New Classification and Treatment for Myotonic Disorders

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Abstract

Myotonia is repetitive firing of muscle action potentials causing prolonged muscle contractions even after mechanical stimulations to the muscles have ceased. Most common myotonic disorder is myotonic dystrophy which is now termed DM1, myotonic dystrophy type 1. In Japan, proximal myotonic myopathy, which is now called DM2 has not been reported. Both DM1 and DM2 have Cl channel abnormality which causes myotonia. Less commonly we encounter Thomsen's disease, and autosomal recessive generalized myotonia (Becker type) which also have a Cl channel abnormality. There are other myotonic disorders related to Na channelopathy which include three disorders: paramyotonia congenita, adynamia episodica hereditaria, and myotonia fluctuans. Myotonia has been treated by various Na channel blockers, mexiletine, phenytoin, and carbamazepine, but they were originally developed for cardiac arrhythmia, or seizure disorders and they have undesirable side effects, weakness. Comprehensive treatment includes myotonia control without reducing the strength, and care for systemic manifestations of DM1.
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Key words: myotonic dystrophy type 1 (DM1), Thomsen's disease, autosomal recessive generalized myotonia (Becker type), paramyotonia congenita, adynamia episodica hereditaria, myotonia fluctuans

History of Myotonia Research

If we quickly review the important investigations of myotonic disorders we can start out from Landau's work in 1952 (1), when he described that myotonia occurs even when we block the peripheral nerves, and neuromuscular junctions; therefore, myotonia occurs due to an abnormality of the muscle membrane. The author performed intracellular recordings of myotonic burst (2) after excitation-contraction uncoupling by t-tubular disruption (3, 4) on rat hemidiaphragm preparations in which myotonia had been induced by Cl channel blocker, anthracene-9-carboxylic acid. From these results it is comfirmed that myotonia occurs even if the neuromuscular junction is blocked and the t-system is disrupted: therefore, myotonia is elicited by muscle membrane abnormality. Then in 1971, Lipicky et al (5) performed intracellular recording of the muscle fibers and found that the membrane resistance of the muscle fibers obtained from myotonia congenita is increased as much as 2.2 times more than normal muscle membrane resistance. Since 80% of membrane conductance is due to Cl conductance, Lipicky et al considered that the increased membrane resistance of the myotonic muscle has decreased Cl conductance. In 1987, Lehmann-Horn et al (6) studied paramyotonia congenita, and found that myotonia of paramyotonia congenita occurs due to disturbance of inactivation of Na channel of the muscle membrane (7, 8). Advanced physiological techniques have clarified that the pathophysiological mechanisms of myotonia are not uniform and they have disclosed that different myotonic disorders are based on different channelopathies: myotonia congenita is based on reduced Cl conductance, and paramyotonia congenita is based on the inability to inactivate the Na channels of the skeletal muscles.

Another remarkable advance in recent neuroscience is the genetic investigation of various disorders. Point mutations have been found in Cl channels in Thomsen's disease, autosomal recessive generalized myotonia (Becker type), and many point mutations are found in voltage-gated Na channels in paramyotonia, familial hyperkalemic periodic paralysis (7–10). These various point mutations, and various channelopathies are now combined in consideration to clarify the pathophysiological mechanisms of different myotonic disorders (11). In another words a new classification of myotonic disorders is necessary due to the advanced knowledge in channelopathies and genetics to explain all types of clinical manifestations.

Myotonic dystrophy (DM1) is the most common form of muscular dystrophy in adults. Recently myotonic dystrophy type 1 (DM1) results from an unstable expansion of a CTG

Table 1. Clinical, Laboratory, and Genetic Abnormalities of Myotonic Dystrophy Type 1(DM1), and Myotonic Dystrophy Type 2 are Summarized in the Table. To Date, There is No Case Report of DM2 in Japan

