Clinical, Electrophysiologic and Pathologic Findings in 10 Patients with Myotonic Dystrophy 2

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ABSTRACT: **Background:** Myotonic dystrophy type 2 (DM2) is an autosomal dominant, multisystem disorder caused by a CCTG tetranucleotide repeat expansion located in intron 1 of the zinc finger protein 9 gene (*ZNF9* gene) on chromosome 3q 21.3.
Objectives: To describe the clinical, electrophysiologic and pathologic findings in patients with myotonic dystrophy 2.
Methods: We evaluated 10 patients genetically, clinically and electrophysiologically during the years 2007 to 2008.
Results: All patients were of Jewish European ancestry. Among affected individuals, eight patients had symptoms of proximal muscle weakness, two had muscle pain, and two exhibited myotonia. On physical examination six patients had severe weakness of hip flexor muscles. Seven individuals underwent cataract surgery, and cardiac involvement was seen in one case. On the initial electromyographic (EMG) examination five patients demonstrated myotonic discharges; repeated studies showed these discharges in nine cases. Six muscle biopsies showed non-specific pathological changes. Seven patients had an affected first-degree relative with either a diagnosed or an undiagnosed muscular disorder consistent with an autosomal dominant trait.
Conclusions: DM2 may often present with proximal muscle weakness without myotonia. EMG may initially fail to show myotonic discharges, but these discharges may eventually show in most cases on repeated EMG. Thus, DM2 may be underdiagnosed and should be included in the differential diagnosis of adult patients of Jewish European ancestry presenting with proximal lower limb weakness.

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KEY WORDS: myotonia, myopathy, myotonic dystrophy type 2 (DM2), electromyography, muscle biopsy

Myotonic dystrophy type 2 was first recognized clinically in 1994 as a milder form of myotonic dystrophy known as DM1 [1]. DM2 was initially named proximal myotonic myopathy [1] or proximal myotonic dystrophy [2] until the genetic basis for this disorder was established in 2001, distinguishing this condition as a separate entity [3]. DM2 is an autosomal dominant, multisystem disorder partially resembling adult-onset DM1 [4]. It is characterized by skeletal muscle weakness and myotonia, cataracts, cardiac conduction abnormalities, and other systemic manifestations [1-4]. The underlying genetic mutation is a CCTG tetranucleotide repeat expansion located in intron 1 of the zinc finger protein 9 gene (*ZNF9* gene) on chromosome 3q 21.3 [5]. In normal alleles there are 11 to 26 tetranucleotide repeats, while in pathogenic alleles the number of repeats ranges from 75 to more than 11,000 (mean 5000 repeats) [6]. The disease has been described only in European patients and it is common in Germany and Finland. It has not yet been described in Israeli Jews.

DM2 = myotonic dystrophy type 2

PATIENTS AND METHODS

During the years 2007–2008 we reevaluated our patients with myopathy of unclear origin. DNA was obtained from 18 patients with a possible clinical diagnosis of DM2. The diagnosis of DM2 was established by genetic studies in 10 patients. The clinical, genetic and electrophysiological data from those 10 patients are reported here. The clinical data were taken from the files in the outpatient neuromuscular clinic and from the patients' reports.

Electrophysiological assessment was performed with the portable Key Point Medtronic EMG machine. Slit-lamp examination of all patients was performed at the ophthalmology clinic. Muscle biopsies were obtained from six patients. The specimens were quick frozen, sectioned, and stained with hematoxylin and eosin, Gömöri trichrome, periodic acid-Schiff, oil red O, NADH-TR, and ATPase at pH 9.4. Blood was drawn for DNA extraction after the patient signed an informed consent. Complete blood chemistry, blood cell count and serology were also studied.

GENETIC STUDIES

DNA samples were analyzed at the neuromuscular diagnostic center of the neurology department, University of Tampere

in Finland. Reverse transcriptase-polymerase chain reaction (repeat prime) was applied to amplify the four bases (CCTG) repeat region located in the first intron of the *ZNF9* gene [5]. The applied RP-PCR methods distinguish mutated expansion from normal DNA region by a pattern of differently sized fragments amplified [6]. Results were analyzed using fragment analysis with Gene-Mapper Software.

RESULTS

- **DM2 patients and families:** We identified 10 DM2 patients (7 were women). Seven individuals had an affected first-degree relative with an either diagnosed or undiagnosed muscular disorder, consistent with autosomal dominant trait. All patients were of European descent [Table 1]. Their age at diagnosis ranged from 31 to 79 years (mean age 65.4 years).
- **Age at onset and initial symptoms:** Patients reported having experienced the first symptoms of the disease from age 27 to 70 (mean age 52.8 years). The time from onset of symptoms to diagnosis ranged from 2 to 17 years (mean 7.5 years). Muscle symptoms (weakness, pain, myotonia) were the most common symptoms reported. Eight patients had symptoms of proximal lower limb weakness, such as difficulties running or walking long distances, rising from a sitting position, squatting or climbing stairs. Two individuals reported muscle pain and two patients described myotonia [Table 2].

