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High incidence of falls in patients with myotonic dystrophy type 1 and 2: A prospective study

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Abstract

We aimed to examine the incidence as well as the circumstances and the consequences of falling in adult patients with myotonic dystrophy type 1 and 2 (DM1/DM2). We performed a prospective cohort study in 209 subjects, of which 102 had DM1, 42 had DM2 and 65 healthy controls. An assessment of their falls was carried out during 100 consecutive days. In addition, falls during the previous year were reported. The primary outcome measure was the number of self-reported falls per participant during these 100 days. The secondary outcome measures included self-reported causes, circumstances and consequences of the falls. Mean (SD) falls per participant in 100 days was seven- to eightfold higher in patients with DM1 (0.74 (0.14)) and DM2 (0.62 (0.20)) compared to the controls (0.09 (0.04); $p < 0.001$)). Sixteen percent of DM1 and 17% of DM2 patients fell at least twice. Two-thirds of the falls occurred inside. Fifty percent of falls resulted in an injury, including a head trauma in four patients. Compared to non-fallers, those patients who fell were older (DM1/DM2), had a lower DM1-Activ score (DM1), had more muscle weakness (DM1), and reported less confidence in balance (DM1). This study demonstrates a high incidence and clinical relevance of falling in patients with DM1 and DM2. Fall prevention strategies in both DM1 and DM2 should focus on adaptations of the home environment and the patient's interaction in this environment.

Keywords: Myotonic dystrophy; Incidence studies; Falls.

1. Introduction

Myotonic dystrophy type 1 and 2 (DM1/DM2) are genetic multisystem disorders with varying symptoms, including muscle weakness, myotonia, cardiac arrhythmias and brain dysfunction [1–5]. Recognized risk factors for falling in DM1 include distal and/or proximal muscle weakness, myotonia, cognitive impairment and daytime sleepiness [6–13]. We recently performed a randomized clinical trial to test the effect of cognitive behavioral therapy including a physical training module on fatigue in DM1, and found that falling is a frequent symptom in DM1 (57% of the adverse events was related to falls) [14]. Up till now, three studies examined falls in patients with DM1: a 13-week prospective study in 13 patients showed a tenfold increase in the risk for falls when compared to 12 healthy controls [15]. Two uncontrolled studies in 43 and 573 patients with DM1 showed that falls in the latest year occurred in 77 and 70% of patients; a longer disease duration and a higher age was associated with a higher risk for falls. [16,17]. Although these studies have provided important data on falls in DM1, the patient sample of the prospective study is relatively small - given the characteristic clinical heterogeneity of DM1 - and the design of the latter two studies may be influenced by recall bias, in particular due to cognitive impairment [9,12]. For DM2 no data on fall rates and consequences could be found, even though mobility limitations are common and gait abnormalities have been reported [8,18,19]. This led us to prospectively examine the

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incidence, circumstances and consequences of falls in a large cohort of adult patients with DM1 and DM2 compared to healthy controls.

2. Materials and methods

2.1. Participants

Patients with DM1 were recruited from the outpatient clinic of the Neurology department at the Radboud University Medical Center, a tertiary referral center for DM in the Netherlands. For patients with DM1, we randomly selected patients from our database until our number was reached. All known DM2 patients in the Netherlands were identified using the Dutch neuromuscular database and approached for participation in the study [20]. Inclusion criteria for DM1 and DM2 were a genetically confirmed diagnosis (DM1 and DM2) or typical symptoms and at least one first-degree relative with genetically confirmed DM (DM1). Exclusion criteria were age < 18 years, the presence of another disorder with an increased risk of falls or severe cognitive problems that might have interfered with the ability to fill out the surveys. Controls were non-affected family members or spouses.

2.2. Ethical approval

Written informed consent was obtained from all participants. The local ethical standards committee approved the study (CMO Arnhem-Nijmegen, 2016/2980).

