Autosomal Dominant Myotonia Congenita in a Taiwanese Family and Beneficial Response to Mexiletine

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Abstract- Autosomal dominant myotonia congenita (ADMC) known as Thomsen's disease is one of autosomal dominant myotonic syndromes. The incidence of ADMC is rare and the effect of treatment and prognosis are different from those in myotonic dystrophy type 1 (DM1). The ADMC can be differentiated from DM1 by clinical features and a genetic test. Therefore, the diagnosis and treatment in ADMC are important. We identify a case of ADMC who were misdiagnosed as DM1 9 years ago. After a detailed clinical investigation and molecular genetic studies, DM1 was ruled out. We herein report the clinical features of ADMC in a Taiwanese family. The 3 probands experienced walking difficulties in their daily activities related to myotonia and slow relaxation. Two probands received mexiletine treatment and showed a marked improvement according to the questionnaires for subjective evaluation and objective tests including eyelid contraction, hand grasping, and walking upstairs and downstairs. We conclude that the diagnosis of ADMC can be differentiated from other hereditary myotonic disorders by a careful evaluation and molecular genetic studies. In addition, mexiletine therapy is effective and safe in the treatment of ADMC.

Key Words: Autosomal dominant myotonia congenita, Thomsen's disease, Therapeutic response, Mexiletine

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INTRODUCTION

Autosomal dominant myotonia congenita (ADMC) (Thomsen's disease) and autosomal recessive generalized myotonia (Becker's myotonia) are a group of genetic diseases caused by mutations in the voltage-gate chloride channel gene (CLCN1) on chromosome 7q35[1-7]. The onset of ADMC usually occurs in infancy or early childhood, and myotonia and muscle stiffness may affect the muscles of the face, neck, tongue and limbs[6,8-10]. Severe myotonia frequently results in disabilities in initiating movement or following sudden stimuli. Furthermore, fluctuating myotonia and/or myalgia are occasionally seen, and the disease tends to run a relatively benign course. Muscle weakness and wasting, which are not found in ADMC, can differentiate ADMC from myotonia dystrophy (DM) and Becker's myotonia. Unlike DM, ADMC does not cause cataracts, frontal

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alopecia, testicular atrophy, cardiac arrhythmias nor mental retardation[8]. However, intrafamilial variability of clinical manifestations is observed in patients with ADMC[11,12].

The mechanisms of the repetitive firing of muscle fiber in myotonia remain unclear. Some mechanisms have been proposed to explain the intrinsic muscle hyperexcitability[2,5,7,8,10,13]. Molecular genetic analyses recently showed an increased number of CTG triplets in the 3'-untranslated region (3'-UTR) of the myotonic dystrophy type1 protein kinase (DM1PK) gene in myotonic dystrophy type1 (DM1) patients[14]. Additionally, the combination of neurological examination, electrophysiology, cold exposure, potassium loading, and pedigree analysis allows accurate classification of these disorders. Satisfactory therapy for myotonia congenita was achieved through various medications[1-2,5,8,10,11,13]. In myotonia congenita, reducing the chloride ion permeability of the muscle cells makes it easier for re-opening of the sodium ion channels and leads to the myotonic hyperexcitability[4-7]. Mexiletine is used primarily for its cardiac actions as an anti-arrhythmic agent. It also has the actions on surface membrane of skeletal muscles with activity-dependent sodium channel blocking properities[2,6]. Recently, low dose of mexiletine was also used in the treatment of mutant sodium channels with paramyotonia congenita and hyperkalemic periodic paralysis and CLCN1 mutation with myotonia congenita[7,15].

A proband initially masquerading as DM1 was encountered 9 years ago. However, while we reviewed the clinical manifestations, the diagnosis of ADMC was suspected. Molecular analysis of the size of CTG repeats for DM1PK was performed from 13 family members to rule out the diagnosis of DM1. The clinical phenotypes in the family were studied and two patients exhibited a marked improvement in myotonic phenomena with mexiletine. The present study emphasizes that a detailed survey of the family members and clinical phenotypes as well as molecular genetic studies to rule out DM1 are crucial in the diagnosis of ADMC and mexiletine can improve the function of daily activities in patients with ADMC.

