

## Original articles

## The expanding clinical and genetic spectrum of the myotonic dystrophies

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## Abstract

Core features of the dominantly inherited myotonic dystrophies are myotonia, muscle weakness and cataract. Classic myotonic dystrophy (Steinert's disease) has been defined as a genetic entity by the underlying CTG repeat expansion on chromosome 19q13.3 (= DM1 locus). Later on, another disorder similar to but different from myotonic dystrophy was described as proximal myotonic myopathy (PROMM). The majority of PROMM families have been linked to a recently discovered locus on chromosome 3q21 (= DM2 locus). — This article analyses the clinical features of 70 patients from 14 German PROMM families linked to the 3q locus. In contrast to Steinert's disease, these patients did not reveal mental deficiency; no congenital type was found; weakness was mainly located in the proximal leg muscles; clinical myotonia was very mild and sometimes absent; episodes of pain occurred. In the majority of patients, the disorder seems to be more benign compared to Steinert's disease. However, life threatening cardiac involvement is possible; rarely, muscle weakness may progress until the patient is bedridden. — Some families with a PROMM-like phenotype do not link to the locus on 3q. The group of the myotonic dystrophies will get new members in the future.

**Key words:** Myotonic dystrophy; Steinert's disease; proximal myotonic myopathy; PROMM; myotonic dystrophy type 2; DM2 gene locus; genotype-phenotype correlation.

## Introduction

Until the year 1992, the designation myotonic dystrophy or dystrophia myotonica (DM) referred to what was believed to be one single genetic disease entity (Harper, 1989). Today this disease is called DM type 1 (Steinert's disease, "classic" myotonic dystrophy). It is caused by a dynamic mutation, a CTG repeat expansion on chromosome 19q (Brook *et al.*, 1992; Buxton *et al.*, 1992; Aslamidis *et al.*, 1992). Meanwhile, it became clear that there exists another disorder quite similar to but distinct from Steinert's disease (Thornton *et al.* 1994). This "new type of myotonic dystrophy" has been named proximal myotonic myopathy, PROMM (Ricker *et al.*, 1994, OMIM \*600109).

Like Steinert's disease, PROMM is a dominantly inherited multisystemic disorder with features like progressive myotonic myopathy, cataracts, cardiac myopathy, hypogonadism and many more. However, this disorder does not link genetically to the DM1 locus on chromosome 19q; patients do not have the CTG repeat expansion. Clinically, there are important differences between Steinert's disease and PROMM. In Steinert's disease, the most severe presentation is the congenital type. So far, a congenital type has not been found in PROMM families. Some patients with Steinert's disease suffer from obvious mental disability. Such a devastating feature has not been seen in PROMM families (Ricker *et al.*, 1995). The designation PROMM refers to the clinical observation that the majority of patients initially experience their weakness in their proximal leg muscles. In Steinert's disease the weakness characteristically is noticed by the patient at first in the hand and lower arm muscles and/or the distal leg muscles. Quite often, this different localisation of weakness in PROMM and Steinert's disease is obvious and striking to the physician. It justifies the designation "proximal" myotonic myopathy. However, this difference may not be looked upon as rock-solid universal law. The difference in localisation may be blurred to some extent in some families (Abruzzese *et al.* 1996; Day *et al.*, 1999). PROMM families have been reported from different countries (Stoll *et al.*, 1995; Meola *et al.*, 1996; Udd *et al.*, 1997; Schuitevoerder *et al.*, 1997; Phillips *et al.*, 1998; Mastaglia *et al.*, 1998; Meola *et al.*, 1998; Newmann *et al.*, 1999; Sun *et al.*, 1999; Kohler *et al.*, 2000).

In 1998, Ranum *et al.* described the genetic mapping of a "second myotonic dystrophy locus" (=DM2) on chromosome 3q21 in a large Minnesota family. Consequently, the gene locus for Steinert's disease on chromosome 19q13.3 has been renamed "DM1" (IDMC, 2000). Furthermore, it became clear that the majority of PROMM families do link to the genetic locus on chromosome 3q (Ricker *et al.*, 1999; Meola *et al.*, 1999; Kress *et al.*, in press). However, not all PROMM families do link to the DM2 locus (Ricker *et al.*, 1999; Meola

Table 1

Diagnostic features in Steinert's disease (DM1) and proximal myotonic myopathy (PROMM)

	<i>DM1</i>	<i>PROMM</i>
Clinical myotonia	Yes	Mild or absent
EMG myotonia	Yes	Yes
Initial muscle weakness	Mainly distal, face	Mainly proximal leg muscles
Muscle and joint pain	No	Yes
Hypersomnia	Yes	No
Mental alteration	Yes	No
Anticipation	Yes	Yes, mild*
Congenital type	Yes	No
CTG repeat expansion at the DMPK gene	Yes	No

\* Schneider *et al.*, 2000.