2.3. Power analysis

We used one study to estimate the number of DM1 patients needed to generate a significant number of falls permitting our planned analyses [15]. Based on a prospective study on falls in 13 patients with DM1, the inclusion of 100 patients with DM1 and a follow-up of 100 days would be expected to lead to 282 falls [15]. Given the heterogeneity of DM1 and the small number of patients in the previous study [15], we anticipated that we could encounter fewer falls than expected. We felt that even a conservative estimate (e.g. half of 282 falls) would generate sufficient data to explore circumstances and consequences of falls in DM1. For DM2, no preliminary data were available for power analysis.

2.4. Data collection

The following demographic and clinical data were collected: age, sex, diagnosis (DM1 or DM2) and medication use. We assessed activity and participation in DM patients with the DM1-Activ scale: a disease specific Rasch-built measure [21]. Scores on the DM1-Activ are calculated on a logit scale and can be translated to centile metrics ranging from 0 to 100 with lower scores indicating more impairment. The discriminative ability of the DM1-Activ to differentiate between patients with various levels of disability has been shown to be high [21].

2.5. Prospective fall assessment

We prospectively assessed falls during a period of 100 days using automated e-mails and telephone calls. A fall was defined as a loss of balance resulting in unintentionally coming to rest on the ground, floor or other lower level [22].

Participants were instructed to keep track of all falls during the period of 100 days by filling out a printed form directly after each fall to reduce recall bias. Additionally, participants received weekly e-mails with the following question: 'Did you fall last week?' using an automated data collection system (Castor EDC) [23]. We instructed participants to answer 'yes' in case of a fall or a possible fall. Participants who answered 'yes' were contacted by phone to collect details about all falls of the previous week using a structured form by one of the researchers. Participants without an e-mail address received weekly calls instead of the e-mail. In case of uncertainty about a fall event, consensus was reached during the weekly meeting of the study team. We sent an e-mail reminder to participants who had not answered the weekly question within four days. On the fifth day, the participants who did not respond to our digital reminder were called.

Secondary outcomes were causes, circumstances, and the consequences of falls and included the following: 1) self-reported cause of the fall by participants (intrinsic/extrinsic); 2) the surroundings: a) inside or outside, and b) familiar or unfamiliar – a familiar environment was defined as a well-known and frequently visited environment; 3) the direction of fall; 4) the need of assistance getting up; 5) suffered injuries (grazes, bruises, sprains, fractures or other); 6) hospital visits.

Participants who fell at least once each week during three consecutive weeks were defined as 'frequent fallers'. We contacted their general practitioner to initiate secondary prevention. If participants dropped out during the prospective fall assessment their results were not included in the study.

2.6. Retrospective fall assessment

We collected fall history of the prior 12 months with a survey that we have used previously in patients with Parkinson's disease and facioscapulohumoral muscular dystrophy (FSHD) [24,25]. We adapted the survey to include complaints of myotonic dystrophy by adding items on cardiac symptoms, muscle stiffness and cataract surgery. The survey includes a retrospective account of incidence and consequences of falls in the prior year and self-reported muscle weakness, muscle stiffness, fear of falling (yes/no), avoiding activities due to fear of falling (yes/no) and confidence in balance during activities of daily life (using a 100 mm horizontal visual analogue scale (VAS)). Other items were self-reported cataract, use of walking aids and alcohol use >2 units daily.

2.7. Data analysis

Continuous variables are presented as mean with standard deviation or as median with interquartile range, depending on

