MOTOR FUNCTION PERFORMANCE IN INDIVIDUALS WITH *RYR1*-RELATED MYOPATHIES

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Accepted 16 April 2019

ABSTRACT: *Introduction:* The objective of this study was to obtain a 6-month natural history of motor function performance in individuals with *RYR1*- related myopathy (*RYR1*-RM) by using the Motor Function Measure-32 (MFM-32) and graded functional tests (GFT) while facilitating preparation for interventional trials. *Methods:* In total, 34 participants completed the MFM-32 and GFTs at baseline and 6-month visits. *Results:* Motor deficits according to MFM-32 were primarily observed in the standing and transfers domain (D1; mean 71%). Among the GFTs, participants required the most time to ascend/descend stairs (>7.5 s). Functional movement, determined by GFT grades, was strongly correlated with MFM-32 (D1; $r \geq 0.770$, $P < 0.001$). Motor Function Measure-32 and GFT scores did not reflect any change in performance between baseline and 6-month visits. *Discussion:* The MFM-32 and GFTs detected motor impairment in *RYR1*-RM, which remained stable over 6 months. Thus, these measures may be suitable for assessing change in motor function in response to therapeutic intervention.

Muscle Nerve **60**: 80–87, 2019

RYR1-related myopathy (*RYR1*-RM) comprises a group of neuromuscular diseases (NMD) that result from mutations in the *RYR1* gene, including central core disease (CCD), centronuclear myopathy (CNM), multiminicore disease (MmD), congenital fiber type disproportion, and core rod disease.[1–6] Mutations in *RYR1* also cause an allelic condition, malignant hyperthermia (MH).[2] These diseases exist on a continuum with clinical and pathological overlap.[7] For example, a retrospective review of outpatient records from 44 *RYR1* patients over 28 years supported the variable presentation of individuals with *RYR1*-RM.[8] Colombo and colleagues[8] showed that, although symptoms from autosomal recessive cases were identifiable at birth and had more severe symptoms when compared with autosomal dominant cases, both groups (74.1% of all patients) achieved independent ambulation with the exception of 6 individuals who became wheelchair-dependent. Although neuromuscular clinicians and researchers are aware of various *RYR1*-RM clinical phenotypes and have anecdotally defined *RYR1*-RM as stable or slowly progressive, no natural history studies have yet focused on assessment-based motor function performance in this population. The lack of quantifiable data on motor function and its trajectory over time affect the clinician's ability to counsel individuals across various severity levels and subtypes of *RYR1*-RM and may compromise the quality of clinical trials.

The Motor Function Measure-32 (MFM-32) was developed to evaluate motor function and to detect functional change over time in NMD.[9] Complementary assessments for functional ability such as timed functional tests are also routinely administered.[9] Motor Function Measure-32 is a valid and reliable motor function scale used to assess 3 domains of motor abilities in numerous NMDs.[10] Graded functional tests (GFT), including 10-m run test, floor to stand, and the 4-stair ascent/descent, capture changes in strength and function based on both timed and qualitative scores. These timed tests are also useful measures for assessing disease progression.[11]

The objective of this study was to describe motor performance in ambulatory individuals with *RYR1*-RM by using the MFM-32 and GFTs during a 6-month time frame. This natural history study was phase 1 of the first randomized, double-blind, placebo-controlled drug trial in *RYR1*-RM.

MATERIALS AND METHODS

Participants. In total, 47 participants (20 males), were enrolled in an *RYR1* double-blind, placebo-controlled N-acetylcysteine (NAC) trial (NCT02362425) at the National Institutes of Health

Additional supporting information may be found in the online version of this article.

Abbreviations: CCD, central core disease; CFTD, congenital fiber type disproportion; CNM, centronuclear myopathy; D1, Domain 1 (standing and transfers); D2, Domain 2 (axial and proximal function); D3, Domain 3 (distal motor function); GFT, graded functional test; MFM-32, motor function measure-32; MH, malignant hyperthermia; MmD, multiminicore disease; NAC, N-acetylcysteine; NIH, National Institutes of Health; NMD, neuromuscular disease; *RYR1*-RM, *RYR1*-related myopathy

Key words: disease progression; GFT; MFM; motor function; *RYR1*
Funding: This work was supported by the National Institutes of Health (Bench-to-Bedside Award, 10-2013); National Institute of Nursing Research; Division of Intramural Research; Office of Rare Disease; National Institutes of Health Clinical Center Rehabilitation Medicine Department.
Conflicts of Interest: None of the authors have any conflicts of interest to disclose.

