AANEM Monograph

Differential Diagnosis of Myotonic Disorders

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AANEM Monograph# 27

CME STUDY GUIDE

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Differential Diagnosis of Myotonic Disorders

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EDUCATIONAL OBJECTIVES
Upon completion of this monograph, the reader will acquire skills to: (1) Explain the differential diagnosis of myotonic disorders, and (2) determine electrodiagnostic studies that may aid the differential diagnosis.

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DIFFERENTIAL DIAGNOSIS OF MYOTONIC DISORDERS

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ABSTRACT: Myotonia is primarily a muscle disorder characterized clinically by muscle stiffness with or without weakness, and electrophysiologically by muscle membrane hyperexcitability manifested by myotonic discharges (electrical myotonia). Myotonic disorders are broadly divided into myotonic dystrophy (type 1 and 2) and non-dystrophic myotonias (myotonia congenita, paramyotonia congenita, and sodium channel myotonias). In addition to stiffness, myotonic dystrophy is distinguished by the presence of fixed weakness and systemic features like cataracts and cardiac disease. Non-dystrophic myotonia is mainly manifested by stiffness; however, periodic weakness may occur in paramyotonia congenita and hyperkalemic periodic paralysis. Although electrical myotonia is a distinctive feature of myotonic disorders, it is not a pathognomonic feature of them. Myotonic discharges are seen in non-myotonic muscle diseases such as Pompe’s disease, myofibrillar myopathies, myotubular myopathy and some toxic myopathies. However, when myotonic discharges are abundant and widespread they are suggestive of a myotonic disorder.

INTRODUCTION
Myotonia can be viewed as a clinical or electrical phenomenon, but from a physiological standpoint, both result from the same process: muscle membrane hyperexcitability leading to repetitive action potentials after a single nerve stimulus. This can result from primary or secondary dysfunction of chloride or sodium channels; the mechanisms will be analyzed in subsequent sections. Patients with myotonic disorders commonly present with one of three symptoms: a) stiffness (the subjective perception of clinical myotonia), b) fixed weakness or c) episodic weakness (attacks of paralysis). Stiffness is the dominant clinical feature of the non-dystrophic myotonias. Fixed weakness is a prominent characteristic of the myotonic dystrophies and it can be proximal in myotonic dystrophy type 2 (DM2), mimicking other limb-girdle muscle dystrophies or acquired inflammatory, endocrine or toxic myopathies, or distal in myotonic dystrophy type 1 (DM1), occasionally causing diagnostic confusion with other inherited distal myopathies or even polynuropathies. The ptosis and facial weakness in DM1 has to be differentiated from myasthenia gravis; the presence of ophthalmoplegia, diurnal fluctuations and fatigable ptosis favor the latter. Mild fixed weakness can also occur in recessive myotonia congenita and long-standing periodic paralyses. Lastly, episodic weakness with myotonia occurs in hyperkalemic periodic paralysis and occasionally paramyotonia congenita. The distinctive clinical and electrodiagnostic characteristics of myotonia will be described in the following paragraphs.

RECOGNIZING MYOTONIA CLINICALLY
Patients with myotonia often complain of muscle stiffness that improves with repeated use of the muscle, the so-called “warm-up phenomenon.” Clinical demonstration of myotonia as delayed relaxation of muscle after voluntary contraction (handgrip myotonia8, 53), or percussion (e.g., at the thenar eminence, see Figs.1 and 2), is the hallmark finding on physical examination. Patients with Isaac’s syndrome occasionally may have pseudomyotonia of their handgrip, but percussion myotonia does not occur.26 In hypothyroidism, myoedema can cause confusion with percussion myotonia, but the skin mounding induced by percussion is electrically silent.25 Eyelid myotonia can be shown by asking the patient to repeatedly close the eyes tightly. After the first closure, there may be a lag in eye opening, which will improve with repeated efforts (Fig. 3A). Patients with paramyotonia also complain of muscle stiffness, but the stiffness often worsens rather than improves with repeated exercise (Fig. 3B). Myotonia and paramyotonia are usually not difficult to distinguish from muscle cramps that present with a sudden and painful focal muscle contracture. Myotonia and paramyotonia are typically painless.
ELECTRODIAGNOSTIC TESTING