	DM1 myotonic dystrophy type 1	DM2 (no case report in Japan) myotonic dystrophy type 2 (proximal myotonic myopathy)
Myotonia	+	+
Cataract	+	+
Muscle weakness	+from distal muscles	+proximal muscles
Muscle pain	–	+
Cardiac arrhythmia	++	+
Muscle enzyme elevation	+	+
Mental disturbance	+	+
Inheritance	autosomal dominant	autosomal dominant
Chromosome locus	19q 13.3	3q 21.3
Genetic abnormality	(CTG)n expansion	(CCTG)n expansion

repeat in 3' untranslated region of myotonic dystrophy protein kinase (DMPK) gene on chromosome 19q 13.3 (12). Myotonic dystrophy type 2 (DM2) results from an unstable expansion of a CCTG tetraplet repeat in intron 1 or the zinc finger 9 (ZNF9) gene on chromosome 3q 21.3 (13–15). DM2 cases have not been reported in Japan, but many DM2 cases have been reported in Germany, Italy, Finland, and America and the comparison of different clinical manifestations between DM1 and DM2 has been done as listed in the Table 1. DM1 and DM2 both have myotonia and cataracts and one big difference is a characteristic muscle pain in DM2 which does not exist in DM1. In both DM1 and DM2 the repeat expansions expressed at the RNA level alter RNA processing by interfering with alternative splicing of the chloride channel gene which causes myotonia (16) and accumulated triplet or tetraplet repeats in the cell nucleus interference with altered splicing of insulin receptor gene leads to insulin resistance, and diabetes. In this way genetics explain the clinical features better with the aids of new findings. Treatment of various myotonic disorders also must be based on the essential mechanisms of the disorders.

Clinical Features of Common Myotonic Disorders

When we see a patient with myotonic disorder we can shake his hand and see whether he can quickly open his grip after shaking hand; grip myotonia prevents him from quickly opening the grip of his hand and it takes time to open his fingers fully. When you hit his thenar muscle using a reflex hammer, percussion myotonia is noted and his thumb adducts. We have to determine whether the patient has muscle atrophy and weakness. If he has Thomsen's disease, or paramyotonia congenita, he has no atrophy of the muscles, nor weakness of the muscles. If he has myotonic dystrophy, he has atrophy of the distal muscles of hands and legs and weakness of the muscle starting from the distal muscle and

extending to the proximal muscles as the disease progresses. The characteristic muscle atrophy in myotonic dystrophy causes what we call hatchet face elicited by atrophy of the masseter muscles. The sternocleidomastoid muscles also become atrophic in myotonic dystrophy. Myotonic dystrophy has systemic involvement as well and frontal baldness, cataracts, and testicular atrophy are characteristic features (17). If we pay attention to these manifestations, it is easy to make a diagnosis of myotonic dystrophy. The needle EMG can confirm the presence of myotonia by demonstrating insertion myotonia. The laboratory data also show systemic involvement of this disorder: hypothyroidism, insulin resistance and diabetes, hypofunction of the adrenal glands, and hypogonadism. Table 2 summarizes the diagnostic steps of myotonic disorders.

In myotonia congenita (Thomsen's disease), and autosomal recessive generalized myotonia (Becker type), the patient is rather muscular and there is no atrophy of the muscles, nor weakness of the muscles. In paramyotonia congenita, the patient has myotonia when he is exposed to cold climate, but in the summer time he is free from myotonia. This is due to a Na channel abnormality of paramyotonia and depolarization of the muscles occurs when he is exposed to cold temperatures; myotonia and muscle weakness develops during the winter, but free from symptoms in the summer time. Therefore, such patients must take a Na channel blocker only during the winter time.

Various Myotonic Disorders and Channelopathy

There are eight different diseases which have myotonia: Myotonic dystrophy type 1 (DM1), mytonic dystrophy type 2 (DM2) (previously called proximal myotonic myopathy), myotonia congenita (Thomsen's disease), autosomal recessive generalized myotonia (Becker type), paramyotonia congenita, hyperkalemic periodic paralysis (adynamia

