

Clinical Spectrum of Proximal Myotonic Myopathy (PROMM) Syndrome

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Abstract

We studied 25 patients with proximal myotonic myopathy (PROMM) from 3 unrelated kindreds and present data on the clinical spectrum of this syndrome. Our data show that phenotypic expression and degree of multisystem involvement may vary widely between and within kindreds. In conclusion our results suggest clinical and genetic heterogeneity of PROMM syndromes.

Key words: proximal myotonic myopathy, myotonic dystrophy, neuromuscular disorders, myopathy.

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The first reports on proximal myotonic myopathy (PROMM) families [8, 9, 14, 15, 19, 20] defined the clinical and genetic data in this syndrome. The diagnosis was based on the finding of autosomal dominant transmission of proximal muscle weakness, myotonia and cataracts in the presence of a normal size CTG expansion on chromosome 19 [2, 3, 4, 5]. The initial reports were all consistent with this clinical picture. From a clinical point of view, autosomal dominant inheritance was always present, onset of symptoms was usually in the 30s or 40s, and no infantile or childhood cases had been described. There was no report of congenital cases of PROMM similar to the severe form described in myotonic dystrophy from affected mothers. The most frequent symptom at onset in the patients with PROMM described was myotonia, often painful and causing stiffness in the hands. A warm-up phenomenon was described in many patients. All patients described had myotonic discharges on EMG. However, it was unclear from the initial reports, that myotonic discharges could be very difficult to find, especially when symptoms of myotonia or muscle weakness were not very prominent, like in at risk individuals from affected parents. The initial reports were also very focused on the proximal distribution of muscle weakness in muscles of normal bulk, compared to the distal atrophy and weakness described in patients with myotonic dystrophy (DM) [7], to the extent that the disorder was termed *proximal* myotonic myopathy [14, 15]. Hypertrophy of the calves was described in some patients and tendon reflexes were normal in all patients examined (even though severely affected) in contrast to the diminished or absent reflexes in patients with DM. The clinical

picture of PROMM initially appeared quite distinct from that of patients with DM.

From a genetic point of view, all patients with PROMM had normal size CTG expansion and linkage to chromosome 19, 7 and 17 was excluded in 4 large unrelated kindreds with PROMM [8, 14, 15], suggesting genetic homogeneity and again underlying that PROMM was a disorder similar to, but distinct from DM.

The increasing number of reports that followed underlying the multisystem involvement and the variability in clinical expression [12], made it clear that the clinical picture of PROMM was not as homogeneous as initially thought, and that PROMM should be considered a syndrome, maybe controlled by multiple and distinct genes from DM. Abruzzese et al. [1] described 3 families with DM phenotype in whom affected individuals within a same family had a normal or abnormal degree of CTG expansion.

It is now clear that careful clinical evaluation of patients with PROMM often reveals that the actual similarities of the signs and symptoms to those in DM are only limited and not exact. Although the distribution of weakness is definitely proximal rather than distal in PROMM and myotonia is present, the clinical manifestations of the disease vary widely. Weakness may be hard to detect and often there may be no underlying muscle wasting [10]. Patients often describe myotonia in a very specific and reproducible manner describing 'locking' of the hands, reduced finger dexterity as in arthritis, stiffness or pain. However, these symptoms may be intermittent and totally absent on clinical testing with no evidence of percussion or grip myotonia. Similarly, electromyography findings

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may not reveal any myotonic discharges even after cooling. Cataracts are not easily detectable on ophthalmoscopic examination and a slit-lamp test is often required to rule out the typical lens opacities found in DM. The diagnosis of at-risk individuals is therefore difficult to establish. This has obvious genetic implications for linkage studies. Given the clinical variability and the apparent low penetrance of the disease, caution is therefore necessary in defining affected individuals, especially because the natural history of PROMM is still being determined. Moreover, the expressivity of the disease varies widely and no specific early diagnostic test for PROMM has yet been described.

Materials and Methods

PROMM- the clinical picture

We describe the clinical spectrum of this disorder based on our experience in 25 individuals from 3 unrelated PROMM families.

The pattern of muscle involvement (Table 1)

Facial weakness

Facial weakness, one of the earliest and most constant features of DM, was not a prominent feature of our patients, although mild facial asymmetries were noticed when the patients smiled or talked. The typical expressionless face resulting from weakness of the facial muscles, and from weakness and wasting of the jaw muscles in patients with typical DM was not a feature of our PROMM patients, independent of age and duration of disease.

Ptosis

Ptosis, generally symmetrical and an integral part of the facies in patients with DM was absent in our patients with PROMM, although fluctuations in myotonia in the *orbicularis oculi* sometimes gave the impression of a variable and fluctuating degree of opening of the eyes.