RECOGNIZING MYOTONIA WITH ELECTRODIAGNOSTIC TESTING

Myotonia on electromyography (EMG) is distinct (Fig. 4), manifesting as spontaneous discharges with a waxing and waning of both amplitude and frequency, producing a characteristic sound often compared to a dive-bomber or revving-engine.1, 28 These potentials are repetitive discharges with a rate of 20-80 Hz and are of two types: (1) biphasic (positive-negative) spike potentials less than 5 ms in duration resembling fibrillation potentials, and (2) positive waves, 5-20 ms in duration, that resemble positive sharp waves. A single myotonic potential may look and sound exactly like a fibrillation potential or positive sharp wave, but it is the multiple runs with the characteristic waxing and waning that distinguish the discharges as myotonic potentials. Needle insertion and movement, muscle contraction, or tapping will often provoke the myotonia. Waning discharges are easily distinguished from myotonic discharges because they lack the characteristic waxing that is part of the classic definition. However, these potentials may represent a subset of myotonia. Logigian and colleagues34 found that 4 of 17 patients with genetically confirmed myotonic dystrophy type 2 (DM2) had only waning discharges without evidence of classic myotonic discharges.

As expected, all of the 16 patients with DM1 in their study had classic myotonic discharges. Myokymic potentials (Fig. 5) are essentially rhythmic firing of grouped motor unit action potentials in groups of 2-10 and with a frequency of 2-60 Hz, sounding like “marching soldiers”. Neuromyotonic discharges (Fig. 6) are very high frequency discharges at 100-300 Hz that originate at the peripheral nerve terminal/axons, based on their termination by a local peripheral nerve block but not by sleep or general anesthesia. These discharges cannot sustain themselves, so they abruptly decrease in amplitude, producing a “pinging” sound on the oscilloscope. Complex repetitive discharges (CRDs, Fig. 7) are repetitive complex potentials with a sudden onset and cessation, resembling the sound of a motorcycle. These potentials do not wax and wane like myotonia, although the waveform shape, amplitude, and frequency may change during discharge. Cramps are rarely captured on EMG, except when the gastrocnemius muscle is tested; they originate at the motor neurons and not the muscle fibers like myotonia, and they are characterized by a sudden painful contraction and on EMG by high frequency discharges, which can be up to 150 Hz. The discharge frequency and the number of motor unit discharges increase gradually during the development of the cramp, and subside gradually as the cramp fades (Fig. 8).

Figure 3-A: Myotonia of the orbicularis oculi. In this series of photographs, the patient is initially looking straight ahead (left). Next the patient is forcibly closing her eyes (center). Then the patient has been told to open her eyes as wide open as possible (right). Note that the patient is unable to open her eyes because of myotonia of the orbicularis oculi muscle. This figure demonstrates classical myotonia, in which the myotonia is most severe after the first contraction. If the patient had repeated the forcible eye closures, the myotonia would have “warmed up” or lessened with repeated closures.

Figure 3-B: Paradoxical orbicularis oculi myotonia. In this series of photographs, the patient has been asked to forcibly close her eye and then to open them fully as quickly as possible. Each photograph was taken immediately after the patient was told to open her eyes. After the first forcible eye closure (photograph on left), the patient has no difficulty in opening her eyes. Note the progressive difficulty in fully opening her eyes. After the fourth forcible eye closure (photograph on the right), the patient is unable to open her eyes.

