Teenage exercise is associated with earlier symptom onset in dysferlinopathy: a retrospective cohort study

INTRODUCTION

Dysferlinopathy, an autosomal recessive muscular dystrophy caused by DYSF mutations, demonstrates a variable phenotype and progression rate, with symptom onset ranging from first to eighth decade and some patients requiring wheelchairs for mobility within 10 years, with others remaining minimally affected. Dysferlinopathy populations have previously been described as having an unusually high level of presymptomatic sporting ability. We hypothesised that this activity could be related to subsequent disease progression and investigated the hypothesis using data from the Jain Foundation’s Clinical Outcomes Study (COS) of 202 patients with dysferlinopathy.

METHODS

Data were used from 182 of the 202 patients enrolled in the Jain COS; 10 dropped out and did not give permission to use their data and 10 did not fully complete the exercise questionnaire.

The questionnaire used in the screening visits (online supplementary information) between 6 November 2012 and 19 March 2015 asked about the type, level and frequency of all physical activity prior to symptom onset. Self-reported age of first symptoms, first wheelchair use and full-time wheelchair use was taken from screening questionnaires.

Exercises were classified based on metabolic equivalents (METs) as moderate (MET 3–6) or vigorous (MET >6) (online supplementary table 1). Participants were coded, based on the maximum frequency of activity reported between ages 10 and 18 years, as 0—no physical activity; 1—vigorous activity occasionally/monthly, or moderate activity once weekly; 2—moderate activity multiple times per week or vigorous activity once weekly; and 3—vigorous activity multiple times per week.

Statistical analysis

Age of symptom onset

Estimated mean age of symptom onset differed by group ($P=0.03$) and was later in group 0 (mean 24.8 (95% CI 22.3 to 27.2)) compared with groups 2 (20.2 (18.1 to 22.3), $P=0.006$) and 3 (20.6 (18.4 to 22.8), $P=0.01$), but not 1 (21.7 (17.7 to 25.7), $P=0.20$). Cox regression analysis suggested that groups 2 (HR 1.56 (95% CI 1.06 to 2.30)) and 3 (HR 1.54 (1.04 to 2.30)) were at increased risk of earlier symptom onset than group 0 (figure 1). This was not significant for group 1 (HR 1.38 (0.78 to 2.45)).

In patients with a clinical diagnosis of LGMD2B, groups 1–3 all showed a significantly increased risk of earlier onset compared with group 0 (1: HR 7.74 (95% CI 3.07 to 19.49); 2: HR 1.71 (1.05 to 2.77); 3: HR 1.91 (1.14 to 3.18)). Significant associations were not seen among those with a diagnosis of MM or ‘other’.

RESULTS

Exercise group 0 had more female patients (65%). Demographic characteristics of each exercise group were otherwise similar (online supplementary table 2).

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Figure 1  Risk of symptomatic disease and wheelchair use over time in dysferlinopathy. Graphs show the probability of remaining event free during the time under study using Cox proportional hazards regression. Events are the onset of symptoms (A), the first time a wheelchair is used (B) and the need to use a wheelchair full time (C). Survival probabilities significantly different from exercise group 0 are marked with an asterisk (*). For first-time wheelchair use (B), this graph shows the results excluding those patients over 50 years of age at the screening visit as including these patients led to a violation of the proportional hazards assumption.
This study raises implications for patients and families. If intensive exercise causes earlier onset and faster progression, asymptomatic patients should consider limiting their exercise and affected siblings should be identified to allow for early disease-modifying advice. However, as the HRs are small, this needs to be balanced against the loss of other lifestyle benefits of exercise. As we did not look at the effects of exercise once symptoms began, we would not advocate that symptomatic patients stop exercising.

This letter describes an association of intensive exercise during the teenage years with earlier disease onset and faster rate of disease progression in patients with dysferlinopathy.

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**REFERENCES**


