Published in final edited form as:
Arthritis Rheum. 2008 November ; 58(11): 3627–3631. doi:10.1002/art.24037.

Myotonic Dystrophy Type 2 Found in Two of Sixty-Three Persons Diagnosed as Having Fibromyalgia

Satu Auvinen, MD[1], **Tiina Suominen, MSc**[2], **Pekka Hannonen, MD, PhD**[1], **Linda L. Bachinski, PhD**[3], **Ralf Krahe, PhD**[3], and **Bjarne Udd, MD, PhD**[4]

[1]*Jyväskylä Central Hospital, Jyväskylä, Finland* [2]*University of Tampere, Tampere, Finland* [3]*University of Texas M. D. Anderson Cancer Center, Houston* [4]*Folkhälsan Institute of Genetics, Helsinki, Tampere University Hospital and University Medical School, Tampere, and Vaasa Central Hospital, Vaasa, Finland.*

Abstract

Because of its high prevalence, fibromyalgia (FM) is a major general health issue. Myotonic dystrophy type 2 (DM2) is a recently described autosomal-dominant multisystem disorder. Besides variable proximal muscle weakness, myotonia, and precocious cataracts, muscle pain and stiffness are prominent presenting features of DM2. After noting that several of our mutation-positive DM2 patients had a previous diagnosis of FM, suggesting that DM2 may be misdiagnosed as FM, we invited 90 randomly selected patients diagnosed as having FM to undergo genetic testing for DM2. Of the 63 patients who agreed to participate, 2 (3.2%) tested positive for the DM2 mutation. Their cases are described herein. DM2 was not found in any of 200 asymptomatic controls. We therefore suggest that the presence of DM2 should be investigated in a large sample of subjects diagnosed as having FM, and clinicians should be aware of overlap in the clinical presentation of these 2 distinct disorders.

Fibromyalgia (FM) is a common chronic pain syndrome characterized by diffuse musculoskeletal aches, stiffness, and exaggerated tenderness. Classification criteria were elaborated by the American College of Rheumatology in 1990 (1). The pathogenesis of FM is incompletely understood. Most investigators favor the view that the major cause of FM is dysfunctional pain processing in the central nervous system (CNS) (2). Muscle histologic data are mixed, but predominantly demonstrate nonspecific changes (3). Core symptoms are chronic widespread pain, generalized stiffness, poor-quality sleep, and fatigue. Chronic widespread pain is defined as pain involving at least 3 quadrants of the body and the axial skeleton, and tenderness of at least 11 of 18 specified tender points (1). Symptoms wax and wane in intensity over days and weeks, and flare with increased exertion, lack of sleep, and exposure to temperature changes and other changes in weather conditions, as well as to psychological stressors. Persistent widespread muscle pain is quite common in the general population, with a prevalence of ~10%, while the prevalence of FM has been estimated to be as high as 2–4% (0.5% in men and 3.4% in women) (4).

Address correspondence and reprint requests to Satu Auvinen, MD, Department of Neurology, Jyväskylä Central Hospital, Keskussairaalantie 19, 40630 Jyväskylä, Finland. E-mail: satu.auvinen@ksshp.fi.

AUTHOR CONTRIBUTIONS

Dr. Auvinen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Auvinen, Hannonen, Udd.

Acquisition of data. Auvinen, Suominen, Hannonen, Bachinski.

Analysis and interpretation of data. Auvinen, Suominen, Hannonen, Bachinski, Krahe, Udd.

Manuscript preparation. Auvinen, Suominen, Hannonen, Krahe, Udd.