Table 2. Clinical Diagnostic Steps are Summarized when You See Myotonic Patients

1) Clinically myotonia can be checked by grip myotonia, and percussion myotonia.
2) Next step:
   to see muscle atrophy and weakness
     muscle atrophy and weakness (+): DM1 (also check frontal baldness, hatchet face, cataract)
     muscle atrophy and weakness (–):
       Thomsen's disease (AD), autosomal recessive generalized myotonia
       paramyotonia, adynamia episodica hereditaria, myotonia fluctuans
    (If the patient has myotonia only when he is exposed to cold temperature, he has paramyotonia)
3) Needle EMG: insertion myotonia (bursts of action potentials elicited by needle electrode insertion)
4) Slit lamp examination of the lens for cataract
5) Genetic studies

Table 3. Common Myotonic Disorders are Classified According to Chloride and Sodium Channelopathy

Cl channellopathy, Muscle atrophy (–)	Cl channellopathy Muscle atrophy (+)	Na chanellopathy Muscle atrophy (–)
1) Thomsen's disease (autosomal dominant)	1) DM1	1) paramyotonia congenita
2) Autosomal recessive generalized myotonia (Becker type)	2) DM2	2) adynamia episodica hereditaria
		3) myotonia fluctuans

episodica hereditaria), chondrodystrophic myotonia (Schwartz-Jampel syndrome), and Pompe's disease (glycogen storage disease type II). Myotonia can be defined as excessive and prolonged muscle excitability and muscle contraction induced by mechanical stimulation. In common myotonic disorders as summarized in Table 3, the mechanism is clarified and it is related to hyperexcitability of the muscle membrane caused by different channelopathies: 1) reduced Cl conductance of the muscle membrane, 2) disturbance of inactivation of Na channel. Recently, we classify major myotonic disorders according to different channelopathies, but some rare myotonic disorders have not been classified according to channelopathies. For example needle electromyographic recordings of myotonia seen in Schwartz-Jampel syndrome are attributed to an abnormality of the neuromuscular junction. The pathophysiology of myotonic bursts seen in Pompe's disease has not been clarified. In Pompe's disease glycogen accumulates in the cardiac muscles of the diseased infant causing death from heart failure, but myotonic bursts recorded by needle EMG help to suspect the possibility to Pompe's disease and lead the pediatrician to perform muscle biopsy to make a definite diagnosis of this rare disorder.

Classification of Myotonia

Major myotonic disorders can be classified as Cl channelopathy without or with weakness, and Na channelopathy. Classic myotonia congenita can be devided into two types: Thomsen's disease (autosomal dominant) and autosomal recessive generalized myotonia (Becker type). Myotonic dystrophy is now termed DM1 and DM2, and both

have muscle weakness. There are three disorders in Na channelopathy: paramyotonia congenita, adynamia episodica hereditaria (myotonia, and hyperkalemic periodic paralysis occurs in this disorder), and myotonia fluctuans (18), which was described by Ricker et al in 1994. The author has not encountered any case of myotonia fluctuans in Japan, but this disorder is named as such due to the fluctuating clinical presentation of myotonia. Ricker et al describe that myotonia develops 20–40 minutes after exercise, potassium causes generalized myotonia, and cooling has no major effect on muscle function. Table 3 shows this classification.

Treatment for Myotonic Dystrophy

In neurology outpatient clinic we often see myotonic dystrophy (DM1), but we rarely meet patients of Thomsen's disease or paramyotonia. In Japan, to date no cases of DM2 have yet been reported. To date we do not have any medication to open Cl channels of the skeletal muscles; therefore, we have been using Na channel blocker for myotonia. Mexiletine, procainamide, phenytoin, carbamazepine are all Na channel blockers which were originally developed for cardiac arrhythmia, or seizure disorders. We have been using them for myotonia control; however, whether or not they are appropriate for myotonic disorders is not certain. Na channel blockers tend to reduce muscle action potentials and reduce muscle power as well. For myotonic disorders which do not show muscle weakness, the above drug effects to reduce muscle power do not become a big hindrance, but for myotonic dystrophy type 1, and type 2 the side effect of muscle weakness is a hindrance. In myotonic dystrophy progressive muscle weakness occurs and the patients have a lot

Table 4. Treatment for Myotonic Dystrophy Type 1 Includes Treatment for Myotonia, Muscle Weakness, and Systemic Manifestations