Figure 3-C: Paradoxical grip myotonia. In this series of photographs, the patient has been asked to forcibly squeeze the examiner’s fingers and then to open the hand as quickly as possible. Each photograph was taken immediately after the patient was told to open the hand. After the first tight squeeze (photograph on the left), the patient has no difficulty letting go. Note the progressive difficulty in letting go of the examiner’s fingers. After the fourth tight squeeze (photograph on the right), the patient is unable to let go of the examiner’s fingers.
Figure 5: Myokymic Discharge
Tracings of three different myokymic discharges displayed with a time scale (left) to illustrate the firing pattern and with a different time scale (right) to illustrate that the individual potentials have the configuration of a motor unit action potential. A myokymic discharge is a group of motor unit action potentials that fire repetitively and may be associated with clinical myokymia. Two firing patterns have been described. Commonly, the discharge is a brief, repetitive firing of single units for a short period (up to a few seconds) at a uniform rate (2-60 Hz) followed by a short period (up to a few seconds) of silence, with repetition of the same sequence for a particular potential. Less commonly, the potential recurs continuously at a fairly uniform firing rate (1-5 Hz). Myokymic discharges are a subclass of grouped discharges and repetitive discharges.

Figure 6: Neuromyotonic Discharge
The timescale was chosen to illustrate the characteristic firing pattern. A neuromyotonic discharge is a burst of motor unit action potentials that originate in the motor axons firing at high rates (150-300 Hz) for a few seconds, and often start and stop abruptly. The amplitude of the response typically wanes. Discharge may occur spontaneously or be initiated by needle movement, voluntary effort, and ischemia or percussion of a nerve.

Figure 7: Complex Repetitive Discharge
A complex repetitive discharge is a polyphasic or serrated action potential that may begin spontaneously or after a needle movement. They have a uniform frequency, shape, and amplitude, with abrupt onset, cessation, or change in configuration. Amplitude ranges from 100 μV to 1mV and frequency of discharge from 5 to 100 Hz. Complex repetitive discharge is the most widely accepted term, though these potentials have also been referred to as bizarre high-frequency discharge, bizarre repetitive discharge, bizarre repetitive potential, near constant frequency trains, pseudomyotonic discharge, and synchronized fibrillation.

Figure 8: Cramp Discharge
A cramp discharge arises from the involuntary repetitive firing of motor unit action potentials at a high frequency (up to 150 Hz) in a large area of muscle, usually associated with painful muscle contraction. Both the discharge frequency and the number of motor action potentials firing increase gradually during development, and both subside gradually with cessation.

ELECTRODIAGNOSTIC STUDIES THAT MAY AID DIFFERENTIAL DIAGNOSIS
Myotonia is the most useful finding on standard EMG and nerve conduction examinations. However, several specialized tests may also aid in making or confirming the diagnosis of a disorder associated with myotonia: repetitive stimulation, the “short” and “long” exercise tests, and the provocative cold test.

Repetitive stimulation: It has long been recognized that in myotonic syndromes, repetitive stimulation at 10 Hz leads to a decrement in the compound motor action potential (CMAP). This decrement has been attributed to
transient inexcitability of the muscle membrane and is more commonly seen in recessive myotonia congenita (rMC). Recently, similar decremental responses specific for rMC were reported with stimulation at 3 Hz. 

**Description of exercise testing and provocative cold test:** There are two variations of the exercise test: “short” and “long”. In the “short” exercise test (SET), the patient is asked to exercise briefly at maximal isometric contraction (10 seconds). A CMAP is recorded immediately after exercise and every 10 seconds thereafter until no change in amplitude is observed. Two repetitions of the SET with 60 seconds of rest between trials may increase the diagnostic yield. For the long exercise test (LET), the CMAP is tested over a 30-45 minute period following 5 minutes of exercise. For the provocative cold test, the limb is immersed in cold water (15° C) for 15-30 minutes; the CMAP for an individual muscle is recorded before and after the cooling. During the SET, normal individuals may show an initial increase or decrease of CMAP amplitude, which will return to baseline values within 10-20 seconds. If a decrement occurs, it generally should not exceed 10% of baseline CMAP amplitude. During the LET, a more prominent decrement can occur; the cutoff value for an abnormal test has been debated, but a >40% decrement of CMAP amplitude from pre-exercise baseline is considered abnormal by most experts. 