*et al.*, 1999 ; Wieser *et al.*, 1999 ; Kress *et al.*, in press). It is obvious that further loci ("DM3 to DMn") will be found in the future. Only then and after the discovery of the underlying mutations a complete genotype-phenotype correlation may be established for this expanding new group of dominant multisystemic myotonic myopathies, DOM-MOP (Ricker, 1999) or "myotonic dystrophies".

The purpose of this paper is to present clinical features of 70 patients from 14 German PROMM families linked to the DM2 locus.

### Patients and Methods

PROMM families were diagnosed according to previously defined clinical criteria, Table 1 (Ricker *et al.*, 1995 ; Moxley *et al.*, 1998). An expansion of the CTG repeat at the 3' untranslated region of the DMPK gene on chromosome 19 (DM1 locus) was excluded by Southern blotting (Shelbourne *et al.*, 1993). In families with a suitable pedigree structure, linkage analysis to chromosome 3q was performed using the tandem repeat markers D3S1589 and D3S1541. Genetic results have been published previously (Ricker *et al.*, 1999, Kress *et al.*, in press).

For the present clinical study, 14 PROMM families were available in which the results of the genetic analysis were consistent with linkage to chromosome 3q (DM2 locus). Symptoms and signs in the 70 affected individuals were evaluated mainly by a careful interview and a neurological examination including an EMG registration.

### Results

Of the 70 patients, 39 were female, 31 male. Their age at examination was 19 to 79 years (mean 49 years). The main clinical features are given in Table 2. The age at onset of the initial symptom (or symptoms) as reported by the patients ranged from 15 to 65 years (mean 37 years). The occurrence of different symptoms and signs in relation to each

other and in relation to age and to duration of the disease were highly variable in the individual patient. At the time of their examination, only 20 patients, aged 37 to 79 years, displayed all three core symptoms : clinical myotonia, muscle weakness and cataract.

### WEAKNESS

Of the 70 patients, 54 had muscle weakness (77%). The main location of the weakness was in the proximal leg muscles. Only 6 patients had additional mild distal weakness in the upper or lower extremity. The muscle weakness began between the age of 25 and 68 years (mean 44 years). The main complaint of all these patients with muscle weakness was having difficulty in climbing stairs. The greater number of them were unable to raise from a squatting position. Fifty-two of the 54 patients with weakness were able to walk comfortably on flat

Table 2

Symptoms and signs in 70 PROMM patients from 14 German families linked to chromosome 3q (DM2 locus)

<i>Symptoms and signs</i>	<i>Number of patients</i>
Clinical myotonia	44
Electrical myotonia	68
Weakness of proximal leg muscles	54
Weakness of anterior neck muscles	47
Weakness of shoulder muscles	14
Mild distal weakness	6
Mild temporal atrophy	5
Mild ptosis	3
Cataract	35
Cataract occurring under 50 years of age	17
Episodic muscle and joint pain	32
Action tremor	16
Action tremor occurring under 50 years of age	8
Painful muscle cramps	16
Cardiac involvement	13
Hypogonadism	3
Elevation of CK in the serum	40
Elevation of g-GT in the serum	30

ground. However, in two women the weakness progressed until they were bedridden at the age of 76 and 72 years. In these two patients, the first symptom of the disorder was mild myotonia occurring at the age of 40 and 45 years. Weakness was first remembered as proximal leg weakness at the age of 53 and 65 years. Today they cannot even sit up or turn around in bed any more. Apart from mild to moderate temporal atrophy no facial involvement is present. They have almost no disability of finger movement. Neither of the two women displays any mental change nor any obvious cardiac involvement.

#### MYOTONIA

Clinical myotonia was present in 44 patients (63%). Myotonia was always very mild and not constantly present. Temperature did not seem to have any obvious effect on the myotonia. Clinical myotonia started at the age of 15 to 56 years (mean 34 years). There were 24 patients who did not recall any myotonic symptoms. However, the EMG registration revealed myotonic discharges (hypotenar muscle, anterior tibial muscle). In two patients no electrical myotonic discharges could be found.

