

Myotonic disorders

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Myotonia reflects a state of muscle fiber hyperexcitability. Impaired transmembrane conductance of either chloride or sodium ions results in myotonia. Myotonic disorders include the myotonic dystrophies and nondystrophic myotonias. Mutations in the genes encoding chloride (*CIC-1*) or sodium (*SCN4A*) channels expressed exclusively in skeletal muscle cause nondystrophic myotonias. Genetic defects in the myotonic dystrophies do not involve ion channel or its regulator proteins. Recent research supports a novel RNA-mediated disease mechanism of myotonia in the myotonic dystrophies. Myotonic dystrophy Type 1 is caused by CTG repeat expansion in the 3' untranslated region in the Dystrophin Myotonia Protein Kinase (DMPK) gene. Myotonic dystrophy Type 2 is caused by CCTG repeat expansion in the first intron in Zinc Finger Protein 9 (ZNF9) gene. The expanded repeat is transcribed in RNA and forms discrete inclusions in nucleus in both types of myotonic dystrophies. Mutant RNA sequesters MBNL1, a splice regulator protein and depletes MBNL1 from the nucleoplasm. Loss of MBNL1 results in altered splicing of *CIC-1* mRNA. Altered splice products do not encode functional *CIC-1* protein. Subsequent loss of chloride conductance in muscle membrane causes myotonia in the myotonic dystrophies. The purpose of this review is to discuss the clinical presentation, recent advances in understanding the disease mechanism with particular emphasis on myotonic dystrophies and potential therapy options in myotonic disorders.

Key words: Alternative splicing, chloride channel myotonia, myotonia, myotonia congenita, myotonic dystrophy, nondystrophic myotonia, nuclear inclusions, sodium channel myotonia

Myotonia is the delayed relaxation of skeletal muscle fibers after voluntary muscle contraction.^[1] Patients with myotonia may report painless muscle stiffness immediately upon initiating muscle activity after a period of rest. For example, inability to release hand grip after a strong handshake or trouble climbing stairs

after a period of sitting. On physical examination, action myotonia can be elicited by isotonic muscle contraction such as asking the patient to make a tight fist or to grip and release the examiner's fingers. Patients may have a lag in opening the eyes after initial tight eyelid closure. Myotonia improves with muscle exercise or repeated efforts, the so-called "warm-up phenomenon". Percussion myotonia is a prolonged muscle contraction after mechanical compression of the muscle with a reflex hammer. Percussion of the thenar eminence results in prolonged adduction of the thumb, and percussion on the extensor digitorum communis in the forearm while the wrist is hanging down results in prolonged extension of the wrist.

Clinical myotonia is the cumulative result of electrical hyperexcitability of individual muscle fibers. Needle Electromyography (EMG) reveals spontaneous runs of motor unit potentials with a characteristic waxing and waning frequency and amplitude [Figure 1]. The frequency may range from 20 to 150 MHz with amplitudes of the myotonic potentials in the 10 to 1000 mV range. Myotonic discharges produce an unforgettable unique sound similar to a motorcycle motor or World War II dive bomber or a chainsaw. By definition, myotonic discharges last 500 ms or longer and should be identified in at least three areas of an individual muscle outside of an endplate region.^[2]

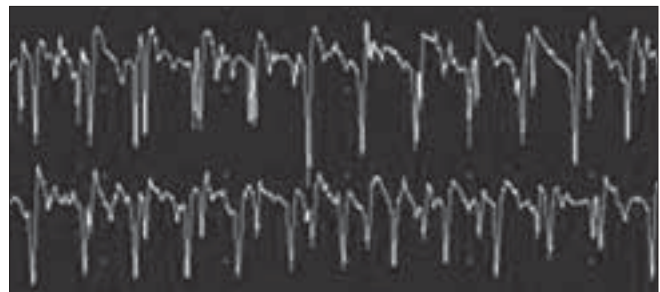


Figure 1: Needle EMG showing myotonia (gain 200 μ V; sweep 500 ms), Courtesy: Professor Vinay Chaudhry, Department of Neurology, The Johns Hopkins Hospital, Baltimore, MD)

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Persistent depolarization of the myotonic muscle is due to abnormal expression of ion channels in the muscle membrane. Point mutations or deletions in the genes encoding either the sodium channel (*SCN4A*) or chloride channel (*CLCN1*) expressed in skeletal muscle result in myotonia without muscle atrophy or degeneration, the so-called nondystrophic myotonias.^[3,4] By contrast, DNA repeat expansion mutations causing myotonic dystrophies (DM) do not involve the ion channel or its regulatory proteins. Recent research has begun to unravel novel mechanisms of myotonia in DM.^[5-8] This review will focus on the current understanding of the disease mechanisms and treatment in DM and the nondystrophic myotonias (see classification of myotonic disorders in Figure 2).