After cooling of a limb and repetition of short exercise testing, most normal controls will show a decrease in CMAP amplitude (in the range of 25%) as well as an increase in CMAP duration (up to 40%)—the latter reflecting the physiologic effect of delayed sodium channel inactivation and repolarization of membranes in cold. The cumulative effect of those two opposite-direction changes in CMAP parameters is a minimal change in the CMAP area. Normal values for CMAP changes after cooling have not been well established so far.

**Interpretation of Short Exercise Test:** Patients with paramyotonia congenita (PMC) show a >20% decrement in CMAP amplitude and area, that returns very slowly to baseline; the abnormality becomes more obvious upon the second or third trial. This is the electrophysiologic equivalent of the worsening of myotonia and weakness with exercise that defines this disorder. In patients with myotonia attributed to chloride channel dysfunction, like myotonia congenita (MC) or myotonic dystrophies, an immediate decrement in CMAP amplitude after exercise, which returns to baseline after 30-60 seconds, is appreciated. This correlates with the clinical occurrence of transient paresis in MC36. Post-exercise myotonic potentials (PEMPs) can be seen in MC18. In the sodium-channel myotonic, the test is either normal or shows non-specific abnormalities68. In hypokalemic periodic paralysis (HyperKPP), an increase in CMAP amplitude is occasionally noted, and may become more prominent upon repeated trials; however, this finding is not consistently observed68. In hypokalemic periodic paralysis (HypoKPP), which lacks myotonia, the SET is typically normal.

**Interpretation of Long Exercise Test:** For the periodic paralyses, the long exercise test (LET) is often required to support the diagnosis. The typical finding is a delayed decline of the CMAP amplitude occurring 20-40 minutes over the course of the test (HypoKPP and HyperKPP). Immediately after exercise, an increase of CMAP (HyperKPP) or no change (HypoKPP) is observed. If the LET is performed in patients with PMC, similar findings to the SET are seen (rapid decline of CMAP followed by very slow return to baseline). In the other myotonic disorders, the results of LET are inconsistent or normal.

**Interpretation of Provocative Cold Test:** In patients with PMC, cooling of limb will usually produce a large decrement of CMAP amplitude or loss of CMAP; those abnormalities may sometimes be absent at room temperature and cooling is required to unmask them. Occasionally, patients with certain rare sodium channel mutations (such as Q270K) will show a pattern resembling MC at room temperature and convert to a more typical paramyotonic pattern after cooling. If EMG is performed after cooling, most patients with PMC will initially show increased myotonic discharges and fibrillations; with prolonged cooling, a gradual reduction of motor unit potential amplitude and recruitment until complete electrical silence is observed.

**Classification Scheme for the Myotonic Syndromes**

To conceptualize the differential diagnosis of myotonic syndromes, two distinctions have to be made: first, between those diseases with clinical and electrical myotonia, and those with only electrical myotonia (such as acid maltase deficiency, myofibrillar and centronuclear myopathies, and drug-induced myotonia). In the first group, a further distinction can be made between those disorders with progressive weakness and systemic features (the myotonic dystrophies type 1 and 2) and those with minimal fixed weakness and no systemic features (the chloride and sodium channelopathies). A proposed algorithm to aid in the differential diagnosis is outlined in Figure 9. Attention to specific clinical features, exercise testing and focused genetic testing can lead to correct diagnosis in the majority of cases. Muscle biopsy is rarely required; it is particularly helpful for the diagnosis of myopathies with myotonia limited to EMG, as long as DM2 is excluded.