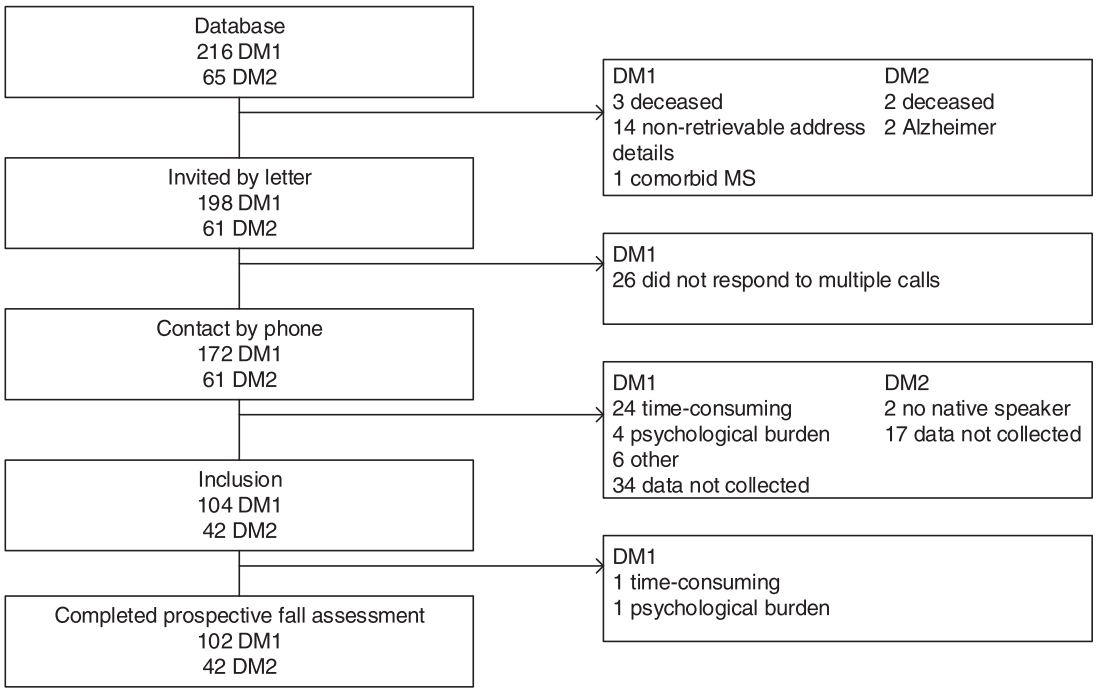

Fig. 1. Flowchart of the inclusion of patients.

the distribution of the data, which was analyzed using the Shapiro-Wilk test. The primary outcome was number of falls per participant in 100 days. We analyzed the primary outcome using a one-way ANOVA or Kruskal-Wallis, depending on distribution of the data. If testing resulted in significant differences ($p < 0.05$), these were explored with post-hoc analysis using Bonferroni. Within groups of DM1 and DM2, characteristics of participants who had fallen were compared with those who did not, using the Student's T-test or the Mann-Whitney test, depending on the distribution of the data. For analysis of dichotomized variables we used the χ^2-test or Fisher exact test. Logistic regression was performed to explore which variables explained the dependent variable (the probability to fall once or more during 100 days, yes/no). We used the following independent variables: age, DM1-Activ score, presence of muscle weakness, presence of cataract and confidence in balance. Mean DM1-Activ scores (0–100) were reported and a stratification in five categories was used for analysis (0–20, 20–40, 40–60, 60–80 and 80–100). We used SPSS version 22 for data analysis [26].

3. Results

Patients were recruited from March 2017 to April 2017. We invited 198 eligible patients with DM1 and 61 patients with DM2, of which 104 (53%) (DM1) and 42 (69%) (DM2) agreed to participate (Fig. 1). Two participants (DM1) dropped out before baseline information was collected. In both DM1 and DM2 patient groups we did not find significant differences between participants and non-participants regarding sex and age. Sixty-five controls were included of whom three dropped out due to lack of motivation.

3.1. Baseline characteristics

Patients with DM1 were younger compared to DM2 and the controls (Table 1). Seven patients (3 DM1, 4 DM2) were genetically diagnosed but asymptomatic. DM1-Activ scores showed a wide range of reduced activity and participation for patients (20–100, with lower scores indicating less activity). The proportion of patients in each category was: 0% (0–20), 9% (20–40), 32% (40–60), 24% (60–80), 35% (80–100).

