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Fatigue in myotonic dystrophy type 1: a seven-year prospective study

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Objectives. Cross-sectional studies reported fatigue in 50-90% of patients with myotonic dystrophy type 1 (DM1). The aim of this research was to assess frequency of fatigue in DM1 patients during a seven-year period.

Materials and methods. Study included 64 DM1 patients at baseline (50% males, age 42 ± 12 years), and 38 after seven years. Following scales were used: Muscular Impairment Rating Scale (MIRS), Fatigue Severity Scale (FSS, score equal to or greater than 36 indicates significant fatigue), and Daytime Sleepiness Scale (DSS, score of more than six is considered significant).

Results. At baseline, 54% of DM1 patients had fatigue and 46% had excessive daytime sleepiness (EDS). Ten (32%) patients with fatigue had no EDS. At the baseline, patients with fatigue were older, were more likely to had adult-onset DM1, worse MIRS and DSS compared to the patients without fatigue. After seven years, FSS score increased (34 ± 15 *vs* 48 14, p < 0.01), fatigue was found in 82% of patients, and EDS in 60%. Still eight (26%) patients with fatigue had no EDS. Fatigue progression did not parallel MIRS increase.

Conclusions. Fatigue is a common symptom of DM1 and its progression during time did not correlate with the progression of muscle weakness.

Key words: myotonic dystrophy type 1, fatigue, sleepiness, weakness, follow-up

Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominant hereditary disease caused by the expansion of CTG trinucleotide repeats in the 3' non-coding region of *DMPK* (*dystrophia myotonica protein kinase)* gene (1). DM1 is considered to be the most common muscular dystrophy in adults, with a frequency of 1 to 20 per 100 000 inhabitants (2). DM1 is a chronic, slowly progressive, multisystemic disease that affects many organs and systems including muscles, eyes, endocrine system, gastrointestinal tract, peripheral and central nervous system (3).

Fatigue may be defined as a subjective feeling of a lack of physical and/or mental energy that only partially withdraws after rest (4). Although fatigue is an important symptom of all progressive, physically disabling diseases, its frequency is greater in DM1 than in other neuromuscular diseases and can be severe even when muscular symptoms are mild (4). Thus, objective muscular weakness cannot fully describe fatigue in DM1.[5] In previous studies, the frequency of fatigue in patients with DM1 varied between 50 and 91% being one of the most common disease symptoms (4, 6-15). Fatigue often occurs in association with the excessive daytime sleepiness (EDS) (14-18). Although some authors believe that EDS and fatigue are most likely to occur as a result of sleep disorders, it seems that these should be considered as two separate clinical entities in DM1 since not all patients with fatigue have EDS and *vice versa* (8). Patients with DM1 reported fatigue as one of the most important factors that disturb their emotional, social and everyday life (14). It also has an impact on the quality of life and safety of DM1 patients (12, 19).

Only two studies so far have longitudinally analyzed fatigue in DM1. Kalkman and colleagues found increase of the Checklist Individual Strength score for fatigue in 70 DM1 patients during a short period of 18 months (19). In the study by Gliem and colleagues, there was no significant progression neither of FSS nor of DSS score during a five-year follow-up period in a small cohort of

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16 DM1 patients (20). Also, percentage of patients with significant fatigue or EDS did not progress during time (21). These contradictory findings raise an importance of further research.

The aim of our study was to analyze fatigue during a seven-year period in a larger cohort of DM1 patients.

Material and methods

We included 64 patients with DM1 who were hospitalized at the Neurology Clinic, Clinical Centar of Serbia in the period from 2011 to 2013 (baseline testing). The diagnosis of the disease was based on the clinical findings, electrophysiological examination and molecular-genetic analysis. Since research was conducted in adult clinic, there were no patients under the age of 18. Patients with congenital and late adult form of DM1 were excluded. Patients were divided into two groups based on their age at the onset of the disease: 1) patients with childhood/ juvenile form of the disease with age at onset between one and 20 years, and 2) patients with classic / adult form with age at onset between 20 and 40 years. During 2018, follow-up testing was carried out. The period between baseline and follow-up testing was 6.7 ± 1.3 years (range 5-8 years). During this period, eight patients died, ten were lost from follow-up (moved, changed phone number, stopped to visit neurologists), while seven refused to participate in retesting. One patient was excluded due to the presence of another serious illness - laryngeal carcinoma. Thus, 38 (59.4%) of 64 patients were retested. This study was approved by the Ethical Board of the Neurology Clinic, Clinical Center of Serbia and all patients gave informed consent to participate.