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Published online 20 April 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.26491

(NIH). This clinical trial, consisting of a natural history and treatment phase, was approved by the NIH Combined Neurosciences Institutional Review Board, and consent and assent forms were collected from all participants. In total, 34 participants completed the natural history phase (0–6 months) of the trial between March 2015 and December 2017. Outcome measures were administered in an identical order and time of day at baseline and 6-month time points. Among the 47 participants, 13 were lost to follow-up. Supporting Information Figure 1 shows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) flow diagram for participants included in this 6-month prospective cohort study. Inclusion criteria required participants to be 7 years of age or older, be ambulatory (able to walk 10 m without assistive devices), and have a confirmed genetic diagnosis of *RYR1*-RM. Participant diagnoses included CCD, MmD, and congenital myopathy (not specified) with rhabdomyolysis or malignant hyperthermia susceptibility. Among these participants, 16 (34%) were children (<18 years). Demographics are presented in Table 1. Participants were excluded if they had a history of liver or lung disease, ulcers, or dysphagia; were pregnant or planned to become pregnant; were breastfeeding; or were consuming medicines that interact with NAC. To document changes and ensure that participants still met eligibility criteria prior to completing the MFM-32 and GFTs at their follow-up visit (6-month), participants underwent another physical examination. The MFM-32 and GFTs were completed in the NIH Clinical Center Rehabilitation Medicine department by the same trained physical therapist (or, when unavailable, the same substitute therapist) at baseline and 6-month follow-up. Test times remained the same for baseline and 6-month visit to exclude bias for time of day.

Motor Function Measure-32. The MFM-32 is a 32-item scale that quantitates functional capabilities in individuals with neuromuscular disorders.[12] The MFM-32 has been validated in the congenital muscular dystrophy, congenital myopathy, spinal muscular atrophy, and limb girdle muscular dystrophy populations.[10] The assessment is divided into 3 domains, with each of the 32 items graded on a 4-point Likert scale. The D1 domain (13 items) examines standing and transfers, including the ability to get into sitting and standing positions and to walk. The D2 domain (12 items) examines axial and proximal motor function, including the ability to roll into prone, bring knee to chest in supine, and to maintain trunk control in sitting. The D3 domain (7 items) examines distal motor function, including the ability to pick up coins, tear paper, and write with a pencil.

Graded Functional Tests. Functional tests were both timed and graded. Items were graded on a 6-point Likert scale based on participants' abilities, as described in detail in McDonald *et al.*[13] A higher score indicates better performance. Two trials were allowed for each item with the best time and grade recorded.

10-Meter Run. Participants were instructed to run as quickly and safely as possible. Start and end points were clearly marked with tape. The timer was started as soon as the lead foot crossed the "start" mark and stopped when the trailing foot crossed the "end" mark.

Supine to Stand. Participants were asked to lie supine on a mat on the floor and then stand up from the floor as fast as they could. The timer was started as soon as the test administrator said "go" and stopped once the participant was in a standing position.

Ascend/Descend 4 Stairs. Participants were asked to climb up and down 4 steps with 2 handrails as quickly and safely as they could, using 2 hand railings if required. Ascending stairs was timed and graded separately from descending stairs.

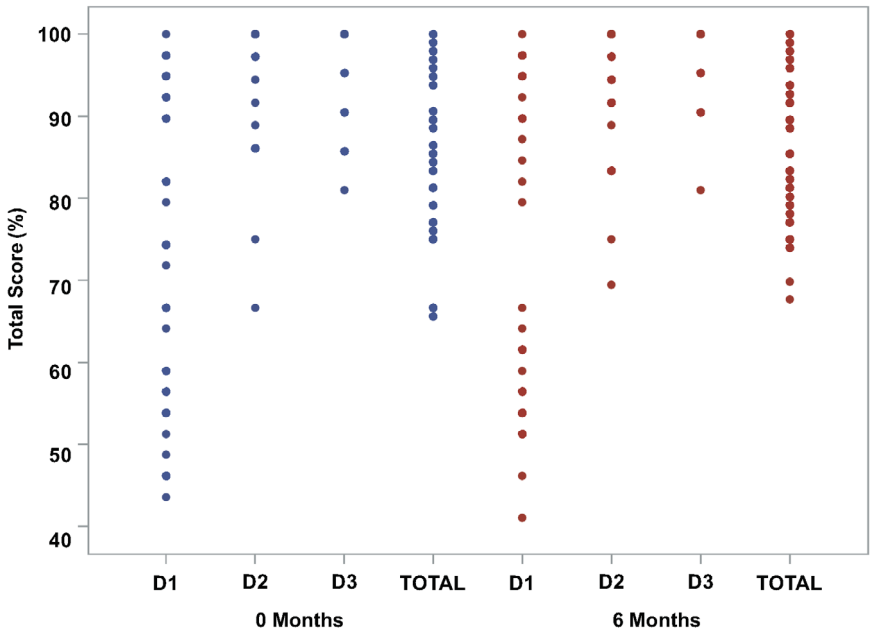

FIGURE 1. Observed comparison of motor function performance for each dimension, based on percentage of achieved of the total (maximum) score, of the Motor Function Measure-32 (MFM-32) between baseline and 6 months. D1, D2, and D3 are the 3 domains of motor function for the MFM-32; D1 represents standing and transfers, D2 is proximal motor function, and D3 is distal motor function. There were no significant changes over this time course in any domain or the total score (D1, $P = 0.941$; D2, $P = 0.280$; D3, $P = 0.205$; Total $P = 0.951$). [Color figure can be viewed at wileyonlinelibrary.com]

Table 1. Demographics of study participants.