Tx for myotonia	Tx for muscle weakness	Tx for systemic manifestations
No medication if he does not want to take. Procaine amide Mexiletine Phenytoin Carbamazepine Dehydroepiandrosterone sulfate (DHEAS)	No effective medicine available. Trials with Creatine, and DHEAS: some improvement	①Cataract: operation and implanting artificial lens ②Ptosis: upper blepharoplasty ③Cardiac arrhythmia: cardiac pacemaker as needed ④Diabetes mellitus: metaformin ⑤Hypothyroidism: thyroxine ⑥Hypogonadism: hormonal replacement is not usually done

of difficulty in their daily life because of muscle weakness rather than myotonia. The ideal medicine for myotonia is one that would abolish myotonia and yet does not cause muscle weakness.

Treatment for Thomsen's disease

Since Thomsen's disease does not cause any weakness of the muscles, the only complaint of the patient is slow action of what he wants to perform due to myotonia which causes undesired muscle contractions and hinders his quick performance. If the patient wants to decrease myotonia, Na channel blockers like mexiletine or phenytoin can help to decrease myotonia as needed. When he needs quick action like when he travels in a group and has to get on and off a bus quickly, he can take the medicine, but otherwise he does not need to take medications regularly.

Treatment of paramyotonia

Myotonia and muscle weakness in paramyotonia occur only during cold climate and the patient simply can take mexiletine during the winter time, and does not need to take during the summer months. No progressive weakness of the muscles occurs in this disorder, and he can live an almost normal life with the help of mexiletine only during the winter time.

Treatment of myotonic dystrophy

DM1 and DM2 have 3 different problems: ①myotonia, ②muscle weakness, ③systemic manifestations like cataracts, diabetes mellitus, cardiac arrhythmia, and others (Table 4). To date, we have been using various Na channel blockers to reduce myotonia. Since myotonic dystrophy has progressive muscle weakness due to the dystrophic nature of this disorder, even if myotonia is reduced, muscle weakness is a bigger problem. Na channel blockers tend to reduce muscle power by decreasing muscle action potentials and these unwanted effects of Na channel blockers are the problem.

We do not have a Cl channel opener; therefore, we are utilizing Na channel blockers which were originally developed for cardiac arrhythmia or seizure disorders. It is important to develop medications for myotonic dystrophy which can reduce myotonia and yet maintain the muscle strength as it is. For this purpose dehydroepiandrosterone sulfate (DHEAS) (19) is a candidate for myotonia control for DM1. When Sugino et al (19) used this steroid medicine for patients 250 mg/day intravenously once a day and it reduced myotonia and improved the activities of daily living. DHEAS does not reduce muscle power as much as other drugs that have been used for myotonia in the past.

① Therapeutic trials to improve muscle strength for myotonic dystrophy
Creatine monohydrate therapy

Creatine monohydrate (CrM) was tried by Tarnopolsky et al (20) for 34 patients with myotonic muscular dystrophy at a dose of 5 g/day for 4 months along with placebo. The mean hand grip was 20.7 kg before CrM and 20.2 kg after CrM therapy. Pulmonary function tests including FVC, and FEV_1 showed no change following CrM therapy.

A double-blind placebo-controlled study of CrM therapy of Schneider-Gold et al (21) for 20 DM2 patients for 3 months duration did not have significant effects on muscle strength; however, 2 DM2 patients showed mild improvement in DM2 specific muscle pain, which is more troublesome than myotonia for DM2 patients.

Creatine monohydrate therapy was done as an open trial for 20 Japanese muscular dystrophy patients including 14 myotonic dystrophy (DM1) cases (22). Twelve patients had subjective improvement of muscle power. It is important to monitor the clinical manifestations of the patients while they are taking creatinine, since there are minor side effects of creatine including excessive sleepiness, diarrhea, and sweating. To date, DM2 cases have not been reported in Japan.