The Myotonic Dystrophies

DM is dominantly inherited with a 50% risk of transmission from the affected parent to each child. Currently, two distinct mutations are known that lead to the clinical syndrome of DM. Myotonic dystrophy Type 1 (DM1) is caused by expansion of CTG repeats within 3' untranslated region in the *DMPK* gene on Chromosome 19.^[9] Myotonic dystrophy Type 2 (DM2) is caused by expansion of CCTG repeats within the first intron in the *ZNF9* gene on Chromosome 3.^[10] Most patients with DM phenotype have DM1 mutation which has an estimated prevalence of 1 in 8000 adult US population. Prevalence of DM2 varies with the population in different continents. For example, DM2 is as prevalent as DM1 in the studied population in Finland and Germany.^[11] It is believed that DM mutations are not as prevalent in the Indian subcontinent; however, well-designed genetic epidemiological surveys are needed to better understand the disease prevalence in India. A search is on for new mutations given that some families with DM-like phenotype do not have either DM1 or DM2 mutations.

The DNA repeat expansion remains stable throughout embryonic development. The repeats significantly vary in size in different tissues in an individual with significantly larger repeat sizes in muscle, heart and

brain, the tissues most severely affected in DM.^[12] The repeat size variability may increase with age.^[13] There appears to be a rough correlation between the size of the repeat and the age of onset of clinical features for CTG <400;^[14] such correlation is lost for larger repeats. DM2 mutation is highly unstable with greater variations and much larger repeat sizes. Fortunately, the phenotype is not worse in DM2 patients with massive repeat expansion. In the same pedigree, family members can show a broad range of clinical severity and sizes of the repeats. Genetic anticipation refers to a more severe and earlier onset of phenotype in the subsequent generation secondary to a much larger increase in the repeat size. One such example is the congenital form of DM1 in which the size of CTG repeat increases from a few hundred base pairs to several thousand base pairs in the ovum and is transmitted from a mother to a child. There is a limit to the size of repeat expansion transmitted by sperm for unclear reasons.

DM is the most common myotonic disorder in adults. Myotonia can be a presenting symptom but generally does not result in disability. Clinical diagnosis of DM can be easily made by the combination of myotonia and the characteristic pattern of muscle wasting and weakness. Myotonia is evident by delayed relaxation after a forceful sustained hand grip and percussion on thenar and wrist extensor muscles. Patients have prominent wasting and weakness of superficial facial muscles, levator palpebrae superioris, temporalis, masseter and palate with resultant ptosis, dysarthria and myopathic face. Swallowing may be impaired early in the disease. Sternocleidomastoids and distal muscles in the extremities are preferentially involved. Diaphragm, intercostal muscles, intrinsic muscles in hands, quadriceps, and external ocular muscles are often involved. Gastrocnemius, soleus, hamstrings, and pelvic girdle muscles are usually spared. Many patients with DM2 mutation present with prominent proximal muscle weakness, the so-called proximal myotonic myopathy.^[15] Distal pattern of muscle weakness similar to DM1 can also be seen in patients with DM2. Cardiac involvement in the form of conduction delay, atrial flutter and fibrillation are common in both types of DM. Sudden cardiac death presumably related to arrhythmia is a leading cause of mortality in DM second only to respiratory complications.^[16] Premature cataract before the age of 40 years is another common feature between the two diseases. Cataract can be present without skeletal muscle or cardiac disease and may lead to a new diagnosis of DM in a pedigree. Early cataract in DM has a characteristic Christmas tree-like appearance with multicolored refractile opacities visible in both anterior and posterior subcapsular regions in the lens when examined with a slit-lamp. Central nervous system disease characterized by apathy, somnolence, and inertia leads to psychosocial and occupational