The myotonic dystrophies are the most common muscular dystrophies in adults. They are multisystem disorders with autosomal-dominant inheritance, progressive muscle weakness and atrophy, myotonia, precocious cataracts, cardiac conduction abnormalities, endocrinologic and gastrointestinal involvement, and CNS symptoms (5). Myotonic dystrophy type 1 (DM1; Steinert disease) was first described more than 100 years ago (5). In 1992 the genetic cause of DM1 was clarified as an expansion mutation of an unstable trinucleotide (CTG) n repeat in the 3′-untranslated region of *DMPK* (the gene for myotonic dystrophy protein kinase) in chromosome 19q (6). Once genetic testing for DM1 became available, it was found that some patients with similar features did not have the DM1 mutation (7–9). In the vast majority of these DM1 mutation–negative families, the clinical features proved to be linked to another locus in chromosome 3q21, which has been designated myotonic dystrophy type 2 (DM2). DM2 is caused by a large (CCTG) n repeat expansion mutation in intron 1 of the zinc-finger protein 9 gene (*ZNF9*) (10).

The clinical picture of DM2 is generally milder and more variable than that of adult-onset DM1 (Table 1). Prominent symptoms in DM2 are pain and muscle stiffness (11–13). Muscle pain in DM2 can be very disabling, especially in individuals who perform physically demanding work.

We noted that a considerable number of our patients in the Jyväskylä Central Hospital region who had DM2 as documented by genetic testing had a previous diagnosis of FM (5 of 36 [14%]) (Auvinen S: unpublished observations). Therefore, we undertook a study of the occurrence of the DM2 mutation in patients with previously diagnosed FM.

METHODS AND RESULTS

Patients

The study was approved by the Institutional Review Board of Jyväskylä Central Hospital and carried out according to the Helsinki Declaration. The Rheumatology Center in the Jyväskylä Central Hospital region has long been involved in FM research and has a database of patients with a standardized FM diagnosis (14). Ninety patients were randomly selected from the database to participate in the study. Of the 90 patients invited, 63 consented to provide blood samples for genetic testing for the DM2 mutation. Six of the 90 patients who were invited were men (6.7%) and 84 were women (93.3%), and the mean age was 45.7 years. Proportions were similar among the group of 63 patients who were studied (4 men [6.3%], 59 women [93.7%]; mean age 49.3 years).

As a disease control cohort, 70 patients with long QT syndrome caused by one single Finnish founder mutation, G589D in the *KCNQ1*gene (15), were tested for the DM2 mutation as a possible modifier gene because of the large variation of the phenotype despite identical channel mutation. A control population of 200 healthy individuals (400 chromosomes) was also analyzed for the DM2 mutation.

Genetic analyses

DNA extracted from peripheral blood leukocytes was used for diagnostic polymerase chain reaction (PCR) (16,17). First, PCR across the DM2 (CCTG) n repeat in the first intron of *ZNF9* was used to identify individuals with 2 heterozygous normal alleles. Samples with only 1 allele were further analyzed by repeat-primed PCR specific for the DM2 mutation, to distinguish mutated expansion alleles from normal homozygous alleles (17). The results from both screening and repeat-primed PCR were obtained using fluorescent fragment analysis with capillary electrophoresis (ABI 3130) and analyzed with GeneMapper software (Applied Biosystems, Foster City, CA).

Results

In the group of 63 patients diagnosed as having FM, we identified 2 patients (3.2%) with the DM2 mutation (see below). No DM2 mutations were identified in the cohort of 70 patients with long QT syndrome or in the 200 healthy controls.

After the DM2 genetic diagnosis was obtained, patients with negative findings were informed about the test result. The 2 patients who tested positive for the DM2 mutation were clinically reexamined, and their previous records were reevaluated. Both patients were also referred for genetic counseling.

CASE REPORTS

Patient 1

Patient 1, a 48-year-old woman, had been diagnosed as having FM at the age of 45 years. She reported having experienced some muscle stiffness since her teens and had difficulty with physical exercise, but there was no proven relationship of these symptoms to the current illness. Since the age of 38, she had had muscle pain, provoked by exercise. Besides myalgia and stiffness, she had difficulty bending her knees, climbing stairs, and working with her arms elevated. Even daily housekeeping activities provoked widespread muscle pain and prevented gainful employment. On reexamination, after the positive DM2 result, very mild ptosis and slightly slow opening of the fist without any activation or percussion myotonia were observed. Her walking was stiff, but no increased muscle tone or weakness was detected upon testing of individual muscles. There was neither proximal muscle atrophy nor calf hypertrophy. Without knowledge of her positive genotype for the DM2 mutation, her clinical signs would easily have been overlooked. Her mother had developed muscle stiffness and walking difficulties at a later age, and many of her 8 siblings were reported to have similar muscle symptoms.

