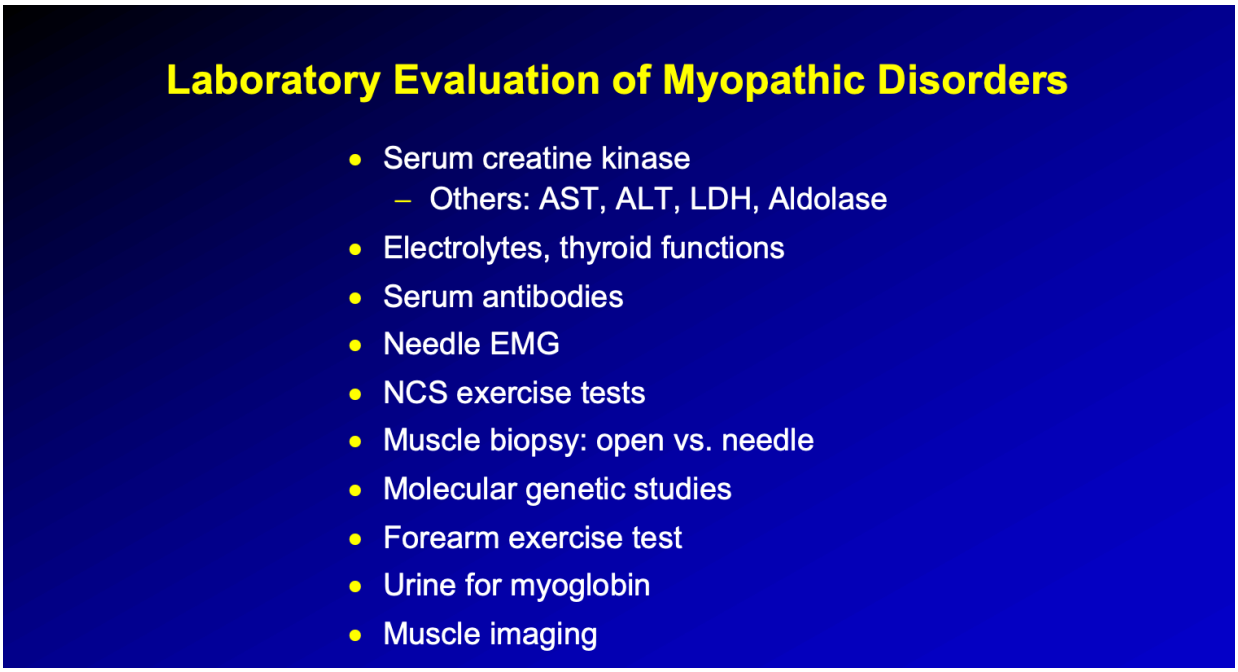
Asymmetric Weakness in McArdle's Disease MUSCLE & NERVE April 2000 641