Degree of muscle weakness was determined according to the Muscular Impairment Rating Scale (MIRS), that classifies DM1 patients in five categories (22). Level of fatigue was measured by Krupp's Fatigue Severity Scale (FSS) (23). FSS is the most commonly used questionnaire for examining severity and frequency of fatigue, and its effect on physical activity, work, family, social and everyday activities. It is considered particularly suitable for chronic disabling disorders such as DM1. It consists of nine questions with responses given on 1 to 7 scale. Total score equal to or greater than 36 indicates significant fatigue. Level of excessive daytime sleepiness (EDS) was determined using the Daytime Sleepiness Scale (DSS). DSS scale is specifically developed for assessing EDS (by asking about its frequency and in certain situations) in patients with DM1 (24, 25). DSS does not analyze the impact of EDS on patient's everyday life. It consists of five questions and DSS score of more than six is considered significant.

During seven-year period patients did not receive any specific medication for fatigue or EDS. The majority of them had annual three-week rehabilitation in spa since this is funded by the Health Fund. However, data on this were not systematically collected.

SPSS software version 20.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis of the obtained data. For group comparisons, χ^2 test, Mann-Whitney U test and Student t test were used as appropriate. χ^2 test and Student t test for paired samples were used to compare results at baseline and at follow-up. If we evaluate delta FSS as a continuous variable, then the sample size of 38 subjects achieves 99.9% power to detect significant difference between the first and the second measurement, at 0.05 significance level. Using FSS as a categorical variable, the sample size of 38 subjects achieves 100% power to detect significant differences between FSS status before and after the evaluation, at 0.05 significance level. Change between follow-up and baseline FSS score was correlated with disease duration, MIRS change and DSS change during same period of time using Spearman correlation coefficient. For all statistical tests, significant testing was two-sided, where alpha was set at 0.05 for statistical significance and at 0.01 for high statistical significance.

Results

Sociodemographic and clinical characteristics of patients with DM1 at baseline are shown in Table 1. No significant differences were observed in patients who did not repeat testing compared to the patients who were retested.

The frequency of fatigue and EDS was evaluated in 64 patients at baseline. Fatigue was present in 31 (48.4%) patients with DM1. Among 31 patients with fatigue, 32.3% had only fatigue, while 67.7% had both fatigue and EDS. In 18 (28.1%) patients only fatigue or only EDS occurred. DSS score was higher in the group of patients with fatigue (8.2 ± 3.2 to 5.2 ± 2.8, $p < 0.01$).

The association of sociodemographic/clinical characteristics and fatigue was examined at baseline. No association was observed between fatigue and gender, education, or disease duration. Patients with fatigue were older compared to the patients without fatigue (45.7 ± 8.6 *vs* 38.8 ± 11.3 years, $p < 0.01$).

Among patients with fatigue, 87.1% had adult onset of the disease, while in the group of patients without fatigue 48.5% had adult form ($p < 0.01$). Muscle weakness was more pronounced in patients with fatigue compared to the patients without fatigue (MIRS 3.6 ± 0.7 *vs* 3.0 ± 0.6, respectively, $p < 0.01$).

Comparison of the sociodemographic and clinical characteristics of 38 patients at baseline and follow-up is shown in Table 2. MIRS score significantly progressed during a seven-year follow-up period (3.2 ± 0.6 *vs* 4.0 ± 0.6, $p < 0.01$) (Tab. 2). Average FSS score was sig-

Table 1. Sociodemographic and clinical characteristics of DM1 patients at baseline.