②Treatment for systemic manifestations
a) Treatment for cataracts: postoperative complication causing decreased vision

It is important to evaluate for visual disturbance after cataract surgery for DM1. In DM1, capsulorhexis contracture (23) tends to occur after cataract surgery and causes decreased vision which may occur a few months after the cataract surgery. Capsulorhexis contracture results from fibrous

metaplasia of lens epithelial cells from the anterior capsule. Myotonic dystrophy has a tendency to develop this problem; therefore, it is important to inform the ophthalmologist before cataract surgery of the diagnosis of myotonic dystrophy.

b) Treatment for myopathic ptosis

Myopathic ptosis is seen in DM1, mitochondrial myopathies, and oculopharyngeal muscular dystrophy. It can be surgically treated by an ophthalmologist using an operative procedure called upper blephaloplasty, in which a physiological sling is placed between the eyebrow and the upper eyelid. Burnstine and Putterman (24) treated 6 patients in such a manner and they did not have postoperative complications like lagophthalmos, corneal exposure keratopathy, nor ocular desiccation complaints.

c) Treatment for cardiac arrhythmia to avoid sudden death

In order to avoid sudden death from cardiac conduction defects and arrhythmia in myotonic dystrophy it is important to examine ECG, Holter monitoring, and echocardiogram. When ECG shows an increased PR interval, measurement of HV interval (infra-nodal conduction delay; HV >70 ms) may help to decide the need for pacemaker implantation. Lazarus et al (25) followed 49 patients with myotonic dystrophy for 53.5 months and 41 cases (83.7%) developed sudden arrhythmia; complete AV block developed in 21 cases, sinoatrial block in 4 cases, and atrial (25 cases) or ventricular (13 cases) tachyarrhythmia. Ten patients died, and 4 of them had sudden death. They recommend implantation of a cardiac pacemaker if the HV interval is over 70 ms in myotonic dystrophy patients to prevent sudden death.

d) Treatment for diabetes mellitus

In myotonic dystrophy, insulin resistance and hyperinsulinism is present. Metaformin can control hyperglycemia of DM1 (26), since metaformin increases glucose uptake of the skeletal muscles independently.

e) Treatment for excessive daily sleepiness: to avoid unemployment

In order to avoid excessive daily sleepiness modafinil which is usually used for narcolepsy was given to myotonic dystrophy patients for 4 weeks along with placebo trial (27). Modafinil was effective and did not have any cardiovascular complications.

f) Treatment for severe constipation in myotonic dystrophy

There is a case report of a 4-year-old girl with Steiner's disease who had severe constipation after a few months of life (28). The rectal biopsy revealed a myopathy affecting the striate muscles of the distal colon. The diseased part of the colon was resected and the normal colon was brought down to connect the rectum and she did well after the surgery. This case indicates that even striate muscles can be involved in myotonic dystrophy.

g) When a myotonic dystrophy patient undergoes surgery

A 50-year-old man with myotonic dystrophy developed gastric cancer. In order to avoid respiratory complications, anesthetic management with a laryngeal mask airway (29) was useful to perform gastrectomy in a patient with muscular dystrophy.

③Experimental therapeutic trials to decrease CTG repeat: Future essential treatment for DM1

a) Furling et al (30) introduced gene therapy for myotonic dystrophy myoblast by using antisense RNA delivered *in vitro* using retrovirus. Myotonic dystrophy is caused by the expansion of CTG repeats located in the 3'untranslated region of myotonic dystrophy protein kinase (DMPK). The expansion of CTG repeat causes accumulation of mRNA with expanded CUG repeats in the cell nucleus and splicing abnormality of pre mRNA of Cl channel eventually results in poor development of the muscle Cl channel, and myotonia occurs. By using antisense RNA complementary to (CUG)13 repeats and the 110-bp region, mutant DMPK transcripts decrease and human myoblast function such as myoblast fusion and uptake of glucose is restored. The *in vitro* success of gene therapy of this type gives hope that this therapy may be further applied to myotonic dystrophy patients after overcoming several obstacles.

b) Systemic manifestations, present including diabetes mellitus, cataracts in DM1

Experimental therapy was performed by using lymphoblast cells of DM1 patients and CTG repeat expansion can be reduced by chemotherapeutic agents; ethylmethanesulfonate, mitomycin C, mitoxantrone, doxorubicin (31). This may be eventually applicable to 17 neurological intractable diseases including spinocerebellar degeneration in addition to DM1.

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