Reference:
Wolfe al. *Muscle Nerve* 2000;23:641-645

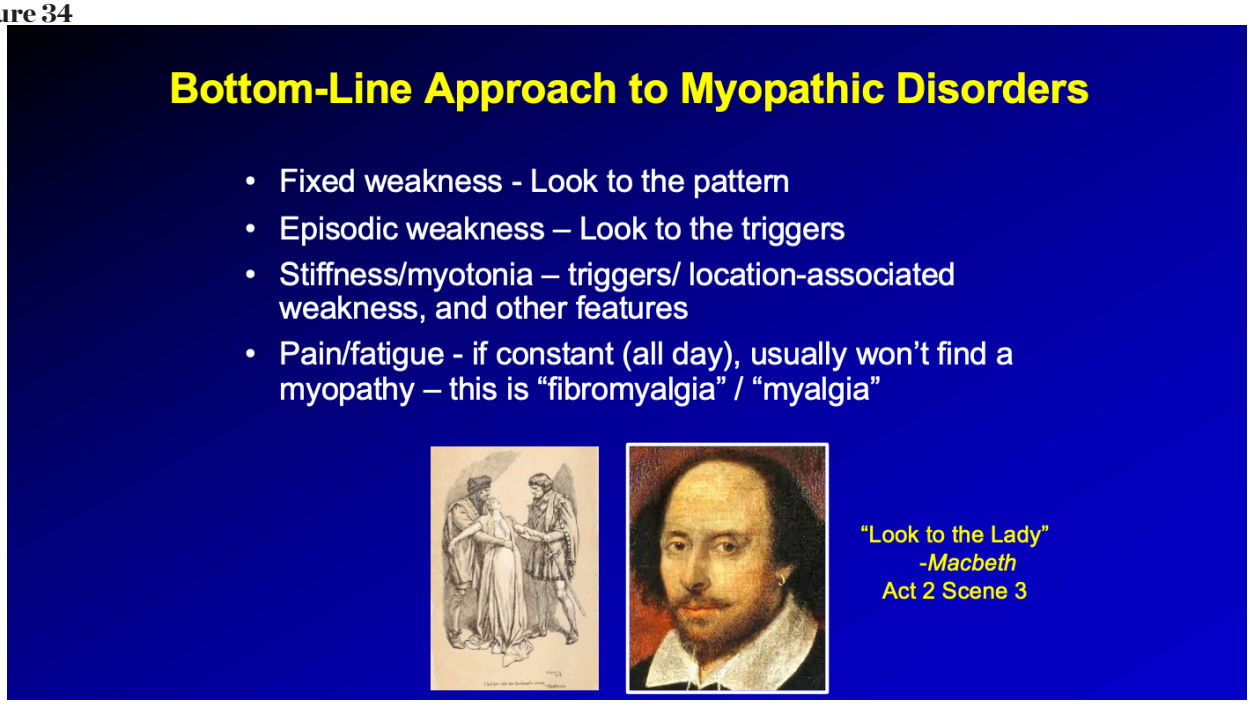
Summary
You should be using this pattern recognition approach to evaluate muscle disease before you order any laboratory or genetic tests. Once you put the patient provisionally in one of the ten patterns, then you can consider what diagnostic laboratory tests are needed (Figure 33)

Figure 33



The bottom-line approach to myopathic disorders is as follows (Figure 34):
If there is fixed weakness, look to the pattern; If there is episodic weakness, look to the trigger.
If there is stiffness or myotonia look to the trigger and location and if there is weakness.
If a patient has constant pain and fatigue, you usually will not find an underlying myopathic or neuromuscular junction disorder. The ten myopathic patterns are outlined in Figure 35.

