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Title: Falls and resulting fractures in myotonic dystrophy: results from a multinational retrospective survey.

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TITLE: Falls and resulting fractures in Myotonic Dystrophy: results from a multinational retrospective survey.

RUNNING TITLE: Falls and fractures in DM1.

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KEY WORDS: myotonic dystrophy; DM1; falls; fractures; balance
Highlights

This is the first high scale survey for falls and fractures for Myotonic Dystrophy 1 DM1 adults showed 2.3 more risk of falling than a healthy over 65 years of age.

These results presented no impact of respondent sex for risk of falls.

Age showed to be a significant predictor for falls in DM1.

Falls in DM1 is still an unpredicted & underestimated factor that requires attention.

ABSTRACT

Myotonic Dystrophy type 1 multisystem involvement leads to functional impairment with an increased risk of falling. This multinational study estimates the prevalence of falls and fall-associated fractures. A web-based survey among disease-specific registries (Germany, UK and the Netherlands) was carried out among DM1 ambulant adults with a total of 573 responses retrieved. Results provided a risk ratio estimation of 30-72% for falls and of 11-17% for associated fractures. There was no significant difference for falls between male and female, but there was for fall-related fractures with a higher prevalence in women. Balance and leg weakness were the most commonly reported causes for falling. This study is based on a voluntary retrospective survey with naturally inherent limitations; however, the sample size allows for robust comparisons. The estimated risk of falls in this cohort with a mean age of 46 years compares to a previous estimation for a healthy population of over 65 years of age. These results suggest a premature-ageing DM1 phenotype with an increased risk of falling depending on age and disease severity that, so far, might have been underestimated. This may have clinical implications for the development of care guidelines and when testing new interventions in this population.
INTRODUCTION

Myotonic Dystrophy type 1 (DM1) is an autosomal dominant neuromuscular disorder that affects approximately 1 in 8,000 people, being the most common of this disease group in adults (1). This disease phenotype is predominantly defined by a genotype of an unstable and variable CTG-triplet expansion that causes mRNA mis-splicing in various cellular processes affecting different tissues and organs (2). Myotonic dystrophy is a progeroid multisystemic disease that affects primarily the muscles and nervous system with impaired function (3, 4).

Falls and stumbles have been a matter of concern among the Myotonic Dystrophy research community since Wiles et al. (5) reported a tenfold increased prevalence when compared to healthy controls. These have been objectively associated with still-ambulant patients with muscle weakness and impaired balance (6, 7), yet there are other characteristics that accompany this population’s phenotype that should also be considered as risk factors for falls: gait and mobility disturbances; visual impairment; inactivity; socio-economic status; intake of cardiac medications; and cognitive impairment (8-11). In addition, due to the low levels of vitamin D3 present in some DM1 patients, particularly males with androgen insufficiency, there is the hypothesis of a higher incidence of fractures that requires further investigation (12).

However, it is thought that falls are under-reported in this population, which might be reflected by an inaccurate estimation of prevalence (13). Additionally, falls should be considered when developing protocols for clinical trials and therapeutic interventions. Patient registries allow for access to large populations of engaged patients, and allow for the easy distribution of questionnaires through web-based surveys. This enables the collection of patient-reported data from large cohorts that would otherwise not be possible in rare diseases such as DM1. This type of recollection has been shown to provide informative data applicable to a range of outcomes or hazards (14). This research has aimed to capture the recent
overall incidence and prevalence of falls and fall-related fractures in DM1 across three countries (United Kingdom, Germany and the Netherlands). It is expected that this report will increase awareness of falls and fall-risk factors both for healthcare providers and clinical research teams.

**METHODS**

*Survey design and procedure*

The data set for this report was obtained from a web-based retrospective survey undertaken between August 2016 and January 2017. Three European centres from different countries (a. The Friedrich-Baur-Institut, Munich, Germany; b. The John Walton Muscular Dystrophy Research Centre, Newcastle-upon-Tyne, UK; c. The Radboud University Medical Centre, Nijmegen, the Netherlands), all representing highly specialized neuromuscular research centres, participated in this process. Experts from the participating centres, taking into account the sites’ differences to ensure understanding and to reduce the risk of recall bias, initially designed the survey in English. This was then translated into German and Dutch. The survey was distributed online to DM1 patients in accordance with the protocols of the relevant patient registries and databases (The UK Myotonic Dystrophy Patient Registry, UK (15); the Dutch neuromuscular database, CRAMP, the Netherlands (16); and the patient registry for myotonic dystrophies in Germany, MD-Net, Germany). Each centre went through local ethical and steering committee approvals concerning each registry’s policies and through what were considered appropriate cultural adaptations. Any resulting differences were considered before analysis to avoid any inappropriate conclusions (e.g. the German version collected falls recall from the last 12 months and the Dutch and the English versions from the last 6 months, hence prevalence estimations were not pulled out as a group). The English version of this questionnaire can be provided as an additional document. This report is limited to the data obtained via this survey so avoiding additional variabilities between registries.
Sample