3.2. Prospective fall assessment

The number of falls differed between patients with DM1 and DM2 versus controls (mean falls per participant, 0.74 (DM1); 0.62 (DM2); 0.09 (HC), $p < 0.001$), but did not differ between DM1 and DM2. This resulted in an eightfold (DM1) and sevenfold (DM2) increased fall frequency in patients compared to controls. The proportion of participants falling at least once differed between DM1 (36%) and DM2 (29%), compared to healthy controls (9%; $p < 0.001$). Seventeen patients with DM1 (16%) and seven patients with DM2 (17%) fell twice or more, while no controls fell more than once Fig. 2. In two patients (1 DM1, 1 DM2) we contacted the general practitioner or rehabilitation doctor, because of falls in three consecutive weeks.

Table 1
Baseline characteristics and results of retrospective analysis.

	DM1	DM2	Controls	*p*-value
N (% female)	102 (47%)	42 (81%)	65 (45%)	<0.001
Age	48.1 (13.2)*	54.2 (14.9)	53.9 (13.8)	<0.05
BMI	24.9 (22.7–28.9)	24.0 (20.9–26.6)**	26.4 (24.1–28.8)	<0.05
DM1-Activ	65.0 (51.0–88.0)	65.0 (52.3–81.8)	–	0.86
Balance confidence	72.5 (49.5–92.0)***	52.0 (38.3–92.5)***	99.0 (90.0–100)	<0.001
VAS (0–100)				
Subjective muscle weakness	78 (76%)	33 (79%)	3 (5%)	<0.001
VAS (0–100)	47.1 (22.5)	48.5 (25.7)	19.0 (20.1)	0.12
Subjective muscle stiffness	56 (55%)	34 (81%)	3 (5%)	<0.001
VAS (0–100)	39.8 (20.6)	45.9 (22.4)	41.3 (42.6)	0.45
Fear of falling	26 (25%)	22 (52%)	7 (11%)	<0.001
Avoiding activity	13 (50%)	14 (64%)	4 (57%)	0.91
Alcohol use > 2 daily	4 (4%)	2 (5%)	3 (5%)	0.99
Cataract	47 (46%)	19 (45%)	5 (8%)	<0.001
underwent surgery	37/47 (79%)	13/19 (68%)	3/5 (60%)	0.95
Betablocker use	11 (11%)	4 (10%)	2 (3%)	0.05
Benzodiazepine use	0 (0%)	1 (2%)	0 (0%)	0.20

Values are mean (SD), median (interquartile range 25–75) or frequency (proportion,%). BMI: Body Mass Index.
* $p < 0.05$ DM1 vs DM2 and control.
** $p < 0.05$ DM1 vs control.
*** $p < 0.001$ vs control. *P*-values are shown for ANOVA, chi-squared, Fisher exact or Mann-Whitney test.

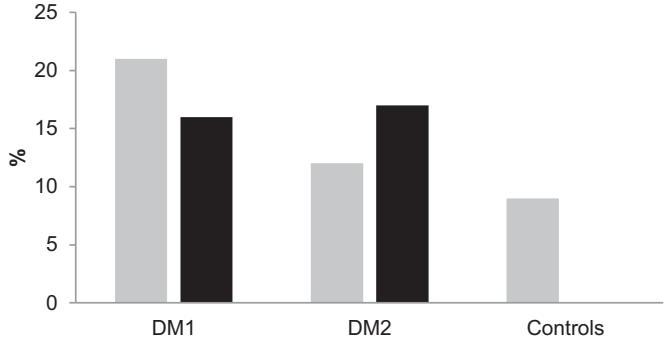

Fig. 2. Proportion of subjects that fell once (gray) or more than once (black) during a prospective fall assessment of 100 days.

3.3. Circumstances of falls

Of all falls, extrinsic factors such as an obstacle on the floor or a slippery surface were named as cause in 55% (DM1) and 46% (DM2) of events. All other falls were a result of intrinsic causes (e.g. light-headedness, fatigue, weakness or stiffness in the legs) or from an unknown cause (Table 2). The majority of falls (63%) occurred in the home environment. The direction of falling could be specified in 85% of cases in patients and showed no dominant direction. Palpitations, vertigo or newly prescribed medication never preceded falls.