RP-PCR = repeat primed polymerase chain reaction

Table 1. Age at diagnosis, descent and family member affected

Patient	Age (yrs)	Gender	Descent	Family member affected
1	77	Female	Romania	Sister
2	79	Female	Romania	Sister
3	31	Female	Poland	Mother
4	57	Female	Poland	Daughter
5	73	Male	Poland	–
6	68	Female	Bulgaria	–
7	77	Male	Germany	Brother
8	60	Female	Romania	-
9	67	Female	Russia	Father, sister
10	65	Male	Russia	Father, sister, uncle

Table 2. Initial symptoms

Initial symptoms	No. of subjects reporting each initial symptom
Myotonia	2
Weakness	8
Muscle pain	2

- **Distribution of muscle weakness:** All 10 patients exhibited proximal upper and lower limb muscle weakness. The iliopsoas muscle was the most severely affected. Other commonly affected muscle groups were the facial, neck flexors, and distal hand muscles [Table 3].
- **Muscle biopsy:** Muscle biopsies from the vastus lateralis and the deltoid muscles were obtained in six patients. Two specimens showed internal nuclei and nuclear clamps. Necrotic fibers, fibrosis with abnormal fiber type distribution, lobulated fibers, and non-specific myopathic changes were noted in one case each [Table 4].
- **Cataract:** Seven patients underwent cataract surgery extraction.
- **Electromyography:** EMG was obtained in 9 of the 10 cases. In five, the first EMG examination demonstrated myotonic discharges, while in four patients it showed either myopathic changes or neurogenic changes without myotonic discharges. On repeated EMG examination nine patients demonstrated myotonic discharges [Table 4].
- **Other manifestations:** Atrial fibrillation and hearing loss was reported by one patient aged 65.

EMG = electromyography

Table 3. Affected muscles

Muscle group	Muscle strength*	No. of subjects affected
Iliopsoas	0–2/5	6
	4/5	4
Facial muscle (orbicularis oculi)	5–/5	7
Neck flexors	4/5	5
Deltoid	4–4+/5	10
Palmar interossei	4/5	4

*Muscle strength was evaluated using the medical research council (MRC) scale

Table 4. Additional laboratory findings

Muscle biopsy results	No. of subjects affected
Fat only	1
Necrotic fibers, fibrosis, abnormal fiber type distribution	1
Lobulated fibers	1
Non-specific myopathic changes	1
Internal nuclei, nuclear clamps	2
EMG results	
1st examination	
Myotonia	5
Myopathy	1
Myopathy + muscle fibrillation	1
Myopathy + neuropathy	1
Neuropathy	1
2nd examination	
Myotonia	9

- **Serum creatine kinase levels:** Creatine kinase levels were mildly to moderately elevated in all patients, ranging from 500 to 1200 IU/L.

DISCUSSION

DM2 shares many clinical features with DM1, such as progressive muscle weakness, myotonia, cardiac arrhythmia, cataracts and other systemic manifestations. DM2 patients may present with endocrine abnormalities such as insulin resistance [7] and, although less common than DM1, testicular failure may also be present [5]. In addition to the common clinical features, DM2 and DM1 also share muscle pathological features [8]. Despite the clinical and histological similarities of DM2 and DM1 there are some important differences: DM2 lacks the congenital and juvenile form of DM1; and mental retardation, a prominent feature of the congenital and juvenile form of DM1, is rare in DM2 [3]. Moreover, in DM1 the increased expansion size of the CTG trinucleotide repeats is associated with an earlier age of onset and more severe clinical phenotype [9], whereas in DM2 there is no definite correlation between repeat length and disease severity [6]. DM2 does not show anticipation, i.e., increased length of repeats with worse clinical course in the next generation. DM2 patients seek medical attention mostly because of muscle pain along with stiffness and fatigue, which can develop before symptomatic proximal muscle weakness appears [4], whereas DM1 patients usually present with symptomatic distal weakness [10]. This difference probably explains the usual delay in diagnosing DM2.

Another important difference between the two clinical presentations is the presence of myotonia at the time of diagnosis. Myotonia is defined as slowed relaxation after muscle contraction; it is most prominent in the early stages of DM1, is aggravated by cold and stress, and is most obvious in facial and hand intrinsic muscles [8]. Myotonia is universally present in DM1 patients, whereas in DM2 it is found in about 75% of patients at the time of diagnosis, irrespective of age [4]. In addition, myotonia occurring in DM2 varies in severity, with patients often reporting myotonia-free periods of days to weeks [5]. In our study, only 2 of the 10 patients came to medical attention because of myotonia, while 8 patients had symptomatic proximal muscle weakness without myotonia. Hence, it appears that DM2 may present with proximal muscle weakness without myotonia.

EMG is a useful tool for demonstrating myotonia when this symptom is not detected clinically. Electrical myotonia typically consists of repetitive discharges of muscle fiber action potentials at 20–80 Hz that 'wax and wane' in amplitude and frequency. In general, myotonia is easier to elicit in DM1 than in DM2 [11]. In our study, myotonia was elicited in five patients on the first EMG examination and in all nine studied patients on the second examination. Only in rare instances is clinical or electrical myotonia absent in patients with DM2 [12].

All subjects in our series were of European ancestry: one was from Bulgaria of Sephardic* descent, and nine were Ashkenazi Jews. Until now, all DM2 patients had been from Europe or had European ancestry [2]. In Germany, DM2 is as common as DM1 [13].

We conclude that DM2 often presents with muscle weakness without clinical myotonia. EMG may not show myotonic discharges initially, hence the need for a repeat test. We believe that the disease is underdiagnosed. DM2 should be included in the differential diagnosis of every adult patient with European ancestry presenting with proximal lower limb weakness.

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*Sephardic refers to Jews of North African or Middle Eastern descent, and Ashkenazi to Jews of East European descent