Figure 34



Summary of Ten Clinical Myopathic Patterns
Figure 35

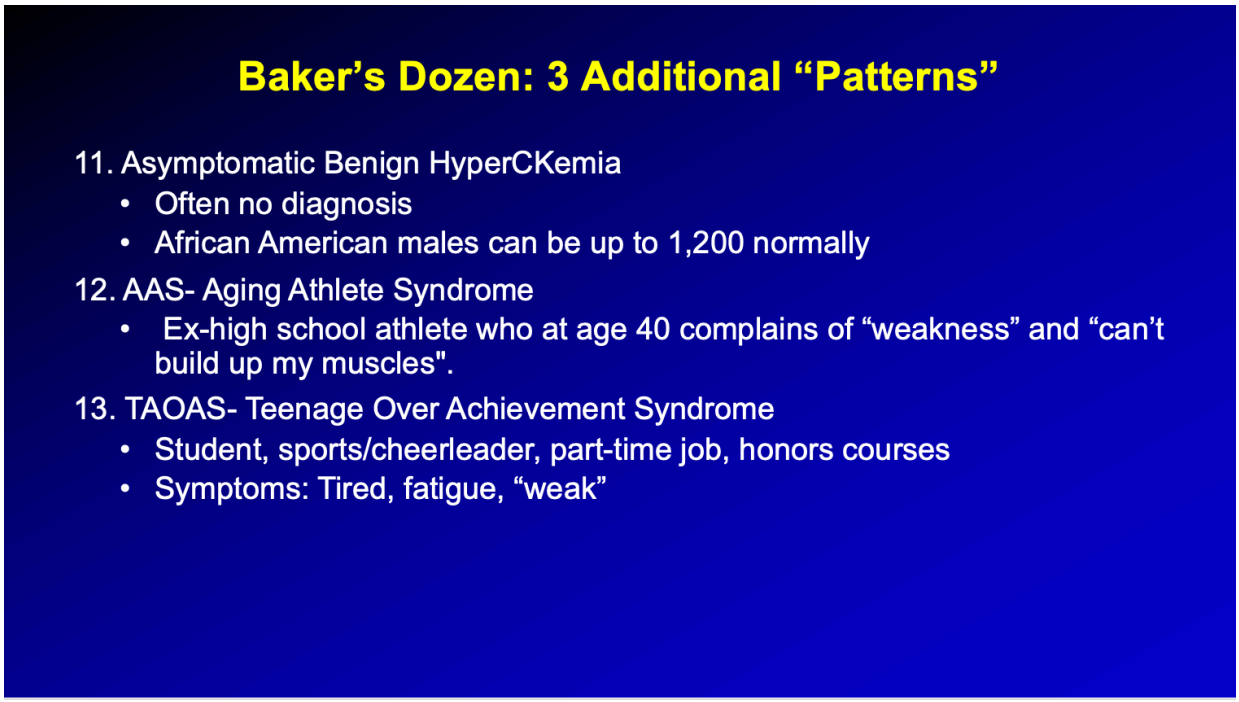
Clinical Patterns of Muscle Disorders

	Weakness						
PATTERN	Proximal	Distal	Asymmetric	Symmetric	Episodic	Trigger	**Diagnosis**
MP1 - Limb girdle	+			+			Most myopathies – hereditary and acquired
MP2 – Distal*		+		+			Distal myopathies (also neuropathies)
MP3 - Proximal arm / distal leg "scapuloperoneal"	+ Arm	+ Leg	+ (FSH)	+ (others)			FSH, Emery-Dreifuss, acid maltase, congenital scapuloperoneal
MP4 - Distal arm / proximal leg	+ Leg	+ Arm	+				IBM Myotonic dystrophy
MP5 - Ptosis / Ophthalmoplegia	+		+ (MG)	+ (others)			OPD, MG, myotonic dystrophy, mitochondria
MP6 - Neck – extensor*	+			+			INEM, MG
MP7 - Bulbar (tongue, pharyngeal, diaphragm)*	+			+			MG, LEMS, OPD (also ALS)
MP8 - Episodic weakness/ Pain/rhabdo + trigger	+			+	+	+	McArdle's, CPT, drugs, toxins
MP9 - Episodic weakness Delayed or unrelated to exercise	+			+	+	+/-	Primary periodic paralysis Channelopathies: Na^{+} Ca^{++} Secondary periodic paralysis
MP10 - Stiffness/ Inability to relax					+	+/-	Myotonic dystrophy, channelopathies, PROMM, rippling (also stiff-person, neuromyotonia)

*Overlap patterns with neuropathic disorders

Adapted from Barohn RJ, Dimachkie MM, Jackson RJ. *Neurol Clin* 2014;32(3):569-593

BONUS PATTERNS: BAKER'S DOZEN (Figure 36)
Figure 36



Asymptomatic Benign HyperCKemia
This is not truly a pattern but refers to patients that are being evaluated because they are found to have elevated creatine kinase, but they have no symptoms or signs. While some of these patients may turn out to have an underlying myopathic disorder, many do not. African Americans may have a higher creatine kinase upper limit of normal than other races, but this finding should not lead, in the absence of weakness, to a diagnosis of myopathy.