**Disorders with both Clinical and Electrical Myotonia: Dystrophies**

**Myotonic Dystrophy I:** This is the best known myotonic disease and the prototypical genetic disorder due to ribonucleic acid (RNA)-mediated toxicity. The CTG-repeat expansion at the dystrophia myotonica-protein kinase (DMPK) gene on chromosome 19 produces an abnormal RNA that sequesters proteins like muscleblind-1 (MBNL1) and CUG triplet-repeat RNA-binding protein 1 (CUGBP-1) and negatively affects the splicing of several pre-mRNAs including those of chloride channel (causing myotonia), insulin receptor and tau, explaining the multisystem manifestations of this disease. Based on this knowledge, animal models have
Myotonia on EMG

Clinical Myotonia (percussion, grip, eyelid)

Prominent weakness +/- systematic features (cataracts, abnormal ECG, frontal alopecia, etc).

If dysmorphic facies, short stature–think SJS

Rule out medication exposure, hypothyroidism

Proximal weakness of adductors, respiratory failure, tongue weakness

DM2 DNA testing

Muscle biopsy if negative

Dry blood spot for a-glucosidase/ GAA genetic testing

Adult Pompe

Short Exercise Testing + Cooling

DM1 – DNA testing

DM2 – DNA testing

Normal

CMAP decrement > 20%

DM2 DNA testing

Muscle biopsy if negative

HyperkPP SCN4A sequencing

Long-exercise testing

Normal

CMAP decrement > 20%

Slow return to baseline

Larger with repeat trials

Return to baseline in < 2 minutes

Smaller decrement on repeat trials

HyperkPP SCN4A sequencing

Leg myotonia, warm-up phenomenon, transient paresis, no cold-worsening or paramyotonia

CLCN1 sequencing

Eyelid myotonia, cold or exercise-induced worsening, prominent pain

SCN4A sequencing

SCN4A gene sequencing

Consider DM2 DNA testing if negative

Figure 9. Algorithm for the differential diagnosis of electrical myotonia. CLCN1= chloride channel protein 1, CMAP= compound muscle action potential, DM1, DM2= myotonic dystrophy 1, 2, EMG= electromyography, PMC=paramyotonia congenita, MC=myotonia congenita, HyperKPP= hyperkalemic periodic paralysis, GAA= glucosidase alpha, SCN4A= sodium channel type 4, subunit alpha, SJS= Schwartz-Jampel syndrome.
been recently developed that reproduce some of the features of the disease.\textsuperscript{49,74} The exact cause of weakness is uncertain; alternate splicing of several proteins associated with muscle has been hypothesized.\textsuperscript{29,46} Incidence is 12-14 per 100,000. Patients with DM1 have a recognizable facial appearance with small temporals muscles, ptosis, and a long, lean face. Cranial muscle abnormalities may also include dysphagia, dysarthria, and sometimes eye-movement abnormalities. Weakness is predominantly distal, with prominent fingerclock and foot dorsiflexion weakness. Other characteristic features include frontal baldness and cataracts in nearly all patients, as well as cardiac, gastrointestinal, endocrinologic and neurobehavioral abnormalities.\textsuperscript{73} Impaired glucose tolerance is more frequent than in the general population, as are low testosterone levels in males. Cardiac abnormalities are apparent on EKG with evidence of heart-blocks and atrial arrhythmias. Extreme sensitivity to sedatives and prolonged respiratory failure after surgical procedures is not uncommon. Dysphagia, intestinal pseudoobstruction, irritable-bowel like symptoms and gallbladder sludging are quite frequent. The rate of disease progression is slow and overall life expectancy is reduced due to sudden deaths from cardiac arrhythmias, and less commonly respiratory diseases and neoplasms.\textsuperscript{39} On examination, handgrip or percussion myotonia is evident, but eyelid myotonia is unusual. Of particular interest is congenital myotonic dystrophy, which is attributed to the phenomenon of anticipation whereby triplet repeat instability in the gametes leads to an increased expansion of the triplet repeat. In DM1 this may be pronounced, with a nearly asymptomatic mother giving birth to a child with a greatly expanded CTG repeat, manifested by developmental delay and severe neonatal hypotonia, generalized weakness and ventilator-dependence. Clinical and electrical myotonia is often absent at birth and may not appear before 3-5 years.\textsuperscript{29} The diagnosis is confirmed by genetic analysis, which is performed widely.