3.4. Consequences of falls

In 40% (DM1) and 46% (DM2) of falls, patients were unable to get up without assistance. Injuries were common: in 54 out of 107 (50%) falls, patients sustained at least one injury; DM2 patients reported more injurious falls (Table 2). Most injuries were minor with bruises or grazes being the most common (84%). Four patients (3 DM1, 1 DM2) suffered a head trauma and their symptoms comprised a headache for a few days, loss of consciousness or post traumatic amnesia with normal brain CT. Healthy controls reported five injurious falls, of which four were minor injuries. One control subject suffered a fracture of his seventh rib.

3.5. Characteristics of falling participants

Compared to non-falling patients, falling patients were older (Table 3). Falling DM1 patients reported less confidence in balance, had more subjective leg muscle weakness, a lower DM1-Activ score and more often used a walking aid (Table 3). There was no significant difference between falling and non-falling DM2 patients.

Age, DM1-Activ score, muscle weakness, confidence in balance, and presence of cataract were identified as explanatory variables following univariate analyses ($p < 0.05$). The logistic regression model explained 26.9% (Nagelkerke R^2) of the variance in falls and correctly identified 74.3% of cases ($\chi^2(5) = 31.085$, $p < 0.001$). Out of the explanatory variables, only the DM1-activ score showed a significant association meaning that for each point on the DM1-Activ (100-point scale, with 100 points indicating normal activity and participation) the risk of falling increased by 1.035 (1.009–1.040).

3.6. Retrospective fall assessment

The proportion of participants who had fallen in the prior year differed between patients with DM1 (54%) and DM2 (50%) versus controls (12%) ($p < 0.001$). For DM1, DM2 and controls the proportion of subjects that fell more than once was 31%, 36% and 2%, respectively ($p < 0.001$). The

Table 2
Causes and consequences of falls.

	DM1 (75 falls)	DM2 (26 falls)	Controls (6 falls)	*p*-value
Causes				
- Obstacle	27 (36%)	8 (31%)	3 (50%)	
- Slippery surface	9 (12%)	3 (12%)	0 (0%)	
- Wrong footwear	5 (7%)	1 (4%)	0 (0%)	
Total extrinsic	*41 (55%)*	*12 (46%)*	*3 (50%)*	
- Lightheadedness	1 (1%)	2 (8%)	0 (0%)	
- Fatigue	4 (5%)	0 (0%)	0 (0%)	
- Stiffness legs	0 (0%)	3 (12%)	0 (0%)	
- Weakness legs	4 (5%)	3 (12%)	0 (0%)	
Total intrinsic	*9 (11%)*	*8 (32%)*	*0 (0%)*	
Cause not specified	25 (34%)	6 (24%)	3 (50%)	ns
Surroundings				ns
- Inside	50 (67%)	18 (69%)	3 (50%)	
○ Familiar	46 (92%)	18 (100%)	3 (100%)	
- Outside	25 (33%)	8 (31%)	3 (50%)	
○ Familiar	20 (80%)	7 (88%)	3 (100%)	
Required assistance standing up	30/75 (40%)	12/26 (46%)	2/6 (33%)	ns
Consequences				
- Injuries	32/75 (43%)	17/26 (65%)	5/6 (83%)	< 0.05
○ Graze/Bruise	26 (81%)	15 (88%)	3 (60%)	< 0.05
○ Sprain	4 (13%)	1 (6%)	1 (20%)	ns
○ Fracture	0 (0%)	0 (0%)	1 (20%)	ns
○ Head trauma	3 (9%)	1 (6%)	0 (0%)	ns
- Emergency room visit	2 (3%)	1 (4%)	1 (16%)	ns

p-values shown are for DM1 versus DM2. Due to the low number of falls in controls, no statistical analysis on these was performed and *p*-values for causes are not calculated, because causes are not mutually exclusive. ns: not significant.

Table 3
Characteristics of falling versus non-falling patients with DM1 and DM2.