Extraocular muscles

Formal testing and symptoms attributable to extraocular muscle weakness were absent in our patients.

Jaw muscles

Wasting of the temporalis muscles is a prominent feature of myotonic dystrophy, but was absent in our patients with PROMM. However, temporo-mandibular dislocation, well-documented in DM, was also a feature of our patients. Recurrent locking of the jaw, difficulty in chewing and frequent clicks were the main complaints.

Palate and tongue

Weakness of the palate contributes to the nasal, indistinct speech that may trouble adults with advanced features of DM, but was not a feature of PROMM, even in advanced cases. None of our patients complained of difficulty swallowing and had a narrow, high-arched palate.

Sternomastoids

Inability to raise the head while in bed was a complaint in some patients and many patients were unable to raise their heads against gravity while supine. This occurred at

a stage when the involvement of most other muscles was relatively mild.

Limb weakness

The onset of muscle weakness was proximal in all of our patients, although often mild and uncomplained of by some patients. Difficulty getting up from a squat or climbing up stairs was often explained on the basis of 'getting older' or 'out of exercise', especially in relatives of affected individuals. In more advanced cases weakness was present in the distal muscles also, independent of the degree of myotonia. Degree of weakness was not correlated to degree of atrophy and weak muscles were usually of normal bulk, in contrast to the findings in other recently described PROMM patients [21]. Pseudohypertrophy of the calves was occasionally seen in some patients. Degree of muscle involvement varied between patients and 4 of our patients were wheel-chair bound, irrespective of age and disease duration. Tendon reflexes were preserved in all patients, even in muscles with severe involvement.

Myotonia

This phenomenon, the hallmark of DM, can be elicited in patients with PROMM but is not as constant and reproducible, especially in presymptomatic individuals, as it is in DM. It is the most frequent symptom at onset in our patients with PROMM. Patients often complain of stiffness, usually painful, but variable, and precipitated by changes in temperature, both high and low. Repeated exercise of the hands, relieves the pain and stiffness locally. Myotonia, best tested in the hand muscles where, following a forceful grip, there is a delayed ability to relax the grip, might be present on examination one day and absent the following day. Even less constant and difficult to find is myotonia on percussion of the thenar muscles. In contrast to patients with DM, patients with PROMM complain of the phenomenon, especially when painful and sometimes interpret it as arthritis. Percussion myotonia in the tongue was a more constant and reproducible feature than grip myotonia. All patients with definite clinical myotonia had myotonic discharges on EMG. However, when symptoms of stiffness and pain in the hands or legs were present, myotonic discharges were difficult to elicit and when present, were often short-lasting, and varied from day to day in the same patient. In a few cases, heating the muscles or performing a long-lasting exercise test [16, 17], precipitated the myotonic discharges. In other patients, no definite myotonic discharges were present, yet there were fibrillation potentials in the muscles examined. These findings are currently being investigated. All our patients show a good therapeutic response to mexiletine, at a dosage of 200mg bid.

Systemic aspects (Table 2)

The occurrence of a variety of abnormalities outside muscle is perhaps the most characteristic emerging feature of PROMM, and these abnormalities are both a help in diagnosis and also a problem when they are the presenting feature rather than an accompanying one. The systemic

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Table 1. Muscle involvement.

FACIAL	+/-
PTOSIS	-
EXTRAOCULAR	-
JAW MUSCLES	-
PALATE, TONGUE	-
STERNOMASTOIDS	++
LIMBS	
lower limbs	++
upper limbs	+
proximal muscles	+
flexors	++
extensors	+

difficulties are also of major importance in management and prognosis, and in many patients in our experience are of considerably greater importance than the muscular aspects.

a) Smooth muscle

From our experience patients with PROMM may complain of difficulties urinating, experiencing cramps and painful contractions during micturition, apparently not justified by tests of the urinary tract. Other patients complain of difficulties with digestion, describing it as slow, often painful in the absence of signs of gastrointestinal structural involvement.

b) Heart

None of our patients presented with conduction abnormalities and none required a pacemaker. Blood pressure and other signs of vascular abnormalities were absent.

c) Peripheral nerve

Many patients experienced a decreased sense of vibration but rarely this was clinically significant.

d) Brain

We studied 10 patients with PROMM with MRI or CT scans and no structural abnormality was found. In some there was an increase in thecal thickness similar to findings in DM. Neuropsychological tests showed impairment in visuospatial functions in all PROMM patients independent of degree of muscle involvement [18].

e) Endocrine

Many of our patients complained of infertility and gonadotrophins were reduced in some patients in association with gonadal atrophy. The significance of these findings is to be determined. Diabetes was not a feature of our patients. However, oral and intravenous glucose challenges showed elevated levels of insulin at rest. There was postprandial hyperinsulinemia in many of our PROMM patients suggesting features of insulin-resistance similar to those found in DM [11, 13].

f) Eye

Iridescent cataracts, identical to those found in DM were present in all our definitely affected patients with

Table 2. Systemic involvement.