Characteristics	Retested patients	Not retested patients
N	38	26
Gender-male (%)	47.7	50
Age (years, mean ± SD)	42.6 ± 9.5	41.6 ± 12.2
Education (years, mean ± SD)	10.6 ± 2.3	10.6 ± 1.5
Age at onset (years, mean ± SD)	23.2 ± 9.4	22.3 ± 9.7
Disease form (%) childhood/juvenile classic/adult	 31.6 68.4	 34.6 65.4
Disease duration (years, mean ± SD)	19.3 ± 8.2	18.7 ± 9.3
MIRS (%) II III IV V	 10.5 55.3 34.2 0	 15.4 50.0 26.9 7.7
MIRS (mean ± SD)	3.2 ± 0.6	3.3 ± 0.8
FSS (mean ± SD)	33.6 ± 15.2	35.2 ± 14.4
Fatigue (%)	44.7	53.8
DSS (mean ± SD)	6.7 ± 3.7	6.4 ± 2.8
EDS (%)	44.7	46.2

SD: standard deviation; MIRS: Muscular Impairment Rating Scale; FSS: Fatigue Severity Scale; DSS: Daytime Sleepiness Scale; EDS: Excessive Daytime Sleepiness

nificantly increased on follow-up compared to the baseline (47.7 ± 14.1 *vs* 33.6 ± 15.2, $p < 0.01$). Fatigue was present in 44.7% of patients at baseline and 81.6% of patients at follow-up ($p < 0.01$). Out of 21 patients who did not have fatigue at baseline, 66.7% developed fatigue at follow-up. In only three patients, FSS score at follow-up improved compared to the baseline, but still remained in the range of significant fatigue. DSS score at follow-up also showed statistically significant progression compared to the baseline (8.0 ± 3.8 *vs* 6.7 ± 3.7, $p < 0.05$), but the frequency of EDS in patients did not significantly change over the years. The frequency of fatigue and drowsiness was retested in 38 patients after a seven-year follow-up period.

Change in the FSS score between follow-up and baseline visit did not significantly correlate neither with

Table 2. Sociodemographic and clinical characteristics of patients with DM1 at baseline and follow-up.

Characteristics	Baseline	Follow-up
N	38	38
Age (years, mean ± SD) **	42.6 ± 9.5	49.2 ± 9.5
Disease duration (years, mean ± SD)	19.3 ± 8.2	26.1 ± 8.0
MIRS ** 	10.5 55.3 34.2 0	0 18.4 65.8 15.8
II		
III		
IV		
V		
MIRS (mean ± SD) **	3.2 ± 0.6	4.0 ± 0.6
FSS (mean ± SD) **	33.6 ± 15.2	47.7 ± 14.1
Fatigue (%) **	44.7	81.6
DSS (mean ± SD) *	6.7 ± 3.7	8.0 ± 3.8
EDS (%)	44.7	60.5

SD: standard deviation; MIRS: Muscular Impairment Rating Scale; FSS: Fatigue Severity Scale; DSS: Daytime Sleepiness Scale; EDS: excessive daytime sleepiness; ** $p < 0.01$; * $p < 0.05$

the duration of the disease between two testings nor with the difference in muscle weakness. On the other hand, moderate correlation was observed between the change in FSS score and DSS score during years (ρ = -0.40, $p < 0.05$).

Discussion

Around half of our patients with DM1 had significant fatigue at the baseline, while 82% developed fatigue after seven-year follow-up. This is in line with the results of cross-sectional studies in which fatigue was usually reported in more than two thirds of DM1 patients (4, 6-10, 12, 13). We observed progression of FSS score and frequency of fatigue during seven years. All the patients with fatigue at the baseline still had fatigue after seven years. Furthermore, two third of the patients that did not have fatigue at the baseline, reported significant fatigue at the follow-up. These results show that the frequency of fatigue increases with the natural course of the disease in DM1. Accordingly, increase of the Checklist Individual Strength score for fatigue was found in 70 DM1 patients during a short period of 18 months (20). However, in another study percentage of DM1 patients with significant fatigue or EDS did not progress during five years, but this cohort was pretty small consisting of only 16 patients (21). Further studies are needed to resolve this contradictory findings. It would be of interest to create a disease-specific fatigue scale and to analyze its sensitivity, specificity and responsiveness at multiple time points in order to be used in clinical trials and everyday practice.