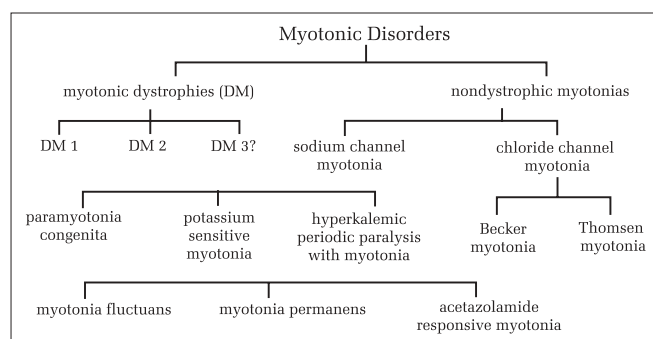


Figure 2: Classification of myotonic disorders

limitations jeopardizing the quality of life. Myotonic dystrophy patients frequently do not report symptoms and their functional abilities are deteriorated earlier and out of proportion to the extent of muscle weakness. Other systemic manifestations common to both types of DM include frontal balding, testicular atrophy, hypogammaglobulinemia, and insulin resistance. Difficulty with protecting airway and hypoventilation are common complications of anesthesia in DM1 patients. Respiratory and bulbar muscles are not severely affected in DM2.

Muscle maldevelopment, hypotonia and mental retardation are prominent in congenital DM. Myotonia is not apparent until after the infancy. Poor fetal movement and polyhydramnios indicate that symptoms may begin as early as in intrauterine life. Severe weakness of face, jaw and elevated diaphragm with thin ribs on a chest X-ray may provide a clue to the diagnosis. Congenital DM is almost always due to large unstable CTG repeat expansions occurring during maternal transmission. Examination of the mother with milder clinical features of DM confirms the diagnosis. Congenital DM has never been reported in DM2.

The DNA test is well established and is commercially available. Greater sensitivity and specificity and easy availability of the DM gene test has virtually eliminated the need for invasive muscle biopsy to establish the diagnosis. Muscle histology reveals prominent pyknotic nuclear clumps, increased internal nuclei, variable muscle fiber size, muscle fiber atrophy involving Type I fibers in DM1 and Type II fibers in DM2 and conspicuous absence of fibrosis, necrosis and regeneration.

DM1 is caused by expansion of CTG repeat in the *DMPK* gene.^[9] DM2 is caused by expansion of CCTG repeat in the *ZNF9* gene.^[10] *DMPK*, a serine threonine kinase shows no functional similarity to *ZNF9*, a 7 zinc finger protein thought to bind RNA. Yet, both mutations result in quite similar clinical features including myotonia, myopathy, cardiac conduction defects, arrhythmia, cataracts and insulin resistance. In both diseases, the repeat transcribed in the mutant RNA forms inclusions in the nucleus.^[17,10] This finding suggested that the mutant RNA might have a significant role in the disease process.

Mice that express expanded CUG repeats in skeletal muscle develop characteristic phenotype of myotonia and progressive myopathy.^[18] Like in human DM, the mutant RNA containing expanded repeats form inclusions in the nuclei. Myotonia is an early and prominent symptom. Clinically, the CUG repeat mice develop muscle stiffness pronounced in hind limbs and lumbar paraspinals. The EMG shows true myotonic discharges in many muscles. Intracellular recordings in individual muscle fibers revealed markedly reduced (>90%) chloride conductance.^[19] Expression analysis of *ClC-1*, a major chloride channel in skeletal muscle,

showed altered splicing of *ClC-1* mRNA. Abnormal splice products of *ClC-1* do not encode functional *ClC-1* protein and cause loss of chloride conductance that leads to myotonia.^[19] Similar splicing abnormalities in *ClC-1* mRNA and loss of chloride channel protein in muscle membrane are also seen in human DM1 and DM2.^[19,20]