SMOOTHMUSCLE	+/-
CARDIAC MUSCLE	-
PERIPHERAL NERVE	+/-
BRAIN	+/-
CATARACTS	+
SKELETAL	+/-
SKIN	+/-
INFERTILITY	+/-
DIABETES	+/-

PROMM. We were unable to use this test to screen for patients with mild symptoms in whom the diagnosis of PROMM was uncertain because the abnormalities found on slit-lamp examination were indistinguishable from those found in the general population.

g) Skeleton

Thickening of the skull was found in many of our patients tested on X-ray or CT scans, but the significance of this is to be determined.

h) Skin

In some of our patients easy blistering, skin allergies and bruises were a common complaint. However there was no evidence of these symptoms being present only in patients with muscle complaints and it was not possible to identify this as a constant feature of these patients.

Diagnostic work-up

Careful clinical assessment, laboratory tests and genetic analysis will allow to recognize predictive tests of proven value in PROMM and tests of limited or uncertain value. Clinical assessment is by far the most important single measure. No relative should be considered unaffected unless a careful search has been made for myotonia and muscle weakness. Electromyography should always be done in at-risk individuals, should be performed after cooling and heating of the muscle and should be repeated at several points in time in different muscles before it is considered negative. Slit-lamp examination is extremely valuable, especially in the elderly to distinguish specific opacities from those changes commonly seen in the elderly. It is not uncommon for nonspecific whitish opacities to be the only finding in at-risk individuals. It is wise to regard this finding as equivocal and to repeat the test in 1 or 2 years. Molecular analysis is mandatory to rule out linkage to the DM gene on chromosome 19. Other predictive tests have limited or uncertain value like CK determination. Definitely affected individuals have been seen with normal CK. The same applies for gamma-GT elevation. Serum FSH, LH and testosterone and insulin response to oral or intravenous glucose are still of uncertain value. Muscle biopsy is of limited value in PROMM. It is important to rule out myotonia congenita on the basis of the presence of type IIB fibres on muscle biopsies of PROMM patients. However, mild to moderate increase in central

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nuclei, some scattered angulated and atrophic fibers in the absence of chronic signs of denervation (i.e. type-grouping). have been found in the majority of PROMM patients. In a few patients several central nuclei, type I fiber atrophy and type II fiber hypertrophy, ring-banded fibers have been seen [6] like in DM.

Conclusions

Natural history

There is no data on the natural history of the disease yet. However, from our experience and from the literature data, the clinical variability is significant, varying from milder cases only with muscle pain to wheel-chair bound patients.

Moreover, since some minor aspects of multisystem involvement are still to be defined, it is difficult to understand whether some features present in at risk individuals (eg infertility, thyroid dysfunction, cognitive abnormalities, etc.) are to be considered as a clinical manifestation of the disease or whether certain abnormalities occur by chance in these individuals and with no statistical difference from the general population. From our 4-year follow-up experience in one large kindred progression of weakness occurs slowly but varies from patient to patient. In particular one 37-year-old patient became wheel-chair bound within 2 years from our diagnosis. In retrospect, onset of symptoms had been around age 13 with myotonic complaints.

Age of onset

PROMM had initially been described as a late-onset myopathy. As more and more patients are being described, onset varies from 10 years of age [14, 15] to 60 years of age. In our experience onset of symptoms was in general in the 30s or 40s but many patients experienced stiffness and pain since their young adulthood. If disorders of menstrual cycle, thyroid dysfunction or other abnormalities will be included as possible manifestations of PROMM, age of onset may vary further.

Prognosis

In general, because of the less frequent involvement of cardiac and respiratory muscles, patients with PROMM have been considered to have a better prognosis compared to patients with DM. Moreover, no congenital form of PROMM has yet been described and although central nervous system involvement has been suggested as a feature of PROMM, this is a possible but unusual presentation of the syndrome. In our experience, the cardiac conduction system is spared and none of our patients required a pacemaker or cardiac treatment. Similarly none complained of respiratory distress or sleep apnea. However, natural history data are lacking and although apparently a better one, caution is necessary before prognostic factors are considered.

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