Although fatigue and EDS are similar symptoms and are caused by similar factors, many authors state that they are different entities in DM1 (8). It has been previously stated that patients with EDS almost always reported fatigue symptoms, while those with fatigue were much less likely to report EDS (13). Some patients with DM1 report that they are tired but not sleepy, because drowsiness is usually perceived as a lack of initiative, while fatigue and exhaustion are more socially acceptable and are most often seen as a consequence of a hard work (26). In line with these findings, the presence/absence of fatigue and sleepiness overlapped in about two thirds of our patients but not in all of them. Besides this, effect of fatigue and EDS on patient's life is different. In one study on 200 adult DM1 patients, fatigue was observed to be an independent factor that significantly influenced the social life of patients, while this effect was not observed for EDS (7). Similar to this, fatigue, but not EDS, was significant predictor of the worse quality of life in DM1 (12). Although these differences exist, overlap between fatigue and EDS is obvious in majority of DM1 patients. Also, we have observed a parallel progression of these two disorders during time. Accordingly, the study group lead by Merkies has developed a specific scale that simultaneously measures both fatigue and EDS in DM1 (28).

At baseline, our DM1 patients with fatigue were about seven years older than patients without fatigue, which indicates that the aging process itself has a certain effect on fatigue. DM1 is often considered a progeroid disease (29). We observed association between fatigue and muscle weakness measured by MIRS score at the baseline. Accordinlgy, in previous study lower muscle strength contributed to lower levels of physical activity, which, in turn, contributed to fatigue severity in three neuromuscular diseases including DM1 (20). Also, Winblad and Lindberg found correlation between Fatigue Impact Scale score and muscle impairment (30). However, we did not notice a parallel progression of fatigue and weakness during time, which suggests that there are other important factors that contribute to the fatigue progression. Alterations in sarcolemmal excitability behind the myotonic phenomenon may also to be considered (31). Fatigue can occur due to the sleep disorders such as periodic limb movements and sleep apneas (5, 16). Besides this, structural brain changes may influence the presence of fatigue in DM1. Previous study found hypochogenicity of the raphe nucleus to correlate with fatigue in DM1 (32). Furthermore, according to Minnerop et al., fatigue was less pronounced in patients with more changes in the brain white matter, probably due to the lack of disease awareness (9).

Main limitation of the study is a small cohort of DM1 patients and lost of patients during time, as well as a lack of multiple testings during time. Also, several further variables would be helpful in understanding fatigue and EDS in DM1, including other concomitant sleep, cardiac and respiratory disorders, and polysomnography data. We also believe that cognitive-behavioural characteristics of DM1 patients, especially unawareness, may affect their report on fatigue and EDS (33).

Conclusions

Fatigue is a common symptom in DM1. Patients with fatigue were older, usually had adult-onset DM1, more severe muscle weakness and more severe EDS. Frequency and severity of fatigue increases during time in DM1, but worsening of the fatigue is independent of the muscle weakness progression.