Patient 2

Patient 2, a 45-year-old woman, had been diagnosed as having FM at the age of 39 years, and sensorineural hearing loss was observed 2 years later. She reported having had muscle stiffness and difficulty with physical exercise since she was a teenager, but these early symptoms cannot be proven to be related to the current illness. Chronic lumbago had started at the age of 20 years and worsened during her pregnancies. Since the age of 37, she had had diffuse muscle pain and could not work with her arms elevated. Climbing stairs was difficult, and she reported having hand tremors and excessive sweating. She had falls, pains in her limbs, fatigue, and palpitations. Her working capacity had been extensively evaluated 1 year prior to this study; this included a full neurologic examination, without abnormal findings recorded. On reexamination after the positive DM2 result, her walking was found to be stiff, but results of manual strength testing of individual muscles were normal. Her calf muscles were large, and she had no clinical myotonia. When she was asked about her family, it was discovered, surprisingly, that she was the sister of patient 1.

The clinical characteristics of the 2 patients with DM2 are summarized in Table 2.

DISCUSSION

In accordance with our initial hypothesis, we identified patients with DM2 from among a cohort of patients in whom FM had been diagnosed at a specialized tertiary referral center. Indeed, the features of myalgia and muscle stiffness in DM2 as described in current diagnostic criteria (13) are in many respects indistinguishable from those recorded in FM. FM is frequent in the general population, with the prevalence of diagnosed cases as high as 1/25–1/50 in many countries (4). Thus, it is of obvious interest to determine whether there are specific, genetically

determined disease entities that go undiagnosed among patients who have been diagnosed as having FM. This is of particular importance with regard to progressive and genetic disorders such as DM2, in which the prognosis, and clinical and social consequences for patients and their families, differ from those associated with FM.

In this pilot study, we found that 2 of 63 patients diagnosed as having FM (3.2%) had DM2. Even if the frequency of undiagnosed DM2 among patients with FM were 10-fold lower than that recorded in the present analysis, the total number of known cases of DM2 would be increased by tens of thousands, which would prompt a profound revision of the current estimates of DM2 prevalence (11,12). There are no exact data available on the prevalence of the DM2 mutation in Finland or elsewhere, but even a 10-fold higher regional prevalence than the current estimate that the frequency is similar to that of DM1 (12/100,000) would not explain this finding of a 3.2% frequency of DM2 among patients diagnosed as having FM.

Are there clinical clues to identify DM2 among patients who have been diagnosed as having FM? Widely fluctuating muscle pain and stiffness, which may be provoked by exercise and other stressors, occur in both disorders. Clinical findings may be minor in both disorders, e.g., muscle tissue changes are not seen in FM, and muscle atrophy is not found in DM2. However, both of our patients who were found to have DM2 presented with several extramuscular symptoms, including fatigue, irritable bowel, and numbness, that are typical in FM, and both clearly fulfilled classification criteria for FM even at reevaluation after DM2 had been diagnosed.

One symptom suggestive of DM2, if present, is myotonia. However, half or more of DM2 patients exhibit no clinical myotonia, and a considerable proportion lack myotonia even on electromyography (EMG) (13). Proximal weakness of the lower limbs is another clue pointing to DM2. Furthermore, if present at a relatively early age, cataracts in the subject or family members, as well as elevated serum creatine kinase (CK) and/or gamma glutamyl transferase levels, are certainly suggestive of DM2. Since not all patients with DM2 exhibit myotonia on EMG, EMG is not a perfect screening method. Even when myotonia is present, multiple muscle insertions may be needed in order for it to become apparent on EMG, which is a fairly invasive and unpleasant procedure. The early onset of muscle stiffness reported by both patients with DM2 described herein is unusual. Onset of muscle stiffness in adulthood is more common, and in women, exacerbation during pregnancy is frequently reported.