PATIENTS AND METHODS

Report of cases

The proband II-3, a 26-year-old woman, began to complain of muscle stiffness in her proximal legs and difficulty climbing stairs since the age of 7 years. The symptoms improved after exercise, and worsened in cold weather. Moreover, the patient often suffered from falls when under emotional stress or in crowded environments. She first visited our hospital at the age of 17, and neurological examinations showed action myotonia in her hands and proximal legs, and limb hypertrophy on the calf and forearm muscles. Mental retardation was also noted. There was neither frontal baldness nor cataract. Laboratory examinations were all normal, including serum CK, blood sugar, electrolytes, liver and renal functions, cortisol, sexual hormones, thyroid and pituitary functions. Electrocardiogram was also normal. Furthermore, EMG studies showed typical myotonic discharges in all the muscles tested which were not aggravated by muscle cooling, while nerve conduction studies were normal. Muscle biopsy from the left vastus lateralis revealed mild muscle atrophy, particularly type 2 B fibers. A congenital type of myotonia dystrophy was impressed and 300 mg of phenytoin daily was given for myotonia, but this treatment was in vain. At the age of 24, myotonic phenomena worsened and began to interfere with her daily activities. She was referred for further confirmation and molecular genetic analysis. However, congenital myotonia was impressed after review of her history. Neuropsychologic study indicated impaired mental function (full IQ: 52, verbal IQ: 54 and performance IQ: 59). Brain magnetic resonance imaging was unremarkable.

The proband II-2, a 29-year-old woman, complained of slow movement, and difficulty in running and climbing upstairs since 12 years old. She also experienced muscle stiffness and pain in cold weather. However, neither fluctuating weakness nor difficulty delivery was noted during her two pregnancies. She was examined after her younger sister was suspected to have ADMC. Evaluation revealed muscle hypertrophy of the distal legs and percussion myotonia on thenar and lingual muscles. Lenticular opacities and frontal baldness were not

observed. The serum creatine kinase (CK) concentration was normal. Electromyography (EMG) study confirmed myotonic discharges. Muscle biopsy from the left vastus lateralis revealed a mild decrease of type 2B fibers. Her 2 children, subject III-4 (3 years 4 months old) and subject III-5 (10 months old) possessed a normal birth history and physical development. No muscle stiffness or percussion myotonia occurred during the interview.

Other proband, their younger brother, a 24-year-old man (II-4) had similar clinical pictures, including action and percussion myotonia, and limb hypertrophy. None of the individual sampled displayed muscular weakness or extra-skeletal system involvement, such as alopecia, cataract, cardiac conduction defect, and changes in brain magnetic resonance images. The individual exhibited characteristic pictures of myotonia congenita including myotonic phenomena and limb hypertrophy.

Molecular genetic analysis of DM1PK

Total DNA was extracted from the blood cells of 13 individuals in this family. Figure presents the pedigree of the family. DNA analysis was conducted for CTG trinucleotide repeats in DM1PK on chromosome 19 to rule out myotonic dystrophy. The methods were performed as described previously[16].

Mexiletine treatment

Two probands (II-2 and II-3) with the most severe symptoms received 300 mg of mexiletine daily for 4 months. To evaluate the efficacy of the medication, the two probands answered questionnaires that subjectively evaluated the efficacy. The questionnaires included bulbar function, chewing and movement of upper and lower limbs. Meanwhile, the therapeutic effects before and after mexiletine treatment were evaluated according to objective tests. Each test was performed 3 times and every patient rested for 15 minutes between the two tests[17]. The tests measured the duration of (1) lid myotonia (opening and closing the eye 10 times) (2) hand myotonia (executing a maximal handgrip 10 times) (3) stairs test (going from a sitting position to climb and descend 11 steps and then sitting down). Finally, a paired t test was performed to analyze the difference in spending time before and after mexiletine treatment.