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Conflict of interest

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Brook JD, Mc Currach ME, Harley Hg 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;69:385.
2. Emery AE. Population frequencies of inherited neuromuscular diseases – A world survey. Neuromuscular Disord 1991;1:19-29.
3. Wenninger S, Montagnese F, Schoser B. Core clinical phenotypes in myotonic dystrophies. Front Neurol 2018;9:303.
4. Kalkman JS, Schillings ML, van der Werf SP, et al. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. J Neurol Neurosurg Psychiatry 2005;76:1406-9.
5. Meola G, Sansone V. Cerebral involvement in myotonic dystrophies. Muscle Nerve 2007;36:294-306.
6. Winblad S, Lindberg C, Hansen S. Cognitive deficits and CTG repeat expansion size in classical myotonic dystrophy type 1 (DM1). Behav Brain Funct 2006;2:16.
7. Gagnon C, Mathieu J, Jean S, et al. Predictors of disrupted social participation in myotonic dystrophy type 1. Arc Phys Med Rehab 2008;89:1246-55.
8. Laberge L, Dauvilliers Y, Bégin P, et al. Fatigue and daytime sleepiness in patients with myotonic dystrophy type 1: to lump or split? Neuromuscular Disord 2009;19:397-402.
9. Minnerop M, Weber B, Schoene-Bake JC, et al. The brain in myotonic dystrophy 1 and 2: evidence for a predominant white matter disease. Brain 2011;134:3530-46.
10. Tieleman AA, Jenks KM, Kalkman JS, et al. High disease impact of myotonic dystrophy type 2 on physical and mental functioning. J Neurol 2011;258:1820-6.
11. Laberge L, Mathieu J, Auclair J, et al. Clinical, psychosocial, and central correlates of quality of life in myotonic dystrophy type 1 patients. Eur Neurol 2013;70:308-15.
12. Rakocevic-Stojanovic V, Peric S, Madzarevic R, et al. Significant impact of behavioral and cognitive impairment on quality of life in patients with myotonic dystrophy type 1. Clinl Neurol Neurosurg 2014;126:76-81.
13. Gallais B, Gagnon C, Forgues G, et al. Further evidence for the reliability and validity of the Fatigue and Daytime Sleepiness scale. J Neurological Sci 2017;375:23-6.
14. Heatwole C, Bode R, Johnson N, et al. Patient-reported impact of symptoms in myotonic dystrophy type 1 (PRISM-1). Neurology 2012;79:348-57.
15. Landfeldt E, Nikolenko N, Jimenez-Moreno C, et al. Disease burden of myotonic dystrophy type 1. J Neurol 2019;266:998-1006.
16. Quera Salva MA, Blumen M, Jacquette A, et al. Sleep disorders in childhood-onset myotonic dystrophy type 1. Neuromuscular Disord 2006;16:564-70.
17. Dauvilliers Y, Laberge L. Myotonic dystrophy type 1, daytime sleepiness and REM sleep dysregulation. Sleep Med Rev 2012;16:539-45.
18. West SD, Lochmuller H, Hughes J, et al. Sleepiness and sleep-related breathing disorders in myotonic dystrophy and responses to treatment: a prospective cohort study. J Neuromuscul Dis 2016;3:529-37.
19. Okkersen K, Jimenez-Moreno C, Wenninger S, et al. Cognitive behavioural therapy with optional graded exercise therapy in patients with severe fatigue with myotonic dystrophy type 1: a multicentre, single blind, randomised trial. Lancet Neurol 2018;17:671-80.
20. Kalkman JS, Schillings ML, Zwarts MJ, et al. The development of a model of fatigue in neuromuscular disorders: a longitudinal study. J Psychosom Res 2007;62:571-9.
21. Gliem C, Minnerop M, Roeske S, et al. Tracking the brain in myotonic dystrophies: a 5-year longitudinal follow-up study. PLoS One 2019;14:e0213381.
22. Mathieu J, Boivin H, Meunier D, et al. Assessment of a disease-specific muscular impairment rating scale in myotonic dystrophy. Neurology 2001;56:336-40.
23. Krupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patiens with multiple sclerosis and systemic lupus erythematosus. Arch Neurology 1989;46:1121-3.
24. Laberge L, Gagnon C, Jean S, et al. Fatigue and daytime sleepiness rating scales in myotonic dystrophy: a study of reliability. J Neurol Neurosurg Psychiatry 2005;76:1403-5.
25. Lou JS. Techniques in assessing fatigue in neuromuscular diseases. Phys Med Rehab Clin North Am 2012;23:11-22.
26. Dement WC, Hall J, Walsh JK. Tiredness versus sleepiness: semantics or a target for public education*?* Sleep 2003;26:485-6.
27. van der Werf S, Kalkman J, Bleijenberg G, et al. The relation between daytime sleepiness, fatigue, and reduced motivation in patients with adult onset myotonic dystrophy. J Neurol Neurosurg Psychiatry 2003;74:138-9.
28. Hermans MC, Merkies IS, Laberge L, et al. Fatigue and daytime sleepiness scale in myotonic dystrophy type 1. Muscle Nerve 2013;47:89-95.
29. Meinke P, Hintze S, Limmer S, et al. Myotonic dystrophy - A progeroid disease? Front Neurol 2018;9:601.
30. Winblad S, Lindberg C. Perceived fatigue in myotonic dystrophy type 1: a case-control study. BMC Neurol 2019;19:45.

31. Baldanzi S, Ricci G, Bottari M, et al. The proposal of a clinical protocol to assess central and peripheral fatigue in myotonic dystrophy type 1. Arch Ital Biol 2017;155:43-53.

32. Peric S, Pavlovic A, Ralic V et al. Transcranial sonography in patients with myotonic dystrophy type 1. Muscle Nerve 2014;50:278-82.

33. Baldanzi S, Bevilacqua F, Lorio R, et al. Disease awareness in myotonic dystrophy type 1: an observational cross-sectional study. Orphanet J Rare Dis 2016;11:34.

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