**Myotonic Dystrophy 2 (Proximal Myotonic Myopathy-PROMM):** DM2 or PROMM is another triplet repeat disorder that shares many of the features of DM1. The disease-causing mutation is a CCTG expansion in intron 1 of the zinc finger protein 9 gene. DM2 is an adult-onset muscular dystrophy which is more prevalent in Northern Europe and is typically associated with myotonia, proximal weakness including neck flexors, cataracts, cardiac arrhythmias, insulin resistance, and other multisystem features of adult-onset DM1.\textsuperscript{13,33,58,73} Later onset, proximal weakness and lack of congenital form allow differentiation from DM1.\textsuperscript{73} Autoimmune disorders also tend to occur more frequently than DM1 patients and the general population.\textsuperscript{69} However, DM2 is often a difficult diagnosis: myalgias mimicking fibromyalgia or other pain disorders;\textsuperscript{2} strikingly focal weakness without clinical myotonia;\textsuperscript{25} calf hypertrophy, prominent myotonia without weakness,\textsuperscript{11} and rhabdomyolysis episodes are some atypical presentations. Laboratory tests reveal multiple non-specific abnormalities, including low IgG levels.\textsuperscript{24} Genetic testing establishes the diagnosis.

**Disorders with both Clinical and Electrical Myotonia: Non-Dystrophic Myotonias**

The disorders included in this subgroup are caused by genetic mutations in chloride or sodium channels. They are classified as non-dystrophic diseases based on the assumption that they do not cause progressive muscle damage over time; this concept however, has been challenged by recent ultrasound\textsuperscript{71} and magnetic resonance imaging (MRI) studies. The tremendous advances in genetics over the last decade have revealed the considerable clinical overlap between chloride and sodium channelopathies, to the point they can become clinically indistinguishable;\textsuperscript{36} they have also allowed recognition of several unusual, very severe or very mild phenotypes across the myotonic spectrum. Some of those complexities, and clues for the differential diagnosis between them, will be presented below. Genetic testing may be performed in specialized centers, which are best located by a National Institution of Health internet-based resource (www.genetests.org).

**Chloride Channelopathies: Myotonia Congenita:** Myotonia congenita is secondary to a mutation in the CLCN1 (chloride channel protein of skeletal muscle), and may be transmitted either dominantly (Thomsen’s) or recessively (Becker’s).\textsuperscript{36} R894X is the most well-known mutation, and, for unclear reasons, it may be recessive in some families and dominant in others.\textsuperscript{15} A dose effect has been recently demonstrated for dominantly inherited mutant alleles.\textsuperscript{3} The effect of the mutations is usually a loss-of-function of the chloride channel, leading to an elevation of the resting membrane potential and thus a tendency toward repeated muscle depolarizations.\textsuperscript{10} At the mildest end of the spectrum, some patients may manifest only increased insertional activity on EMG.\textsuperscript{43} Myotonia is the prominent clinical symptom,\textsuperscript{36} and typically presents in early childhood, causing stiffness when initiating an activity. Once these patients have “warmed up”, they may perform activities at a normal or advanced level, including competitive sports. Parents may describe this as weakness and clumsiness in addition to or instead of stiffness. Affected children appear “athletic” with increased muscle bulk, presumably because of the sustained muscle activity. The symptoms often improve with age but do not completely disappear. In the recessive form, Becker’s, myotonia tends to be more severe than the dominant Thomsen’s, and transient weakness upon initiation of exercise often occurs. Myotonia is appreciated in the limbs more than the eyelids, and cold-sensitivity is not common.