Taken together, our findings indicate that DM2 appears to be a true candidate in the differential diagnostic of FM. Molecular genetic DNA testing is the gold standard to distinguish DM2 from FM. Serum CK elevation is nonspecific and is sensitive to even moderate physical exercise or minor muscle trauma. Moreover, in many patients with DM2, serum CK levels remain within the normal reference range. Nevertheless, in adult patients with myalgia and elevated CK levels, referral for genetic testing for DM2 should be considered. We suggest that the frequency of DM2 should be investigated in a larger sample of subjects who have been diagnosed as having FM, and clinicians should be aware of overlap in the clinical presentation of these 2 distinct disorders.

ACKNOWLEDGMENTS

We gratefully acknowledge Prof. Kimmo Kontula and Heikki Swan, MD, PhD for disease control patient material used in this study.

Dr. Auvinen’s work was supported by Jyväskylä Central Hospital medical research funds. Ms Suominen’s work was supported by Tampere University Hospital medical research funds. Dr. Krahe’s work was supported by NIH grant AR-48171. Dr. Udd’s work was supported by the Folkhälsan Research Foundation, by Liv & Hälsa Foundation grants, and by Tampere University Hospital and Vaasa Central Hospital District medical research funds.

REFERENCES

1. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. Arthritis Rheum 1990;3:160–172. [PubMed: 2306288]
2. Dadabhoy D, Clauw DJ. Therapy insight: fibromyalgia—a different type of pain needing a different type of treatment. Nature Clin Pract Rheumatol 2006;2:364–372. [PubMed: 16932722]
3. Bengtsson A. The muscle in fibromyalgia [review]. Rheumatology (Oxford) 2004;41:721–724. [PubMed: 12096218]
4. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19–28. [PubMed: 7818567]
5. Harper, PS. Myotonic dystrophy. 3rd ed. London: WB Saunders; 2001.
6. Brook JD, McCurrah ME, Harley HG, Buckler AJ, Church D, Aburatani H, et al. Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3′ end of a transcript encoding a protein kinase family member. Cell 1992;68:799–808. [PubMed: 1310900]
7. Ricker K, Koch MC, Lehman-Horn F, Pongratz D, Speich N, Reiners K, et al. Proximal myotonic myopathy: clinical features of a multisystem disorder similar to myotonic dystrophy. Arch Neurol 1995;52:25–31. [PubMed: 7826272]
8. Meola G, Sansone V, Radice S, Skradski S, Ptacek L. A family with an unusual myotonic and myopathic phenotype and no CTG expansion (proximal myotonic myopathy syndrome): a challenge for future molecular studies. Neuromuscul Disord 1996;6:143–150. [PubMed: 8784800]
9. Udd B, Krahe R, Wallgren-Pettersson C, Falck B, Kalimo H. Proximal myotonic dystrophy—a family with autosomal dominant muscular dystrophy, cataracts, hearing loss and hypogonadism: heterogeneity of proximal myotonic disorders? Neuromuscul Disord 1997;7:217–228. [PubMed: 9196902]
10. Liquori CL, Ricker K, Moseley ML, Jacobsen JF, Kress W, Naylor SL, et al. Myotonic dystrophy type 2 caused by a CCTG expansion in intron 1 of ZNF9. Science 2001;293:864–867. [PubMed: 11486088]
11. Udd B, Meola G, Krahe R, Thornton C, Ranum L, Day J, et al. Report of the 115th ENMC workshop: DM2/PROMM and other myotonic dystrophies. 3rd Workshop, 14–16 February 2003, Naarden, The Netherlands. Neuromuscul Disord 2003;3:589–596. [PubMed: 12921797]
12. Udd B, Meola G, Krahe R, Thornton C, Ranum LP, Bassez G, et al. The 140th ENMC International Workshop: myotonic dystrophy DM2/PROMM and other myotonic dystrophies with guidelines on management. Neuromuscul Disord 2006;16:403–413. [PubMed: 16684600]
13. Day JW, Ricker K, Jacobsen JF, Rasmussen LJ, Dick A, Kress W. Myotonic dystrophy type 2: molecular, diagnostic and clinical spectrum. Neurology 2003;60:657–664. [PubMed: 12601109]
14. Valkeinen H, Hakkinen A, Hannonen P, Hakkinen K, Alen M. Acute heavy-resistance exercise-induced pain and neuromuscular fatigue in elderly women with fibromyalgia and in healthy controls: effects of strength training. Arthritis Rheum 2006;54:1334–1339. [PubMed: 16575859]
15. Piippo K, Swan H, Pasternack M, Chapman H, Paavonen K, Viitasalo M, et al. A founder mutation of the potassium channel KCNQ1 in long QT syndrome: implications for estimation of disease prevalence and molecular diagnostics. J Am Coll Cardiol 2001;37:562–568. [PubMed: 11216980]
16. Sallinen R, Vihola A, Bachinski LL, Huoponen K, Haapasalo H, Hackman P, et al. New methods for molecular diagnosis and demonstration of the (CCTG)n mutation in myotonic dystrophy type 2 (DM2). Neuromuscul Disord 2004;14:274–283. [PubMed: 15019706]
17. Bachinski LL, Udd B, Meola G, Sansone V, Bassez G, Eymard B, et al. Confirmation of the type 2 myotonic dystrophy (CCTG)n expansion mutation in patients with proximal myotonic myopathy/proximal myotonic dystrophy of different European origins: a single shared haplotype indicates an ancestral founder effect. Am J Hum Genet 2003;73:835–848. [PubMed: 12970845]