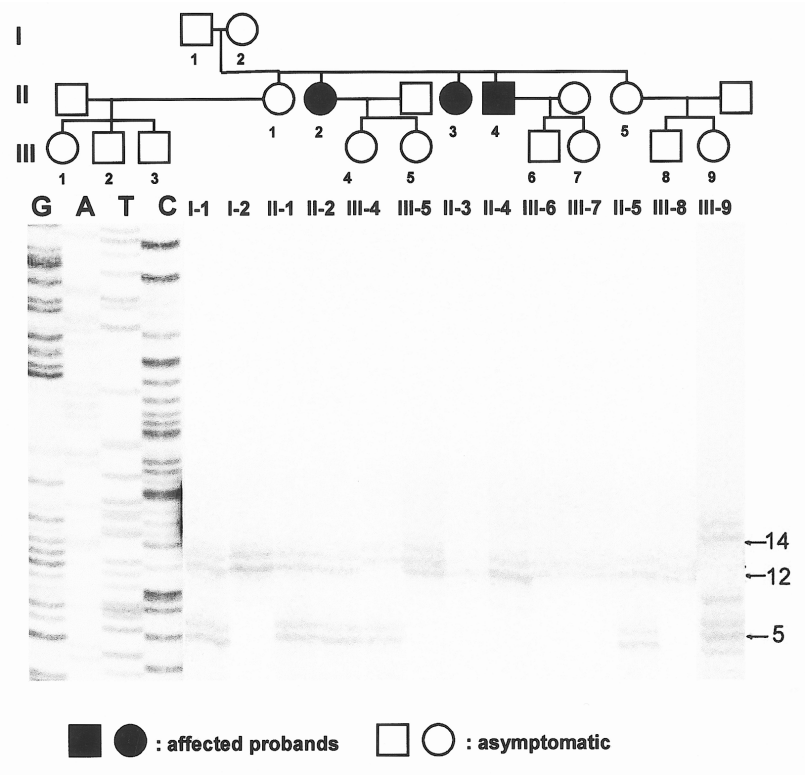

Figure. The pedigree and molecular genetic analysis of a family with autosomal dominant myotonia congenita. Molecular genetic analysis shows that the PCR analysis of the CTG trinucleotide repeats of DM1PK locus in leukocytes were between 5 and 14 for 13 members in this ADMC family. The four tracks on the left contain pGEM sequence, which was used to determine the size of alleles.

RESULTS

Molecular genetic studies

The PCR products were resolved by electrophoresis on 6% urea-polyacrylamide gels in parallel with a pGEM sequencing ladder and were visualized by autoradiograph. In molecular genetic analysis, the number of CTG repeats at DM1 locus was 5-14 in 13 individuals of the family (5-25 for the normal controls) (Fig.).

Mexiletine treatment

Two probands received the mexiletine treatment. Table 1 reveals an improving tendency after medication, including hand movement such as teeth brushing, writing, and leg movement, particularly in walking, running, and going up or down stairs. However, no definite improvement was evident in swallowing, speaking and chewing. After mexiletine treatment, a statistically significant improvement in hand myotonia and climbing upstairs occurred in 2 probands ($p<0.05$). However, no statistically significant improvement in going downstairs and in lid myotonia, for these 2 probands (Table 2).

During the mexiletine treatment for at least 3 years, there were no significant adverse effects. In series follow-up studies, complete blood counts including white blood counts and platelet counts were normal. In addition, electrocardiograms were also within normal limits.

Table 1. *Questionnaires of functional improvement after mexiletine treatment*

Functional activities	II-2	II-3
Swallowing	−	−
Speaking	−	−
Chewing	−	−
Hand movement		
Brushing teeth	+	−
Eating	−	−
Writing	+	+
Leg movement		
Walking	+	+
Running	++	++
Upstairs	++	++
Downstairs	+	+

++: prominent improvement; +: slight improvement; −: no change.