	DM1			DM2		
	Falling	Non-falling	*p*-value	Falling	Non-falling	*p*-value
N	37	55		12	30	
Sex (M/F)	22/15	33/32	0.40	2/10	6/24	1.0
Age	51.9 (12.1)	46.0 (13.4)	<0.05	65.6 (9.4)	49.7 (14.4)	< 0.05
Balance confidence	50.0 (29.5–73.5)	82.0 (55.5–99.0)	<0.001	50.6 (26.9)	63.5 (42.0–96.3)	0.15
Subjective leg muscle weakness	34/37 (92%)	44/65 (68%)	<0.05	11/12 (92%)	22/30 (73%)	0.19
- VAS	52.0 (24.0)	43.4 (20.7)	0.09	57.0 (29.9)	44.2 (22.9)	0.18
Fear of falling	11/37 (30%)	15/65 (23%)	0.46	8/12 (67%)	15/30 (50%)	0.33
DM1-Activ	53.9 (18.8)	81.0 (59.0–96.5)	<0.001	58.8 (16.7)	71.1 (20.7)	0.07
Walking aid	19/37 (51%)	12/65 (18%)	<0.05	6/12 (50%)	8/30 (27%)	0.35
Alcohol use (>2 daily)	1/37 (3%)	3/65 (5%)	0.63	1/12 (8%)	1/30 (3%)	0.49
Use of betablockers	5/37 (14%)	6/65 (9%)	0.50	2/12 (17%)	2/28 (7%)	0.36
Use of benzodiazepines	0/37 (0%)	0/65 (0%)	–	1/12 (8%)	0/30 (0%)	0.11
Cataract	22/37 (59%)	25/65 (38%)	<0.05	7/12 (58%)	12/30 (40%)	0.28

Values are mean (SD), median (interquartile range 25–75) or frequency (proportion,%).

number of participants who reported fear of falling was 26 (25%) for DM1, 22 (52%) for DM2 and seven (11%) for controls (DM1 and DM2 versus controls, $p < 0.001$, DM1 versus DM2 $p < 0.05$). The number of participants avoiding activities because of this fear was 13 (50%) for DM1, 14 (64%) for DM2 and four (57%) for controls (Fisher exact, $p = 0.94$). Other retrospectively collected items are shown in Table 1.

4. Discussion

This study shows an eightfold increased fall frequency in patients with DM1 and a sevenfold increased fall frequency in DM2 as compared to controls. A second finding is that most falls in DM occur inside, in a familiar environment. Thirdly, this study shows that a large number of falls (50%) resulted in injuries, including head trauma.

4.1. DM1

The fall frequency in DM1 patients in the current study (eightfold) is slightly lower compared to a previous prospective study in 13 patients with DM1 (tenfold). A comparison of the clinical characteristics of the patients between the latter study and our study is difficult as we did not examine the muscle strength of our patients, and,

on the other hand, the DM1-Activ was not available for the previous study in 2006 [15]. Based on the DM1-Activ results of our study, our cohort consisted of patients with a broad range of activity and participation, including a proportion 16% of patients with a maximum DM1-Activ score (100). In comparison, in the cohort used to construct the DM1-Activ score 7% had a maximum DM1-Activ score [21]. Consequently, the relatively large proportion of patients with normal activity and participation in the current study could have contributed to a lower fall rate in our study compared to the previous prospective study on falls in DM1 [15]. Nevertheless, our study showed that in a representative cohort of DM1 patients, comprising a large range of disease severity, the fall frequency is still eightfold higher than in healthy controls.

4.2. DM2

Another finding of our study is that falling is a prevalent and clinically relevant problem in patients with DM2. Falls in DM2 may result from a combination of predominantly proximal leg muscle weakness and cognitive (i.e. executive function) dysfunction, as suggested in a previous study [19]. The authors of the latter study have shown a higher degree of variation of the swing time during dual-task gait in DM2 patients, a parameter that reflects posture and balance. In addition, a correlation between executive functions and gait pattern changes was shown in DM2 patients [19,27]. Our study is the first to examine the incidence and clinical consequences of these balance disturbances in DM2 as described below.