Table 1

Clinical manifestations of myotonic dystrophy type 2

Core features	
Clinical myotonia	Present in fewer than half
Myotonia on electromyography	Absent or variable in many patients
Muscle weakness	Onset may occur after age 60–70 years
Cataracts	Present in a minority of patients
Localization of muscle weakness	
Facial weakness, jaw muscles	Usually absent
Bulbar weakness, dysphagia	Absent
Respiratory muscles	Exceptional cases
Distal limb muscle weakness	Flexor digitorum profundus on testing, only in some patients
Proximal limb muscle weakness	The main disability in most patients
Sternocleidomastoid weakness	Prominent in few patients
Muscle symptoms	
Myalgic pain	The most disabling symptom in many patients
Muscle strength variations	Can be considerable
Visible muscle atrophy	Usually absent
Calf hypertrophy	Present in half or more
Muscle biopsy findings	
Fiber atrophy	Highly atrophic type 2 fibers
Nuclear clump fibers	Scattered early, before weakness is clinically evident
Cardiac arrhythmias	From absent to severe
Brain	
Tremors	Prominent in many patients
Behavioral change	Not apparent
Hypersomnia	Infrequent
Cognitive decline	Not apparent
Other features	
Anticipation	Exceptional
Childhood-onset central nervous system involvement	Absent
Congenital form	Absent

Table 2

Clinical findings in the 2 fibromyalgia-diagnosed patients who were found to have myotonic dystrophy type 2

	Patient 1	Patient 2
Age at fibromyalgia diagnosis, years	45	39
Age at evaluation, years	48	45
Age at symptom onset, years	38	37
Symptoms at onset	Muscle pain and muscle stiffness	Muscle pain and muscle stiffness
Years of subjective weakness	5	7
Clinical myotonia	Absent	Absent
Myotonia on electromyography	Present and widespread	Absent
Cataracts	Absent	Absent
Myalgia	Present and widespread	Present and widespread
Serum creatine kinase, units/liter (normal 35–210)	411	60
Serum gamma glutamyl transferase, units/liter (normal 10–75)	76	Not tested
Other	Cholecystectomy at age 39 years	Sensorineural hearing loss, excessive sweating, tremor of hands