DISCUSSION

In ADMC (Thomsen's disease), myotonia is usually painless, widespread and benign. The myotonia in myotonia congenita is generally aggravated by rest, and emotional stress and improved after repetitive muscle contraction, which are different from myotonia in DM1, paramyotonia congenita, and hyperkalemic periodic paralysis[6,8]. It is commonly associated with diffuse muscular hypertrophy, particularly in affected males[8,9,10,11]. Herein, the involvement of most family members and the main characteristic features were compatible with the diagnosis of ADMC. In addition, the clinical features made the diagnosis of other hereditary myotonic disorders impossible. The incidence of ADMC is rarer than

Table 2. *Clinical evaluation before and after mexiletine treatment*

Probands	II-2			II-3		
Medication	Before	After	P value	Before	After	P value
Tests						
1. Lid myotonia (eye open and close for 10 times)						
Mean	8.32	6.52		21.82	21.74	
SD	0.83	0.20	0.022	2.14	0.79	0.933
2. Dominant hand myotonia (maximal hand grip for 10 times)						
Mean	10.65	6.12		22.21	15.76	
SD	0.67	0.23	0.0004*	2.54	0.75	0.014*
3. Stair tests						
(upstairs, 11 steps)						
Mean	10.37	7.10		13.79	9.31	
SD	0.75	0.08	0.0016*	0.31	0.3	0.0000*
(downstairs, 11 steps)						
Mean	6.15	5.80		7.44	7.44	
SD	0.14	0.17	0.12	0.16	0.19	0.16

*: p value < 0.05

that of DM1[8,10,18]. Although muscle weakness and wasting are not present in Thomsen's disease, severely affected probands may experience difficulties in daily activities, as evidenced in the muscle cramps in our proband II-2, II-3 and II-4.

The DM1 is a multisystem disease with variable clinical presentations. The DM1 may affect specific tissues such as skeletal muscles (distal limbs and facial muscles), heart (mainly the conduction system), the lens (cataracts), brain (cognitive impairment) and endocrine system, which are not found in ADMC[18]. In addition, prominent muscle hypertrophy was not seen in DM1. The intellectual impairment was identified in 24-50% of the DM1 patients. In muscle biopsy, the DM1 may show numerous internal nuclei, pyknotic nucleus, variability of fiber size and type 1 fiber atrophy[18]. However, the muscle biopsy demonstrated a reduction of type 2B fibers in our 2 probands, which was not seen in DM1, but was compatible with that in ADMC.

Molecular genetic advances exhibited an elongation of the CTG triplet repeats in chromosome 19q13.3 in DM1. Herein, the numbers of CTG triplet repeats were all within normal ranges, making the diagnosis of DM1 unlikely.

Myotonic discharges are caused by hyperexcitability of the skeletal muscle membrane. Two mechanisms have been proposed including high resistance of sarcolemma chloride conductance, and altered sodium channel activity[1-3,4,5,7,11,13]. Antimyotonic agents may block voltage-dependent sodium channels to stabilize muscle membrance potential. Many drugs were effective in treating myotonia congenita, including phenytoin, carbamazepine, dantrolene, acetazolamide, antihistamine and some anti-arrhythmic agents[15,19-21]. High dosage of phenytoin (400-600 mg daily) is effective in treating myotonia, but the toxic effects limit its usefulness[15]. Herein, probands II-2, II-3 and II-4, were treated with phenytoin 300mg/day for 2 months previously, but no beneficial effects were observed. Two probands, II-2 and II-3, displayed a significant improvement in running, climbing upstairs, walking and writing following mexiletine treatment, and the treatment produced no side effects during the 3 years observation period. Weckbecker et al[13]. suggested that mexiletine was effective in myotonia through phasic blocking of sodium channels using a patchy-clamp technique.

Although the clinical differences such as frontal baldness, lenticular opacity, testicular atrophy and muscular hypertrophy exist between ADMC and DM1, ADMC and DM1 should be carefully differentiated as our case II-3 who had mental retardation caused by unrelated condition and myotonia. We suggest that a detailed clinical evaluation and molecular genetic studies can provide an important clue to rule out DM1. In addition, a low dose of mexiletine is effective in treating myotonia congenita, if there is no contraindication of second or third degree atrioventricular block or lactation. A further molecular analysis in CLCN1 chloride channel gene in this family is warranted to confirm the diagnosis.

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