Aging Athlete Syndrome (AAS)
This refers to patients who at one point in their youth or young adult years were very athletic followed by a decade or two of relative inactivity at which point they try to "get into shape". They can present to a physician with a variety of complaints including myalgias and fatigue and also that they believe something must be wrong because they cannot reclaim the physical endurance that they had in their younger years. The best treatment here is reassuring the aging athlete.

Teenage Over Achievement Syndrome (TOAS)
This refers to teenagers who are brought in to see a physician by their concerned parents because the child is always tired, weak, and fatigued. These overachievers are often extremely bright, straight-A students, who are involved in after-school activities and also have a part-time job. No wonder they are tired and fatigued! The best treatment here is counseling the parents.

Conclusion

As in the Pattern Recognition Approach to Neuropathy lecture, we end this review by showing a quote from William James who said, "The rivalry of the patterns is the history of the world" (Figure 37). We have paraphrased William James in the following ways:

The recognition of the patterns is the key to understanding neuromuscular disease
And
The patterns are like the operating system for how we are supposed to think about neuromuscular disease (Figure 38)

Figure 37

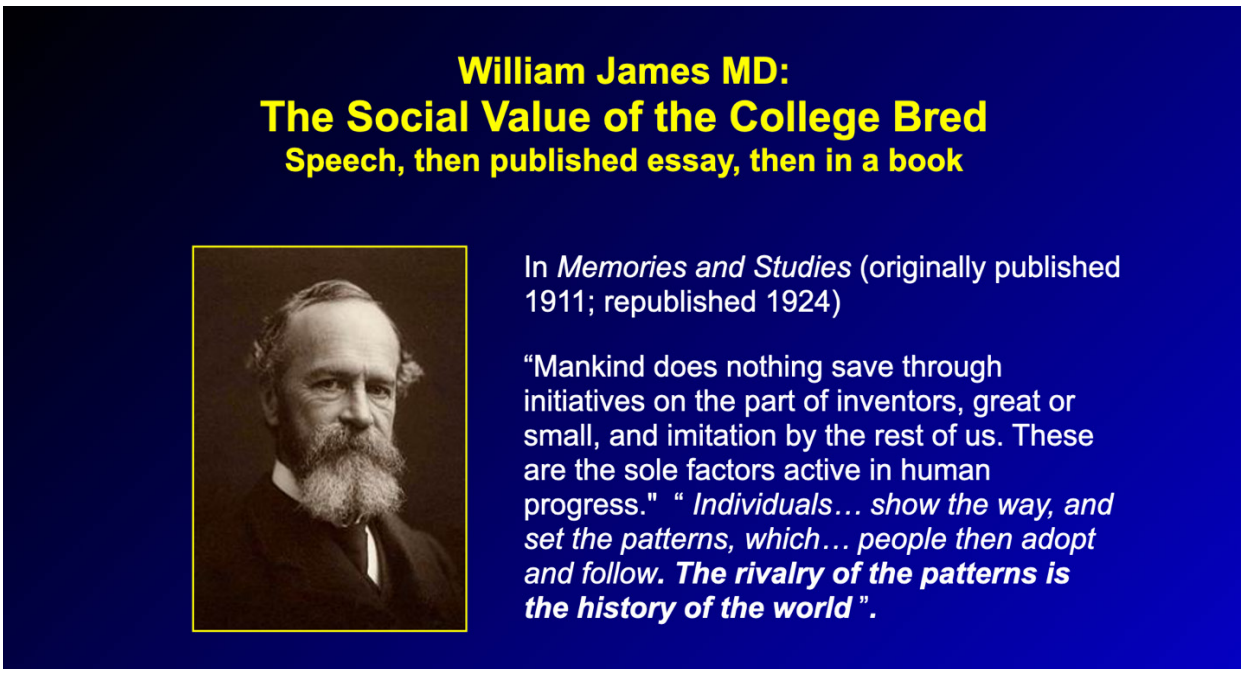


Figure 38

Figure 39

We would like to thank Amanda Sebok for her assistance in preparing the PowerPoint figures and Lauren Peck for her editorial assistance in preparing the manuscript.

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