**Sodium channelopathies:** Hyperkalemic periodic paralysis, paramyotonia congenita, sodium-channel myotonias, and other unusual phenotypes

Mutations in the sodium channel type 4 subunit alpha protein (SCN4A) can cause a very broad spectrum of disorders: from life-threatening infantile myotonia presenting as laryngospasm,\textsuperscript{22,32} or congenital hypotonia with dysmorphic features,\textsuperscript{37} to the more common phenotypes of PMC and HyperkPP, to non-myotonic disorders such as HypoPP or congenital myasthenic syndrome. The mutations are dominantly inherited, or may occur de novo, particularly with the more severe infantile phenotypes. They are usually
gain-of-function, leading to enhanced activation or loss of slow or fast inactivation\textsuperscript{11} of the sodium channel, which makes the muscle fibers persistently depolarized. Loss of function mutations are less common and are associated with some cases of periodic paralysis.\textsuperscript{16,27} The most common residues affected are T704M and M1592V in HyperKPP, and R1448C and T1313M in PMC41. Genotypic-phenotypic correlations are far from perfect, however: for example, the same mutation causing PMC can manifest as stridor in infancy.\textsuperscript{38} Other mutations, such as Q270K produce a clinical picture hard to distinguish from chloride-channel MC.

HyperKPP is characterized by attacks of weakness, provoked by resting after exercise, fasting, or eating potassium-rich foods.\textsuperscript{9,41,56} The attacks occur relatively frequently (one per day to one per week), are short-lived (minutes to hours), and usually are not completely disabling. EMG studies show myotonia in approximately 75\% of HyperKPP patients.\textsuperscript{41} Some of them complain of stiffness and show clinical myotonia as well. During the attack, the serum potassium level is often elevated. Muscle biopsy shows a vacuolar myopathy.

Patients with PMC mainly complain of stiffness worsened by repeated exercise, but can also have attacks similar to those of HyperKPP. The major factor provoking stiffness in these patients is cold temperature. EMG consistently demonstrates myotonia, but unusual high-amplitude bursting, “tornado-shaped”, as well as low amplitude high frequency “music” discharges were recently reported.\textsuperscript{68} In both HyperKPP and PMC, the paramyotonia and attacks of weakness decrease in middle age. In cases where periodic paralysis or PMC are being questioned, the exercise test and cooling test may be particularly helpful (see previous sections for details). Nearly all cases of PP are associated with mild to moderate weakness in later adult life.\textsuperscript{6,31,41} The term “Sodium-channel myotonia” refers to a spectrum of disorders characterized by pure, often episodic myotonia, without attacks of weakness. Some of these disorders are aggravated by potassium administration, but not by cold exposure; examples are myotonia fluctuans, in which myotonia appears after exercise in a delayed fashion;\textsuperscript{59} myotonia permanens, which is severe, persistent, and painful and can lead to respiratory compromise\textsuperscript{12} and acetazolamide-responsive myotonia.\textsuperscript{54,72} Others appear as late adult-onset, painful, cold-aggravated myotonia.\textsuperscript{4,6,16} Exercise testing is often normal or non-specific.\textsuperscript{16,68}

Differential diagnosis of the latter group of disorders includes the chloride channelopathies. The following characteristics, although imperfect, favor an SCN4A mutation:\textsuperscript{36} myotonia limited to eyelids,\textsuperscript{67} marked cold sensitivity or paramyotonia, prominent pain, lack of warm-up phenomenon and transient paresis.\textsuperscript{79} Electrodiagnostic studies and genetic testing can sort out difficult cases.

When considering HyperKPP or PMC, the main differential consideration is HypoKPP,\textsuperscript{9,56} which does not show any clinical or electrical myotonia.\textsuperscript{41} Attacks of weakness are more prolonged in HypoKPP (lasting hours to days) and more severe, often leaving the patient unable to walk. Inherited forms of HypoKPP are secondary to calcium-, or less commonly sodium-channel mutations. Metabolic causes are most often secondary to hyperthyroidism, although chronic potassium wasting (e.g., renal tubular acidosis) may also cause episodic muscle weakness. Andersen-Tawil syndrome, which is associated with mutations in potassium channel, inwardly rectifying, subfamily J, member 2 (KCNJ2) gene,\textsuperscript{2} consists of the triad of cardiac arrhythmias, dysmorphic features, and periodic paralysis. There is no myotonia.