Invited participants represent genetically confirmed DM1 adults who are registered on the DM registry or database in their country. Only DM1 patients who were over 18 and still ambulant were included in this report.

Statistical analysis

Descriptive statistics were performed where applicable.

Prevalence of falls in the German sample was calculated as a proportion of individuals who have had at least one fall within the previous year. Prevalence of fractures in the German sample was calculated as a proportion of individuals who have had at least one fracture within the last year. The estimations for the English and Dutch samples were calculated in the same manner, as the prevalence of at least one fall in the last six months and as the prevalence of at least one fracture in the last two years, accordingly.

The prevalence estimates were age-standardised by using weights based on the age distribution of the entire sample of patients combined (German, English, and Dutch). Prevalence was reported as percentages both for crude and age-adjusted estimates. For every estimate a 95% confidence interval (CI) was calculated. Each sample was substratified into two strata based on sex and into six age strata: 18-25, 26-35, 36-45, 46-55, 56-65, and 66-85 years old. The proportions of the six age strata in the overall sample were used as weights for the age-standardised estimates.

Odds ratios (OR) with 95% CI were calculated for sex and age for the entire sample of 570 patients. For this purpose, patients were further categorised into two groups of exposure: younger (18-65) and older (66-85).
We performed sensitivity analyses by estimating individual OR for different sub-groups: young (18-35), middle-aged (36-55), and old (56-85), as well as for the above-mentioned six age categories. OR are presented for each centre separately and for both sex and age.

Raw data were collected in Microsoft Excel and further analysed using the R statistical computing system, version 3.2.2 (17).

RESULTS

A total of 1211 questionnaires were sent out (510 via the UK Registry, 132 via the Dutch registry and 569 via the German Registry). A total of 570 responses were received with a response rate of 47% (49% UK, 76% the Netherlands and 39% Germany). The respondents’ demographic distribution showed 46% of males (50% UK, 50% the Netherlands and 45% Germany) and a mean age of 46 (SD 13) (min 18 – 82 max) (Figure 1).

Results have been summarized in Table 1. The overall estimates predict a prevalence of falls and fractures of 30% and 6-11% respectively when asked about the last 6 months and of 70% of falls and 17% of fractures when asked about the last 12 months. From all those reporting a fall, one to three falls within the periods of 6 and 12 months was the most common answer-option selected. Five percent of the respondents complained about falling more than five times within 6-month periods and 12% when asked within a year. Among the three countries, the most common reported causes for falling were weakness in legs (22-44%) and impaired balance (38%) (Figure 2). Among the responses identified as ‘other’, they were explained by respondents: 1) by referring to particular daily life situations, such as cycling, walking the dog, getting out of the car, walking on uneven surfaces or walking too fast; 2) to lack of concentration,
distractions or ‘clumsines’ (9 times); 3) to other symptoms like fatigue (3 times), low blood pressure (twice) or dizziness (once); or 4) reported alcohol consumption (twice).

Figure 1 presents the age distribution of those reporting falls against the total sample size stratified by age groups. The age group with the highest number of falls was reported by those 56-65 years old (with a prevalence between countries of 42-89%) followed consecutively by the groups 36-45 (30-73%) and 46-55 (28-71%). The age group with the highest number of fall-associated fractures was consistently the age group of those who were 56-65 years old (with a prevalence between countries of 13-30%). Distal joints were the most frequent site of fractures, with the ankle and foot (toes included) accounting for half of the fractures (Table 1). There were no hip fractures reported. Fractures mentioned as ‘others’ included the ribs, sternum and maxilla. In total 16 (14%) patients reported fractures in more than one region of the body. The English and German questionnaire versions included items on fracture treatment, and 18 (23%) of the fractures were treated with surgery, 14 of which were from the UK cohort (45%).

When analysing the full sample by sex, men showed a significantly higher incidence of falls in the UK and the Netherlands, but women presented the higher incidence of fractures overall. However, when the data were standardised to age differences in falls the prevalence between the sexes disappeared in the cohort from the Netherlands. On the other hand, in fall-associated fractures, sex differences prevail (Table 2).

Odds ratio estimates

Estimated odds ratios for sex and age are given in Table 3. The odds ratio for females over males indicate the odds of having a fall of 0.94 [95% CI: 0.68, 1.31] and the odds of having a fracture as an outcome were 1.28 [95% CI: 0.78; 2.10]. Odds ratio estimates comparing an older cohort (65-85 years old) to the younger one (younger than 65 years) were 0.44 [95% CI: 0.23; 0.83] and 1.00 [95% CI: 0.41; 2.44], for falls and fractures respectively. Sensitivity analyses were consistent with the primary findings regarding sex. However, the results showed that when stratifying the sample into three instead of two age groups and changing the thresholds for the age ranges into: young (18-35); middle-aged (36-55); and old (56-85), the
middle-aged group had higher odds of falling compared to the young patients – OR: 1.61 [95% CI: 1.06; 2.44]. Sub-stratifying the sample further into six age categories confirmed the primary findings and those of the first age sensitivity analysis. The middle-aged group of 36-45 years old had higher odds of falling compared to the younger group of 26-35 years old – OR: 1.78 [95% CI: 1.05; 3.02]. The oldest group of 65-85 years old had lower odds of falling compared to the group of 56-65 years old – OR: 0.27 [95% CI: 0.13; 0.57].

**DISCUSSION**

This study identified and quantified the prevalence of falls and fall-associated fractures in myotonic dystrophy type 1 via a retrospective multinational survey. The total sample size obtained (N=573) constitutes a significant achievement in a rare disease such as DM1 and allowed for the identification of the prevalence of falls with high confidence (18, 19). The respondents’ demographics provided an even distribution by sex and a similar age distribution between the three countries. The mean age of this study compares to previous reports on falls in DM and other neuromuscular disorders so allowing for meaningful comparisons (6, 19-21).

As part of healthy ageing, people of 65 years old and over have been identified as the cohort with the highest risk of falls, with at least 1 in every 3 persons >65 years old falling per year (annual incidence of 30%) (22, 23). However, in the particular case of DM1, older patients seem to have 56% lesser odds for falling, and inversely patients younger than 65 have 2.3 times higher (Figure 1 and Table 3). Still, this does not seem to affect their odds of having a fracture. Due to the natural progression of the disease, this might be explained by an assumption that the cohort of DM1 patients between 30 and 60 years old is more likely represented by classic or earlier disease-onset respondents, while those over 60 years old (still ambulant) may represent in part a milder or late-onset phenotype, who are characterized by a better
preserved muscle strength and less disease severity, but this is just an assumption as no other variable for disease severity has been included for analysis except for the fact that all report to be non-wheelchair users.

Approximately 10-20% of falls in the elderly population result in fractures, which is a similar rate as presented in this report for DM1 (24). The clinical relevance of lower-limb distal fractures in progressive muscle disorders is that these fractures may lead to permanent loss of function and wheelchair dependency (25). This might not always be the case in DM1 as there is a slower progression of muscle weakness, but it is certainly a potential risk to consider when dealing with fractures in more severely affected patients. Other types of injuries or consequences due to falling should also be considered and investigated as these might impact on patients’ subsequent functional and emotional status. The most common fracture location associated with osteoporosis is hip fracture, which was not reported in this study. However, it would be necessary to correlate vitamin D3 levels and bone density to draw further conclusions (26, 27). We should also consider that hip fractures are in general more common in older people. This may represent the more severely affected patients who are likely to be non-ambulant and were therefore excluded from this study (20).

In DM1, men more frequently present severe combined muscular disability with weakness, atrophy and myotonia, and cognitive impairment than women (28). These findings present men with a higher prevalence of falls compared to women, but women have a higher prevalence of fractures. However, odds ratio (OR) estimations showed that sex does not play a role in the odds of having a fall with a fracture (Tables 2 and 3).

The associated limitations of this study are those naturally associated with a retrospective survey-based study. This questionnaire is not a validated falls-reported outcome, neither a falls-specific survey, but a
registry-based questionnaire created specifically for this disease group and among a few other events queried, falls and fall-related fractures prevail. Additionally, as no official definition of “fall” has been introduced to the respondent, this provides room for different interpretations. No distinction between falls or stumbles was made and it would have been expected to see more stumbles than falls (5). Still, this report included the largest number of adult DM1 patients in a study on falls so far and under the authors’ understanding, the largest among neuromuscular disorders as well. As a voluntary survey, it may primarily attract participants with a specific interest in the study results so leading to recruitment bias. However, there is a good distribution of age and sex among the respondents, representative of the registry populations overall and as a non-exclusive falls survey, it is likely to have included respondents more interested in any of the other topics included.

CLINICAL IMPLICATIONS

These results provide more detailed information on the prevalence of falls and related fractures in a relatively large DM1 population from European countries. This registry-based sample represent a likely population to be included in prospective clinical trials which makes our study results relevant as a benchmark for possible adverse events (falls and associated fractures) which will be encountered when conducting a trial in DM1. This should be considered both when reporting adverse events and considering an endpoint selection in clinical trials. Furthermore, in the clinical and research setting steps should be taken to prevent falls where possible.

So far, very few attempts to improve patients’ balance and strength have been made and with no clinical significant success (11, 29-31). However, there are other factors associated with falling still to be addressed and that multidisciplinary teams involved with these patients should consider preventive approaches. Hammaren (6, 31) suggested a minimum annual follow-up for patients with Muscular
Impairment Rating Scale (MIRS) scores of 3 or higher and the recommendation of ankle orthotics (AFOs) where appropriate as minimal standard of care in this population. This team also demonstrated the impact of a balance exercise-programme on the balance self-confidence (31). DiPaolo (8) suggested that timely introduction of a walking assistive device may be a preventive method for severe falls in DM1. Additionally, preventable factors that can increase the risk of falling are: alcohol consumption; risky daily life activities; or associated symptoms such as fatigue or low blood pressure, to be identified by treating clinicians, physiotherapists or occupational therapists, and potentially expert teams for falls and fall prevention.

CONCLUSIONS

To the best of the authors’ knowledge this report represents the largest sample looking at the prevalence of falls in Myotonic Dystrophy type 1 to date. These results suggest that middle-aged ambulant patients have the highest risk of falling similar to a healthy population of 20 years older and an increased risk of fractures in women. Clinicians and researchers should be aware of these risks and consider fall prevention methods when developing care plans for patients with DM1.

ACKNOWLEDGEMENTS

a OPTIMISTIC Consortium
b Registry curators and c Registry steering committees


https://www.dm-registry.org/uk/

Germany ethical approval number: 521-16.
UK ethical approval number (Newcastle and North Tyneside): NE/11/0179
The Netherlands: no ethical approval required

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CONFLICT OF INTEREST

The authors have no conflict of interest relevant to this study.

AUTHORS’ CONTRIBUTIONS

SW and BS led the full study design. AJM and SW carried out the main data extraction, interpretation and manuscript drafting. HB led the statistical analysis. LW and JR led the data capture process. BE, HL and BS supervised the whole manuscript process. All authors read, commented on and approved the final submitted manuscript.

REFERENCES


Table 1. Demographics and distribution of responses related to falls and fractures due to falling. NA (not applicable) when the question was not part of the country-specific questionnaire. For questions of “cause of falling” and “type of fracture”, respondents were allowed to select more than one option. *Stumbling was only included as an option in the Dutch version of the questionnaire.

Figure 1. A. B. and C. Age distribution of those reporting falling in the last 12 months for the German (A) (German Registry) sample and for the last 6 months for the English (B) (UK Registry) and the Dutch (C) (The Netherlands Registry). D. Age distribution within the whole sample.

Figure 1. Summary of the distribution of causes of falls reported among the whole sample (prevalence %).

Table 2. Estimated prevalence of falls (A and B) and fall-associated fractures (C and D) by sex. A. presents the distribution of falls between the sexes overall, and table B presents the estimates when age-standardized. C. presents the distribution of associated falls between the sexes and table D presents the estimates when age-standardized. *Significantly higher (p <0.05).

Table 3. Odds ratio estimations for the entire sample of 570 patients: number of individuals, stratified based on sex and age, who have fallen and had an associated fracture. ns (non-significant or p≥0.05).
Figure 2. A. B. and C. Age distribution of those reporting falling in the last 12 months for the German (A) (German Registry) sample and for the last 6 months for the English (B) (UK Registry) and the Dutch (C) (The Netherlands Registry). D. Age distribution within the whole sample.

Figure 3. Summary of the distribution of causes of falls reported among the whole sample (prevalence %).
Table 1.

<table>
<thead>
<tr>
<th></th>
<th>TOTAL</th>
<th>UK</th>
<th>The Netherlands</th>
<th>Germany</th>
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<tbody>
<tr>
<td>N (% males)</td>
<td>570 (48%)</td>
<td>250 (49%)</td>
<td>100 (50%)</td>
<td>220 (45%)</td>
</tr>
<tr>
<td>Age - mean (SD)</td>
<td>46.3±13</td>
<td>47±13</td>
<td>46±13</td>
<td>46±13</td>
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<tr>
<td>Subjects reporting falling in the last 12 months (%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>155 (70%)</td>
</tr>
<tr>
<td>Prevalence of fractures among fallers in the last 12 months (%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>16 (10%)</td>
</tr>
<tr>
<td>Subjects reporting falling in the last 6 months (%)</td>
<td>NA</td>
<td>74 (29%)</td>
<td>45 (45%)</td>
<td>NA</td>
</tr>
<tr>
<td>Prevalence of fractures among fallers in the last 2 years (%)</td>
<td>NA</td>
<td>16 (22%)</td>
<td>7 (16%)</td>
<td>NA</td>
</tr>
<tr>
<td>Overall prevalence of falls (age-standardised) (95% CI)</td>
<td>48% (29-72)</td>
<td>29.6% (29.2-29.9)</td>
<td>30.6% (29.7-31.5)</td>
<td>69.7% (67.7-71.8)</td>
</tr>
<tr>
<td>Overall prevalence of fractures (age-standardised) (95% CI)</td>
<td>27% (11-17)</td>
<td>10.9% (10.8-11)</td>
<td>6.6% (6.5-6.7)</td>
<td>16.9% (16.7-17)</td>
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Attributed cause of falling
N (% among responses)

<table>
<thead>
<tr>
<th></th>
<th>TOTAL</th>
<th>UK</th>
<th>The Netherlands</th>
<th>Germany</th>
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<tbody>
<tr>
<td>Balance – 260 (39%)</td>
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<tr>
<td>Leg weakness – 244 (37%)</td>
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<tr>
<td>Stiffness – 100 (15%)</td>
<td></td>
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<tr>
<td>Other – 45 (7%)</td>
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<tr>
<td>Impaired vision – 16 (2%)</td>
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<tr>
<td>Balance – 131 (38%)</td>
<td></td>
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<tr>
<td>Leg weakness – 115 (33%)</td>
<td></td>
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<tr>
<td>Stiffness – 56 (15%)</td>
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<tr>
<td>Other – 35 (10%)</td>
<td></td>
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<tr>
<td>Impaired vision – 11 (3%)</td>
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Type of fracture
N (% among fractures)

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<th>TOTAL</th>
<th>UK</th>
<th>The Netherlands</th>
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<tr>
<td>Upper limb – 39 (41% of all reported fractures)</td>
<td></td>
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<tr>
<td>Lower limb – 49 (52%)</td>
<td></td>
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<tr>
<td>Other – 6 (6%)</td>
<td></td>
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<tr>
<td>Hand – 7 (23%)</td>
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<tr>
<td>Shoulder – 3 (10%)</td>
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<tr>
<td>Elbow and arm - 2 (6%)</td>
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<tr>
<td>Foot – 11 (35%)</td>
<td></td>
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<tr>
<td>Leg – 4 (13%)</td>
<td></td>
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<tr>
<td>Ankle – 3 (10%)</td>
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<tr>
<td>Other – 2 (6%)</td>
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<tr>
<td>Spine – 1 (3%)</td>
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Table 4. Demographics and distribution of responses related to falls and fractures due to falling. NA (not applicable) when the question was not part of the country-specific questionnaire. For questions of “cause of falling” and “type of fracture”, respondents were allowed to select more than one option. *Stumbling was only included as an option in the Dutch version of the questionnaire.
Table 5. Estimated prevalence of falls (A and B) and fall-associated fractures (C and D) by sex. A. presents the distribution of falls between the sexes overall, and table B presents the estimates when age-standardized. C. presents the distribution of associated falls between the sexes and table D presents the estimates when age-standardized. *Significantly higher (p < 0.05)

Table 6. Odds ratio estimations for the entire sample of 570 patients: number of individuals, stratified based on sex and age, who have fallen and had an associated fracture. ns (non-significant or p≥0.05)