A large body of evidence indicates that the mutant DM RNA interferes with the activities of two protein families that act antagonistically to each other. Amongst many functions, these two groups of proteins directly act on RNA splicing. Whereas *MBNL1* a protein in the muscleblind family promotes transition of splicing from fetal to adult exons, CUG binding protein or *CUGBP1* helps retain the fetal exons.^[21] *CUGBP1*, contrary to its name, binds to single-stranded RNA adjacent to repeats^[22] and does not localize to the nuclear RNA foci in DM.^[23] By unknown mechanisms, amounts and activity of this protein are increased in DM1 cells.^[24] The amounts of *CUGBP1* are not changed in skeletal muscle in DM2.^[25] By contrast to *CUGBP1*, *MBNL1* directly binds to the repeat rich double-stranded RNA hairpin^[26] and localizes to the nuclear RNA foci in both types of DM.^[23] A semiquantitative analysis showed more than 80% depletion of *MBNL1* in nucleoplasm in DM1 and DM2 compared to normal controls.^[25] The net result therefore is expression of fetal splice isoforms in adult tissues in DM.^[21,26]

Does sequestration of *MBNL* protein(s) by repeat expansion RNA lead to loss of its function? Are *MBNL* proteins essential for processing of *ClC-1* pre-RNA in myonucleus? If so, can loss of *MBNL* protein(s) by itself cause myotonia independent of the repeat expansion RNA? To address these questions, transgenic mice were generated with a specific defect in *Mbnl* gene so that these mice did not express the CUG repeat RNA binding isoforms of *MBNL* protein.^[27] These mice developed myotonia, myopathy and cataracts reminiscent of human DM. In addition, these mice had processing defects of *ClC-1* pre-mRNA in myonucleus and loss of *ClC-1* protein in the muscle membrane similar to that observed in DM muscle. This study provides key evidence that *MBNL* proteins are at least one of the culprits that mediate toxic effects of DM RNA. To prove the point that loss of *MBNL1* is primary mechanism for myotonia, a specific isoform of *MBNL1* protein which is severely depleted in DM muscle was overexpressed in the skeletal muscle in the CUG repeat mice. Overexpression of *MBNL1* restored splicing in *ClC-1* resulting in reversal of *ClC-1* channels expression in muscle corresponding with improvement in myotonia.^[28]

Nuclear RNA foci are seen in skeletal muscle, heart and brain, the most commonly and severely affected tissues in DM.^[23,29,30] Depletion of *MBNL1* has been demonstrated in all the three by

immunofluorescence.^[25,29,30] Developmentally regulated splicing of a broad range of target mRNAs is affected in all the three tissues.^[25,29,30] (reviewed in^[6])

In summary, expanded repeats are transcribed in RNA and form discrete inclusions in nucleus. Mutant RNA sequesters MBNL1 and depletes MBNL1 from nucleoplasm. Loss of MBNL1 alone is sufficient to result in expression of fetal splice isoforms inappropriately in adult tissues. In addition to the CLC-1, several target pre-mRNAs have been identified that may have relevance in disease mechanism in DM (reviewed in^[6]). It is not clear whether the cumulative result of altered splice products in different tissues can entirely explain the complex phenotype in DM. For further reading on recent advances in the RNA pathogenesis in DM, please refer to the recently published excellent review articles.^[5-8]

Insights into the disease mechanism have already paved the way for potential therapies which may become available in the near future to DM patients. For example, simple engineering of a splice site in CLC-1 mRNA such that it is no longer amenable to the altered splicing effect of CUG repeat RNA resulted in improvement of myotonia in CUG repeat mice.^[31] Alternatively, overexpression of MBNL1 resulted in reversal of myotonia in CUG repeat mice.^[28] However, myotonia is rarely disabling in DM. Patients often do not require specific medical therapy for myotonia. Management of DM remains at best supportive comprehensive care including patient education, genetic counseling, regular monitoring of cardiac rhythm, early detection of respiratory and swallowing problems, avoidance of anesthesia-related complications, cataract surgery, and provision of physical therapy, occupational therapy, speech and swallowing therapy, and community outreach social welfare programs.

The Nondystrophic Myotonias

The nondystrophic myotonias are pure skeletal muscle diseases without the involvement of the heart, brain, eye or other tissues. Myotonia can be dramatic and sometimes disabling. Emotional surprises, cold, potassium or exercise are potential triggers for myotonia. Muscle weakness and wasting are not prominent. The nondystrophic myotonias are ion channel disorders caused by conventional point mutations or deletions in the chloride or sodium channel genes with exclusive expression in skeletal muscle.^[32-35] Diagnosis is mostly based on clinical presentation by careful history and physical examination. Ancillary tests such as EMG and nerve conduction studies may be helpful. Gene tests are usually not required to make the diagnosis. Myotonia and other symptoms are easily manageable by activity modifications, avoiding certain triggers, and pharmacological therapies. Prognosis is

generally excellent. Please refer to these excellent review articles for further reading.^[3,4]

Chloride Channel Myotonia

The nondystrophic myotonias due to chloride channelopathy include Thomsen's myotonia congenita, Becker myotonia congenita, myotonia levior and fluctuating myotonia congenita. All forms of myotonia congenita are caused by mutations that result in loss of function of the chloride channel CLC-1, which is expressed exclusively in skeletal muscle membrane.^[36] Potassium accumulation in transverse tubular system with each muscle action potential in the setting of low surface chloride conductance in skeletal muscle fibers result in myotonia.^[37] More than 70 mutations in the *CLCN1* gene have been identified in patients with myotonia congenita.^[38] Mutations at the same gene locus can cause either autosomal dominant or recessive disease. Molecular testing for *CLCN1* mutations is commercially available. The DNA testing is generally not indicated as it is very expensive and often there is a technical limitation to screen for so many mutations described in each of the myotonic disorders.

Thomsen's myotonia congenita

The name Thomsen's myotonia congenita is derived from the original description of the disease in the 1870s by the Danish physician in himself and his family members with autosomal dominant inheritance pattern. The symptoms begin during infancy or childhood. Patients report painless muscle stiffness on muscle activation after rest. Myotonia may decrease on repetitive muscle efforts, the so-called warm-up phenomenon. Emotional surprises, cold, or pregnancy may worsen myotonia. Physical examination may reveal athletic appearance with muscle hypertrophy in extremities and facial muscles in some patients. Patients demonstrate hand grip myotonia and eyelid myotonia. Patients may have trouble sitting up quickly after lying supine for several minutes reflecting myotonia in paraspinal and proximal muscles in the extremities. Muscle strength is normal. Serum CK levels are normal or only mildly elevated. The EMG reveals typical myotonic discharges in many muscles. Motor unit potentials are normal in morphology. Sensory and motor conduction studies are normal. Repetitive nerve stimulation at 3 Hz may produce a decrement of up to 65% in the amplitude of the Compound Muscle Action Potential (CMAP). Faster rate of stimulation may produce a greater decrease in the CMAP amplitude. A transient decrement in the baseline CMAP may be produced by a short exercise test which involves serial measurements of CMAP in a hand muscle after a period of brief exercise (5-20 sec). A long exercise test with several minutes of muscle action is not sensitive. Prognosis is good in most patients. The

symptoms are not progressive. Patients enjoy normal lifespan. There are no social or occupational limitations. Myotonia may be managed by activity modification in most patients. Patients with disabling myotonia may benefit by mexiletine 150 mg by mouth twice a day with a gradual titration to maximum dose of 300 mg by mouth three times a day. Side-effects are mild and include rash, diarrhea, tremor and light-headedness. Tocainide or acetazolamide are alternative options if the symptoms are refractory to mexiletine. Tocainine has an unfavorable side-effect profile with agranulocytosis, interstitial lung disease and occasionally death. It is no longer available in the United States.

Myotonia Levior and fluctuating myotonia congenita are likely clinical variations of Thomsen's myotonia. Muscle hypertrophy is absent. Symptoms are milder and fluctuate with time.

Becker's myotonia congenita

Becker's myotonia is an autosomal recessive chloride channel myotonia. The name is derived from the researcher who described this condition in the 1970s. Clinical presentation includes generalized myotonia and muscle hypertrophy similar to Thomsen's myotonia. However, there are important differences. 1. Onset is insidious and later during childhood. 2. Symptoms are often in the lower extremities at onset (the so-called ascending myotonia congenita). 3. Slowly progressive weakness in some patients. 4. Transient episodes of proximal muscle weakness lasting for seconds or minutes and may be triggered by asking the patient to arise quickly after several minutes of supine rest 5. More pronounced hypertrophy of muscles in the lower extremities. Exposure to cold, prolonged muscular strain, pregnancy, menses, and emotional tension can exacerbate myotonia. Physical examination reveals athletic appearance with muscle hypertrophy, particularly involving muscles in the lower extremities and around shoulders. Some patients may show muscle atrophy in the forearms, hands and anterior neck. Myotonia is easily recognized in many muscle groups including masticatory muscles, tongue and neck muscles in addition to grip myotonia and eyelid lag. Most characteristic finding is marked difficulty in arising from the supine position and climbing stairs which gradually improves after several steps, secondary to warm-up phenomenon. This is thought to be due to a combination of myotonia and muscle weakness. Most patients notice muscle weakness upon activity after a period of rest. Some patients may have persistent lower extremity weakness which can be disabling in the activities of daily living. Muscle stretch reflexes may be depressed in the lower extremities. Creatine Kinase (CK) levels may be increased. Repetitive nerve stimulation and short exercise test may show decline in CMAP amplitude. Long exercise test may reveal a

small decrement which is not a feature in Thomsen's myotonia. Most patients enjoy good quality of life. Symptoms are only slowly progressive and may stabilize after a patient reaches the third decade. Treatment is directed towards activity modifications, avoidance of triggers for myotonia and weakness. In some patients with disabling myotonia pharmacological therapy including mexiletine, tocainide or acetazolamide is beneficial.

Sodium Channel Myotonia

Myotonias secondary to sodium channelopathy are characterized by sensitivity to cold exposure, potassium ingestion and paradoxical worsening after muscle exercise in contrast to the warm-up phenomenon seen in the chloride channel myotonias.^[36] All sodium channel myotonias are inherited in autosomal dominant pattern. Sodium channel myotonias are classified as paramyotonia congenita, potassium-sensitive myotonias which include myotonia fluctuans, myotonia permanens and acetazolamide-responsive myotonia.^[36] Like chloride channel myotonias, several different mutations are identified in pedigrees.^[36] DNA testing for mutations is not indicated for it is expensive and there is obvious limitation to screen for so many mutations causing an individual disorder. There is no easy explanation for disease mechanism in each sodium channel myotonic disorder. It is believed that almost all mutations alter activation kinetics of the sodium channel and enhance prolonged sodium entry into muscle cells contributing to persistent depolarization, a physiological state of myotonia.^[36] Care must be taken in each of these disorders to prevent rigidity and rhabdomyolysis during or immediately after surgery.

Paramyotonia congenita

Paramyotonia refers to myotonia which worsens with exercise, particularly in cold temperatures. Symptoms begin during infancy or childhood. Typical presentation includes prolonged eye closure after crying in infants or washing face in cold water and "frozen tongue" after eating ice cream. Some patients may report flaccid weakness after exercising in cold temperatures. Potassium ingestion, rest followed by exercise and prolonged fasting may also aggravate paramyotonia. Physical examination reveals prominent eyelid paramyotonia manifest as inability to open the eyes after repeated sustained eye closure or sustained lid retraction after a prolonged upward gaze. Placement of ice pack on eyelids may aggravate paramyotonia. Immersion of the hand in ice cold water for 10-15 min prior to hand grip exercise may provoke paramyotonia and subsequent weakness. Motor and sensory nerve conduction studies are normal. Repetitive nerve stimulation at 5 Hz may

result in decrement in CMAP amplitudes. Similarly, short exercise test after cold exposure may also result in decrement response. The EMG reveals myotonia in many muscles. Fibrillation potentials and positive sharp waves may become evident after exposure to cold. Silent muscle contracture may occur with extreme cold exposure. Single-fiber EMG may show increase jitter and occasionally blocking. Muscle biopsy is not indicated for the diagnosis. In most patients avoiding triggers such as exercise and cold exposure are sufficient to maintain good quality of life. Mexiletine can be used for disabling paramyotonia. Thiazide diuretics may be added in patients with prominent symptom of weakness.

The potassium aggravated myotonia

There are three distinct sodium channel myotonic disorders in which the myotonia is aggravated by potassium ingestion. Cold exposure generally does not worsen myotonia like it does in paramyotonia congenita. Weakness is not a prominent symptom.

Myotonia fluctuans is characterized by generalized myotonia triggered by potassium ingestion or by exercise. In contrast to paramyotonia, patients may have a warm-up effect after initial exercise, however, the myotonia becomes more pronounced after a second bout of exercise following a period of rest of about 20-40 min. Patients report fluctuation in the severity of myotonia with periods of no evident myotonia lasting for hours to days. Muscle bulk and strength are normal. The CK levels may be elevated by two to three-folds. The EMG may reveal myotonia and fibrillation potentials. Nerve conduction studies are normal. Muscle biopsy may reveal mild abnormalities such as increased internal nuclei, fiber size variability and subsarcolemmal vacuoles. Most patients do not require medication. Simple avoidance of potassium-rich food items may be sufficient. Mexiletine can be helpful to relieve disabling myotonic stiffness.

Myotonia permanens is a rare and severe form of nondystrophic myotonia. Clinical presentation includes onset before age 10 years, severe generalized myotonia, and muscle hypertrophy. Muscle weakness is not prominent. Severe myotonia involving intercostal muscles may result in respiratory compromise with hypoxemia and acidosis. Potassium ingestion and exercise are the usual triggers for myotonia. The EMG reveals generalized myotonia with normal motor unit potentials. Mexiletine or Tocainide may provide partial relief from myotonic stiffness. Acetazolamide may help relieve exercise-induced muscle stiffness or cramps.

Acetazolamide-responsive myotonia is characterized by generalized myotonia worsened by potassium ingestion, cold and fasting, and excellent recovery with acetazolamide. Patients present during childhood with progressive generalized myotonia which is easily

evident on clinical examination and by EMG. Eyelid paramyotonia may be seen in some patients. Myotonic stiffness can be painful. Exercise generally has no significant effect on myotonia. Treatment includes acetazolamide with starting dose 125 mg daily with gradual titration up to 250 mg three times a day if required. Side-effects include kidney stone formation, parasthesia, nausea, confusion, mood irritability, depression, rash and liver function abnormalities. Regular monitoring of complete blood count and liver functions is recommended. Mexiletine can also relieve myotonia.

Hyperkalemic periodic paralysis with myotonia

Symptoms begin during childhood with episodes of focal or generalized muscle weakness usually sparing the face and respiratory muscles. Symptoms usually last for minutes to hours and are triggered by cold temperatures, potassium ingestion, rest after exercise, fasting or emotional tension. Myotonia is easily evident by clinical examination and by EMG. Myotonia is alleviated by repeated exercise. Serum potassium levels may be elevated during the episodes. The CK levels can be elevated. Treatment includes avoidance of triggers such as potassium-rich food items and exhaustive exercise followed by rest. Acetazolamide can reduce frequency of episodic weakness and myotonia.

Differential Diagnoses for Electrical Myotonia

Electrical myotonia with variable muscle weakness can be seen in acid maltase deficiency, myotubular congenital myopathy, polymyositis, hypothyroidism, malignant hyperthermia and exposure to certain drugs including clofibrate, HMG CoA inhibitors, propranolol, cyclosporine, colchicine, and penicillamine. Myotonia-like discharges can be seen in Schwartz Jampel syndrome and Isaac's syndrome of neuromyotonia. Continuous muscle fiber activity in these disorders does not wax and wane like true myotonia. These disorders can also be easily diagnosed based on associated clinical features and distinct gene mutations.

In summary, myotonic disorders are easily recognized by careful history and physical examination. Expensive DNA tests are not routinely indicated. Myotonia results from abnormal expression of either chloride or sodium channels in skeletal muscle. Disease mechanism of myotonia in nondystrophic myotonias is straightforward from conventional mutations in the genes encoding either chloride or sodium channels. In DM, myotonia results from impaired transmembrane chloride conductance by an unprecedented RNA-mediated disease mechanism. Mutant DM RNA sequesters MBNL1 and depletes MBNL1 in nucleoplasm. Subsequent loss of MBNL1 function leads to altered splicing of CIC-1. Abnormal splice products do not encode functional CIC-1, the

major chloride channel in skeletal muscle. Loss of ClC-1 protein in muscle membrane results in impaired chloride conductance and myotonia. Mutant DM RNA interferes with splicing of several other transcripts in the skeletal muscle, heart and brain. Further research is needed to determine if abnormalities in intracellular metabolism of select target RNAs, splicing or otherwise, can explain multisystem involvement in DM. Initial stages of understanding the disease mechanism has already opened a new era of novel therapies in DM.

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