**Schwartz-Jampel Syndrome:** Schwartz-Jampel syndrome, also known as chondrodytrophic myotonia, is associated with severe myotonia, muscular hypertrophy, and many dysmorphic features, such as short stature, diffuse bone disease, contractures and oculofacial abnormalities (blepharophimosis, micrognathia, etc.).\textsuperscript{47,66} Muscle stiffness is one of the first symptoms that presents in childhood. There is no warm-up phenomenon. The EMG findings more closely resemble neuromyotonia or CRDs. Unlike typical myotonia, the repetitive, high-frequency discharges in this disorder do not wax and wane. Schwartz-Jampel syndrome is caused by loss-of-function mutation in the HSPG2 (heparan sulfate proteoglycan 2 or basement membrane-specific heparan sulfate proteoglycan core protein) gene that encodes perlecan, a proteoglycan secreted into basement membranes.\textsuperscript{47}

**Electrical without Clinical Myotonia**

As mentioned previously, several patients with DM2 may have proximal weakness with myotonia appreciated only on EMG. In addition, adult-onset acid maltase deficiency (AMD, Pompe disease or glycogenosis type II) is the classic example of this pattern.\textsuperscript{50} AMD presents with slowly progressive truncal, tongue and proximal limb weakness, particularly affecting the hip adductors and pectoralis muscles. Unlike other glycogen storage diseases, the heart and liver are not enlarged, although EKG is often abnormal showing a pre-excitation syndrome. Serum creatine kinase levels are increased and EMG shows evidence of multiple spontaneous discharges including myotonic discharges, fibrillation potentials, positive sharp waves, CRDs, and small motor unit action potentials, with predominance in proximal muscles, particularly paraspinal. Muscle biopsy shows periodic acid Schiff positive vacuoles, and acid phosphatase positive granules. Diagnosis is confirmed by one of the following:\textsuperscript{52} a) direct measurement of alpha glucosidase (GAA) activity on fresh muscle, fibroblasts or blood or b) genetic testing for GAA mutations. A more malignant form of the disease may present in infancy with heart muscle and neuronal involvement. It is important to recognize AMD, because enzyme replacement therapy is now available.

Electrical myotonia almost never occurs in congenital myopathies, with the exceptions of centronuclear (CNM)\textsuperscript{23} and myofibrillar myopathies (MFM). The phenotype of CNM varies from severe neonatal hypotonia and respiratory failure, to adult-onset distal weakness. Ophthalmoplegia is typical feature. MFM\textsuperscript{50} are characterized by highly variable ages of onset, patterns of weakness, and degrees of cardiac, respiratory and peripheral nerve involvement. For both conditions, the diagnosis is established by muscle biopsy and genetic testing.
Other Disorders:
There are other disorders in which myotonia is occasionally recognized, although usually not as a predominant or essential part of the presentation. Muscle diseases such as polymyositis and inclusion-body myositis, or severe active denervation are rarely associated with myotonic potentials. In some of these cases, CRDs may be mistaken for myotonic potentials. Fibrillation potentials, positive sharp waves, and myotonic discharges have been reported previously in hypothyroid patients, but myotonic discharges are not common. Electrical myotonia may also be caused or unmasked by some drugs: 20,25-diazacholesterol, clofibrate, clofibrate, 2,4-dichlorophenoxyacetate, chloroquine, colchicine, cyclosporine, propranolol, and hydroxymethylgutaryl coenzyme A reductase inhibitors.

Conclusions:
Recognizing the associated clinical and EMG characteristics of myotonia and paramyotonia greatly aids neuromuscular diagnosis. During routine electrodiagnostic testing, a few additional historical details and a brief physical examination are likely to provide the correct diagnosis or suggest further investigations.

References:


