Proximal myotonic myopathy: A new dominant disorder with myotonia, muscle weakness, and cataracts

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Article abstract—We describe three families with a dominantly inherited disorder. Affected individuals have myotonia, proximal muscle weakness, and cataracts. There was no abnormal CTG repeat expansion of the myotonic dystrophy (DM) gene in DNA from blood and muscle. The structure of the three families permitted linkage analysis, and there is no linkage to the gene loci for DM or to the loci for the muscle chloride channel disorders or muscle sodium channel disorders. The collection of symptoms in these three families seems to represent a new disorder.

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Myotonia congenita, paramyotonia congenita, and myotonic dystrophy (DM) are well-defined autosomal dominant clinical disorders with specific gene defects. Mutations in the gene for the skeletal muscle chloride channel on chromosome 7 lead to myotonia congenita.[1,2] Mutations in the gene for the alpha subunit of the muscle sodium channel on chromosome 17 cause paramyotonia, hyperkalemic periodic paralysis, and myotonia fluctuans.[3-6] An unstable region on chromosome 19 that produces an abnormal, variable expansion of a trinucleotide repeat, CTG, represents the gene defect for DM.[7-9] Investigators have used DNA analysis to identify both symptomatic and asymptomatic DM carriers, and virtually all DM families have shown an abnormal expansion of CTG repeats.[10-13] Severity of symptoms in DM is generally believed to correlate with the size of the CTG repeat expansion. A recent finding is a retraction of the CTG repeat expansion which is associated with milder symptoms of the disease.[14-19]

We describe three families in which the affected individuals had originally appeared to have a very mild type of DM or a peculiar form of myotonia congenita, manifested as myotonia, proximal muscle weakness, and cataracts (PROMM). None of the affected individuals had an expansion of the CTG repeat in the DM gene.

Methods. Three families were studied, including neurologic evaluation and EMG. Muscle biopsies were performed in two patients (table 1).

In vitro investigations of muscle fiber bundles. Two patients, from families 1 and 2 (nos. 1-10 and 2-7; table 1, figures 1 and 2), gave informed consent for study of their quadriceps muscle fibers. All procedures were in accordance with the Helsinki convention and were approved by the Ethical Committee of the University of Ulm. The procedures used to prepare the muscle fiber bundles and the associated electrophysiologic and mechanographic techniques were as previously described.[20] In vitro contracture tests were performed according to the European test protocol.[21,22]

DNA studies. Genomic DNA was isolated from blood samples, and aliquots were digested with restriction enzymes, subjected to electrophoresis, and transferred to nylon membranes by standard methods.[23] Filters were hybridized to the radiolabeled inserts of the following markers: DM locus ApoCII,[24] CKMM,[25] D19S63,[26] pM10M6,[27] and ClCN1 locus pL7.[28] PCR analysis was set up using standard conditions with minor modifications.[29] The primers used were previously described: DM loci DM101/102[27] and X75b,[30] TCRB locus Vb6.7L/R,[31] and SCN4A loci $(dGdA)_n$ and $(dGdT)_n$.[32] Multipoint lod scores were calculated by the method of maximum likelihood and the computer program LINKAGE 5.04.[33] In two patients (1-10 and 2-7), CTG repeat analysis was also performed on muscle DNA.

The following are illustrative case reports of members of family 2 (figure 2, table 1).

Case reports. Patient 2-4. As a young married woman, this patient developed intermittent problems opening her fist and had occasional leg stiffness. At about 50 years of age she developed bilateral cataracts, which later were removed. Constant problems in walking and climbing stairs

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Table 1. Summary of clinical and laboratory findings

Family	Pt no.	Sex	Age (yr)	Onset of myotonia (yr)	EMG myotonia	Onset of weakness (decade)	Muscle biopsy	CK (normal = <80 IU/l)	Cataract	
									Present	Age at detection (yr)
1	4	M	72	*	+	6		42	+	65
	3	F	74	*	+	7		32	+	72
	8	M	43	34	+	†		200		
	10	M	36	33	+	†	+	105		
2	4	F	70‡	30	ND	6			+	48
	7	F	49	11	++	4	+	150	+	48
	9	M	46	30	+	5				
	12	F	58	*	+	†				
	14	F	24	22	+	†				
3	5	F	52	30	+	†			+	49
	7	M	50	35	+	5		68		
	9	F	46	44	+	†		58	+	46
	10	F	27	19	+	†				
	11	M	31	*	+	†				
	12	F	27	26	+	†		89		

* No clinical myotonia present.
† No clinical weakness present.
‡ Patient deceased.
ND Not done.

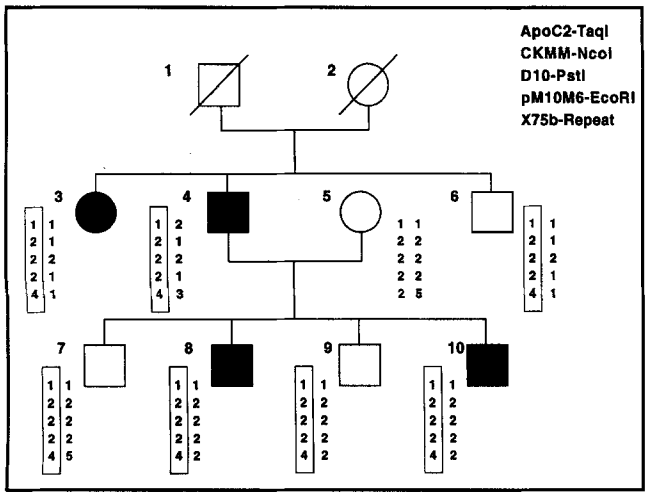

Figure 1. Pedigree of family 1 and haplotyping for markers of the DM1 locus.

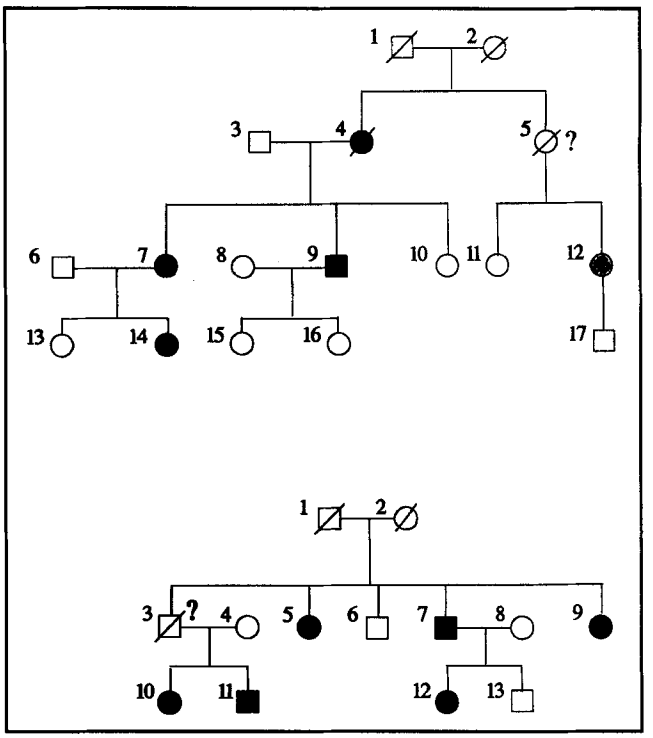

Figure 2. Pedigree of families 2 (upper part) and 3 (lower part).

were obvious. By 60 to 70 years of age, she required assistance in climbing stairs. No muscle atrophy or other manifestations were noted by her family.

Patient 2-7. At 11 years of age she experienced stiffness in her hands when writing in school and when exercising in gym class. When she attempted to run, she would occasionally develop leg stiffness and fall. At about 35 years of age, her myotonic stiffness got worse and sometimes involved chewing and swallowing. At age 40 she developed weakness of her upper legs and consistently had problems climbing into a bus. She had difficulty turning in bed and became unable to carry her grandchild.

On examination, she had proximal weakness. There was no muscle atrophy. Tendon reflexes were normal. She had to use her arms to pull herself from a squatting position to standing. When supine, she was unable to lift her head or lift both legs together. At times, after rest, there was marked weakness of elbow flexion and extension which improved considerably after several repeated contractions. She was not able to walk on her heels, but had no significant weakness of dorsiflexion on direct testing. There was very mild weakness of eyelid closure and no other facial weakness or ptosis. She had no myotonic lid lag, but there was a mild delay in opening her eyes after

forceful closure. She had grip myotonia showing a stepwise, jerky, slowed relaxation of her fingers, most prominent in the index finger and the thumb. Myotonia lessened with repeated contractions. She needed 18 seconds to climb 10 steps of a staircase on her first trip and 7.5 seconds on the fourth trip (normal, 3 to 4 seconds). EMG of several muscles showed myotonic discharges without other gross abnormalities. CT of the upper and lower leg muscles revealed no atrophy of muscle tissue. On slit-lamp examination the patient had mild bilateral cataracts.

Patient 2-9. This patient developed intermittent grip myotonia and muscle stiffness in his thighs at 30 years of age. Later, he occasionally had shortlived stiffness in his neck muscles when turning his head and rarely had some stiffness of his facial muscles when laughing. He thought that the strength in his upper leg muscles had gradually diminished. He had mild grip myotonia only in his left hand. After forceful lid closure, there was a mild delay in lid opening. On climbing a staircase, he slowed down briefly on the second and third steps due to momentary leg stiffness. He could arise from a squat only with some effort. Otherwise, his muscle strength was normal.

Patient 2-12 did not recall having any symptoms. On examination she had no signs of myotonia or weakness. Surprisingly, EMG revealed myotonic discharges.

Patient 2-14 was active in sports and had no symptoms until she was 22 years of age. She noticed that once in a while she would have difficulty relaxing her grip and that while riding a bicycle her thigh muscles would become hard and stiff. If she continued to exercise, this stiffness would disappear. Only rarely did she have stiffness of her neck muscles, which occurred when suddenly turning her head. She had well-developed muscles without atrophy. There was mild grip myotonia mainly in her left hand. When climbing a staircase, at the fourth step she slowed down briefly due to stiffness in her right leg.

Clinical overview of the three PROMM families (figures 1 and 2, table 1). There were 15 affected individuals; fourteen were examined. Onset of the disorder was between 20 and 40 years of age in the majority of patients. They initially experienced myotonic symptoms in their hands and later in their proximal leg muscles. In most patients, myotonic symptoms occurred only infrequently. Myotonia sometimes involved only one hand or leg and developed after a sudden forceful movement. A few patients had stiffness of their neck muscles provoked by sudden turning of the head. Some could open their eyes only slowly after forceful closure. The myotonia had a "warm-up" period, improving with repetitive exertion.

Six patients developed proximal leg weakness between the fourth and seventh decades (table 1). Patient 2-7 had more widespread weakness (see Case report). None of these patients had apparent muscle wasting, and their tendon reflexes were normal. They had no ptosis or weakness of mastication, swallowing, or respiration.

Six of the 15 affected individuals had cataracts (table 1). In two patients, 2-7 and 3-9, the lens opacities were in the posterior capsule, but no iridescent coloration was seen. No specific descriptions of the cataract were available in the other four patients who already had their cataracts removed.

There were three parent-child pairs. In patients 1-4/1-10 and 3-7/3-12, the onset of symptoms occurred earlier in the child than in the father (table 1). In patients 2-7/2-14, the mother developed her first symptoms at 11 years, while her daughter's onset was at 22 years of age. Affected individuals within each of these families had a variable severity of their symptoms.

No patient had cardiac symptoms, and resting ECGs were normal. Two patients, 2-7 and 3-12, had muscular problems after anesthesia. Both experienced generalized weakness and muscle pain for 2 days. One patient, 3-11, was mentally retarded from infancy from an unknown cause. His only muscular findings were myotonic discharges in the EMG. None of the patients had hypersomnia, gonadal atrophy, hearing deficits, or gastrointestinal hypomotility. There was no evidence of a shortened lifespan.

Nerve conduction studies were normal. Routine blood chemistries were normal except for an elevation of CK (table 1). Treatment with mexiletine, 600 mg daily, produced no improvement in patient 1-10 and gave only slight improvement in patient 2-7.

Muscle morphology. Histochemical staining of muscle biopsy tissue from two patients with PROMM revealed a nonspecific, mild myopathy. The biopsies were taken from the quadriceps muscle. There was a mild to moderate increase in the number of central nuclei in the muscle fibers. There was hypertrophy of type 2 fibers, with a greater variation in diameter as compared with type 1 fibers. Fiber type grouping did not occur. A few scattered small atrophic fibers were found in case 2-7. Type 1 fibers had no selective atrophy, and we did not see ringbinden or subsarcolemmal masses.

In vitro investigations of muscle fiber bundles. In case 2-7, muscle fibers had normal resting membrane potentials of -83.4 ± 3.5 mV (n = 12 fibers). When the fibers were impaled, long-lasting runs of repetitive action potentials occurred. Tetrodotoxin completely abolished this activity. The chloride conductance of the muscle fiber membrane was normal. The steady-state current-voltage relationship was determined in solutions with Cl^- (242 ± 84 μsiemen/cm^2; n = 7 fibers) and without Cl^- (50 μsiemen/cm^2). The difference of the conductance values was 79% of the total conductance; ie, normal.