4.3. Causes, circumstances and consequences of falls

This study did not have enough power to identify risk factors for falling in this population, but our data may provide some clues for patients with DM1 and DM2. Risk factors for falling have been investigated in diverging populations of mostly elderly people (without DM) showing that visual impairment, distal leg weakness, mild cognitive impairment, psychotropic medication, and alcohol use, all separately, yield about a two-fold increased risk of falling [7,29,30]. Out of these factors, in our study, psychotropic medication and alcohol use were comparable between DM1/DM2 patients and controls - whereas visual impairment and leg weakness were more prevalent in DM1 [31]. Cognitive impairment was not investigated in the current study, but it is well known to occur in DM1 and DM2 with deficits across several cognitive domains [12,27,32-33]. Indeed, in addition to executive dysfunction, visuospatial deficits have been related to gait changes in DM [19]. Consequently, it is conceivable that leg weakness, visual impairment and cognitive dysfunction contribute to an increased fall frequency in DM1 and DM2.

In the current study, fear of falling differed between patients with DM2 (55%) and DM1 (26%) while the incidence of falls was comparable. The frequency of fear of falling in patients with DM2 is comparable to that in patients with FSHD (assessed in a similar fashion – 51%) [25]. This lower frequency for the fear of falling in DM1 as compared to other disorders, such as DM2, may be related to different amounts of severity and characteristics of affective symptoms and disease awareness [18,27,34–37]. The effect of fear of falling on fall frequency varies considerably: in other disorders fear of falling increased fall frequency, creating a vicious circle [38]. On the contrary, reduction of activities due to increased fear may lead to decreased fall frequency because of a reduced risk exposure [24].

Another novel finding of our study is that most falls of patients with DM1/DM2 (67/69%) occur inside, in a familiar environment. Compared to patients with FSHD (39%) this high proportion may reflect that patients with DM are more housebound [25]. This study and a previous study show that obstacles in the patient's environment or slippery surfaces in home environment account for a significant proportion of falls in DM1/DM2 [15]. However, it should be noted that causes for falls are self-reported in these studies which in addition to the reduced disease awareness might lead to a judgment bias resulting in an overestimation of extrinsic causes. Consequently, future strategies to prevent falling in patients with DM1/DM2 should focus on the home environment and on reinforcing the patients' awareness of risks in the environment as well as on intrinsic causes such as muscle stiffness.

The consequences of falls did not differ between DM1 and DM2. Both groups often needed assistance getting up after a fall (DM1 (40%) and DM2 (46%)) which is similar to a previous study in DM patients (46%), but higher compared to patients with FSHD (24%) [15,25]. These findings, together with a lower proportion of DM1 patients with a partner as compared to e.g. FSHD, underlines the social and clinical relevance of falls in DM [39,40]. Although no fractures were observed in the current study (lasting 100 days), a recent multinational retrospective survey on falls in DM1 estimated the prevalence of fall-associated fractures in the preceding 12 months to be 17% [17].

In addition to its strengths (prospective design, large cohort of patients, inclusion of patients with DM2), our study has some weaknesses. First, to minimize the burden of participation, we did not clinically examine the participants, which therefore does not allow for an analysis of the effects of proximal and distal muscle weakness on our results [28]. Secondly, we did not collect detailed data on cognitive dysfunction in our participants. Although severe cognitive impairment was an exclusion criterion, minor cognitive impairment or poor disease insight may have influenced the patient's risk of falling and ability to adequately report falls [6].

In summary, this prospective study shows that patients with DM1 and DM2 have a seven-to-eightfold fall frequency - in particular inside and in familiar surroundings. Patients with DM1 and DM2 are at risk for serious injuries, including head injuries. Future studies should focus on further examination of clinical outcome measures to identify DM patients in need for

fall prevention, and on the evaluation of treatment strategies such as physical therapy and occupational therapy including home visits to reduce the risk of falling in patients with DM1 and DM2.

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