#### CATARACT

In 35 patients (50%), cataract occurred on one or both eyes at the age of 31 to 74 years (mean 50 years). Seventeen patients with cataract were not older than 50 years of age. Only a few of them revealed "typical myotonic" cataract with coloured spots. In patients older than approximately 60 years, it was of course difficult to distinguish if the cataract was a sign connected with DM2 or if it was cataract "of old age". Surgery for removal of cataract was performed in 26 patients.

#### PAIN

Almost 50% of the patients complained about episodes of peculiar pain in their muscles (quite often the thigh muscles) and /or their joints. These episodes lasted weeks or months, sometimes years. Details of the quality of the pain have been described elsewhere (Ricker, 1999).

#### CARDIAC INVOLVEMENT

In three patients, progressive cardiomyopathy was detected at the age of 40, 60, and 64 years. The youngest one of the three died suddenly at the age of 44 years. His first symptom of the disorder had been mild myotonia at the age of 30 years, cataract at 35 years. He developed mild temporal atrophy but had no other muscle weakness until he died. In 10 patients, arrhythmia occurred and a cardiac con-

duction block was detected. No systematic study of possible cardiac involvement could be performed in the other 57 patients.

#### Discussion

Myotonic dystrophies are multisystemic disorders. It seems as if almost any conceivable organ system may in rare instances be involved in an individual patient. However, the defining core features are myotonia, muscle weakness and cataract within a given family. Regarding the genetic entity, a line has been drawn between families with a CTG repeat expansion at the DM1 locus and families with core features but without the CTG repeat expansion and without genetic linkage to the DM1 locus (Ricker *et al.* 1994). The majority of the later group has so far been published with the clinical designation PROMM. Now it is possible to separate families in this later group that link to the DM2 locus on chromosome 3q from those that do not (and of course not to the DM1 locus). It seems more than likely that the Minnesota family with "a new type of myotonic dystrophy" named myotonic dystrophy type 2 (Day *et al.*, 1999) and the 14 German PROMM families described above are one and the same disease entity. However, proof will come only when the mutation at the DM2 locus has been discovered.

Telling a patient and his family the diagnosis PROMM (in contrast to Steinert's disease) may implicate the "good news" that the risk of mental deficiency is obviously minimal. Furthermore, until now no new borne baby with a congenital type of PROMM has been seen. Clearly, more clinical observation is necessary until sound advice can be given regarding this risk. The patient does not need to worry that his or her facial looks or speech may change significantly. In contrast to Steinert's disease, there is almost no facial weakness or ptosis to any extent in PROMM patients (with the exception of a rare mild temporal atrophy). There will be no serious disability of finger movement worth mentioning. Myotonia, if present at all, is rather mild and episodic. Rarely mild distal weakness may occur in the upper extremity. However, the patient should be aware that sooner or later in life he or she will experience proximal leg weakness which will make him unable to get up from a squatting position, making it progressively difficult or impossible to climb a stair case. Only then, mild to moderate weakness of the shoulder muscle may also be present. There is only a low risk that the ability to walk on the flat will eventually be lost.

Unfortunate details may also be mentioned. There is a near 50 % risk that a patient may develop at one point of his life disturbing episodes of pain located within his leg muscles or joints, shoulders or chest. It is not known what causes this painful episodes. Muscle weakness in old patients

may rarely progress to the extent that they become completely bedridden. Yet, in stark contrast to Steinert's disease these patients still have control of moving and using their hands and fingers; their face and speech is not noticeably altered. Severe muscle involvement has been reported by Udd et al. (1997), in a family which turned out to be linked to the DM2 locus (Meola et al., 1999). There exists a serious possibility of life-threatening cardiac involvement (cardiac conduction block and/or dilated cardiomyopathy) developing independently of the degree of skeletal muscle weakness in PROMM families linked to the DM2 locus. The detection and management of cardiac involvement in these patients clearly needs further clinical research (Mühlen et al., 1998).

In the future, the detailed clinical picture will be outlined in those families presenting the core features of the myotonic dystrophies but with normal CTG repeat size at the DM1 locus and without linkage to the DM2 locus. A few such families have been seen in Germany presenting mainly with the PROMM phenotype.

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