Force recordings from muscle bundles from patients 2-7 and 1-10 showed intense spontaneous twitching at 37 °C and to the same extent at 27 °C. The twitching was not influenced by 100 nM apamin; it was abolished by 10 μM EMD (potassium channel activator). Surprisingly, in case 2-7 the twitching was consistently diminished by increasing the potassium concentration in the bathing solution from 3.5 to 7 mM, whereas decreasing the potassium concentration to 1 mM caused the twitching to in-

Table 2. Linkage comparison for recombination fraction ($\theta = 0.01$)

Family	DM1*	ClCN1†	SCN4A‡
1	−3.04	−1.50	−2.80
2	−2.57	−4.49	−3.20
3	−3.31	−3.87	−3.29

* Gene locus on chromosome 19q for myotonic dystrophy.
† Gene locus on chromosome 7q for muscle chloride channel disorders.
‡ Gene locus on chromosome 17q for muscle sodium channel disorders.

crease. Addition of 100 IU/l insulin further increased the frequency of twitching but also reduced the twitch force by about 50%. Similar studies of fiber bundles from patients with myotonia congenita, paramyotonia, or DM did not give such a response. The in vitro contracture test was normal in both of the above cases, ruling out a susceptibility to malignant hyperthermia.

DNA analysis. Southern blot analysis of genomic DNA from leukocytes using the probe pM10M6 revealed normal *Eco*RI and *Bgl* I DNA fragments in all affected members of the three families. No expanded fragments were observed. The distribution of length variation of the CTG region in the DM gene showed in all affected individuals a distribution of alleles that was comparable to the normal population. The number of CTG repeats for both chromosome 19 alleles in the index cases of each family (1-4, 2-7, and 3-9) was 5/14. Genomic DNA from muscle tissue from patients 1-10 and 2-7 showed no expansion of the CTG region.

For the three PROMM families, the pedigree structure (figures 1 and 2) was sufficient to permit linkage analyses. Table 2 summarizes the linkage data for these three families. Negative cumulated lod scores were obtained for the three loci, DM1 (myotonic dystrophy), ClCN1 (muscle chloride channel diseases), and SCN4A (muscle sodium channel diseases). Figure 1 shows that the established chromosome 19 haplotypes do not segregate with the disease phenotype, and, therefore, the phenotype is not linked to the DM gene locus.

Discussion. We have described three families with a myotonic disorder that seems to be a new autosomal dominantly inherited disease. The underlying genetic defect is yet to be discovered. Affected individuals have late-onset myotonia at 20 to 40 years of age, with mild proximal leg weakness and sometimes cataracts. There are mild myopathic changes in studies of muscle tissue. None of these patients have distal weakness or wasting of muscles in the arms and legs or in the face. There is no ptosis and no cardiac arrhythmias or respiratory weakness, features that commonly are present in cases of DM.[34,35] The clinical course is mild, showing only slow progression. The absence of an abnormal CTG repeat expansion in the DM gene in DNA from blood and from symptomatic skeletal muscle in these individuals, and, in particular, the results of linkage analysis, excluded the diagnosis not only of DM but also of myotonia congenita and paramyotonia.

As in many other autosomal dominantly inherited disorders, there is a considerable variation in the manifestation of symptoms within these families with PROMM. Unlike DM, the pattern of symptoms did not suggest the presence of anticipation.[36-38] Whether PROMM produces a congenital type of the disease comparable to DM[39] is unknown. One affected individual has had mental retardation from birth. Clearly, this could be an incidental occurrence.

Certain findings may provide clues about the underlying pathogenesis. The cataracts have some of the features of cataracts in DM. This suggests that the posterior capsular lens opacities in PROMM and DM may share a common pathophysiologic pathway. But, unlike PROMM, the cataracts in DM have a colorful, iridescent appearance.[40]

The clinical and laboratory evaluations of myotonia and weakness in PROMM demonstrate differences when compared with the myotonia and weakness in DM and other myotonic disorders. In PROMM, the myotonia is usually intermittent and often occurs asymmetrically. The myotonic relaxation of the fingers shows a sometimes jerky, stepwise appearance. The weakness is mild to moderate, and it is not accompanied by significant muscle wasting or severe structural muscle damage.

One patient with PROMM with a more severe and generalized weakness clearly has improvement of strength when she repeatedly contracts a muscle. This "transient weakness" has occurred in recessive generalized myotonia, a muscle chloride channel disorder.[41] However, in the PROMM case, muscle fibers had a normal membrane chloride conductance in contrast with patients with recessive generalized myotonia.[42]

The in vitro studies in two PROMM patients confirmed that the myotonia originates in the muscle fibers in this disorder. Unlike findings in DM, apamin[43,44] did not prevent the myotonia in these fibers. Lowering the extracellular potassium concentration increased the myotonia in these fibers and vice versa. This type of response has not occurred in studies of muscle fibers from patients with other myotonic disorders. Subsequent investigations may reveal a new pathomechanism for the myotonia in PROMM. Identification of the underlying genetic cause of PROMM is a pressing challenge for future molecular genetic studies.

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