Participants	*n*	Age ($\bar{x} \pm$ SD)	Disease type*				
			CCD	MmD	CCD/MmD	CFTD	Other†
Total	47	28.9 ± 17.2	15	1	19	5	7
Adults	31	38.8 ± 12.3	13	1	13	0	4
Children	16	9.69 ± 2.82	2	0	6	5	3
Men	20	25.9 ± 16.4	4	1	10	2	3
Women	27	31.2 ± 17.8	11	0	9	3	4

CCD, central core disease; CFTD, congenital fiber type disproportion; MmD, multiminicore disease.

**In most cases, all phenotypes, primarily CCD, have MHS.*

†*Includes RYR1-*RM *congenital myopathy (indeterminate disease type) with malignant hyperthermia susceptibility (MHS) or rhabdomyolysis.*

Statistical Analysis. Statistical analysis was performed in SPSS v23 (IBM, Armonk, New York). Descriptive statistics were obtained for MFM and GFT, including mean values. For GFT graded categories, the median was obtained. Because both timed and qualitative scores are obtained during the GFTs, scatterplots were used to observe the relationship between these 2 variables.

Changes between baseline and 6 months in MFM percentage, MFM score, and GFT time were assessed with paired *t* tests for the 34 participants who completed both baseline and 6-month visits. The Wilcoxon signed-rank test was used to determine whether GFT grades (1–6) changed within 6 months. Regression analyses were used to determine whether there was an age effect on motor performance over time. Correlative analyses were used to determine the relationship between MFM percentage and GFT time (Pearson) and grade (Spearman's ρ).

RESULTS

Motor Function Measure-32. Although on average participants performed >90% for D2 and D3, motor function deficits were observed in D1. Participants performed at a mean of 71% (±20.2) on D1 (range, 30.8%–100%) at the baseline visit. There was no significant difference between baseline and 6-month performance (Figure 1).

Graded Functional Tests. Most participants were able to complete GFTs with little difficulty. The most frequently observed qualitative ratings of movement for the 10-m run were 4 ($n = 22$) and 6 ($n = 19$), with 6 being the highest level of function. Most participants completed the supine to stand test at a grade of 5 ($n = 15$) or 6 ($n = 10$). For both stair ascent and descent, most participants performed these tasks at a grade of 6 ($n = 28$ and $n = 27$, respectively), whereas the remaining participants ($n = 10$) performed this task at a grade of 5 for stair descent. Figure 2 illustrates longer times required to complete the tasks when qualitative scores are lower, which is most apparent during stair ascent (Fig. 2C).

Motor Function Measure-32 and Graded Functional Tests. Strong positive relationships (as indicated by a value of $0.7 < r < 1$) were observed between D1 (%) and functional grade for 10-m run, supine to stand, stair ascent, and stair descent (Fig. 3A–D) such that the higher the motor function on D1 the better the qualitative grade on GFT. Similar results were observed between D1 (%) and time to complete 10-m run ($r = -0.673$), supine to stand ($r = -0.756$), stair ascent ($r = -0.830$), and stair descent (−0.708); lower D1 (%) was associated with longer times to complete GFTs. D2 (%) demonstrated moderate relationships with GFT qualitative grades but not with time except when performing supine-to-stand transfers. Because D3 is related to distal function, which is often not affected in individuals with *RYR1*-RM, we did not assess the relationship between D3 and GFTs.

Disease Progression. *Motor Function Measure-32.* The MFM total score remained consistent between baseline and 6-month visits, $P = 0.951$. Because the total score can be affected by the individual domains, we also assessed the stability of motor function within domains. However, as with the total score, D1, D2, and D3 scores did not change significantly between baseline and 6 months. Figure 1 depicts stability in MFM-32 performance between baseline and 6-month visits.

Graded Functional Tests. On average, participants completed the 10-m run test in 5.58 s (±0.408) at baseline and 5.66 s (±0.464) at the 6-month visit. The mean time to stand from supine position was 8.14 s (±1.28) at baseline and 7.58 s (±1.08) at 6 months. Participants took a longer time to ascend (3.06 ± 0.279 s) than to descend (2.40 ± 0.179 s) 4 stairs at baseline, and similar mean times were observed at 6 months.

The time for *RYR1*-RM-affected individuals to complete all GFT's remained stable from baseline to 6 months (Fig. 4). Participants with *RYR1-RM* also exhibited little to no change in qualitative score (Fig. 5); the observed difference in grade between 0 and 6 months was not significant for any of the GFTs.

There was no age-effect on motor performance for all assessments over the 6 months.

DISCUSSION

Motor Function in *RYR1*-RM. *Motor Function Measure-32.* Motor Function Measure-32 has been used in several NMD studies, specifically to assess motor function and disease severity and progression.[9,10,12] Participants in this study exhibited the greatest

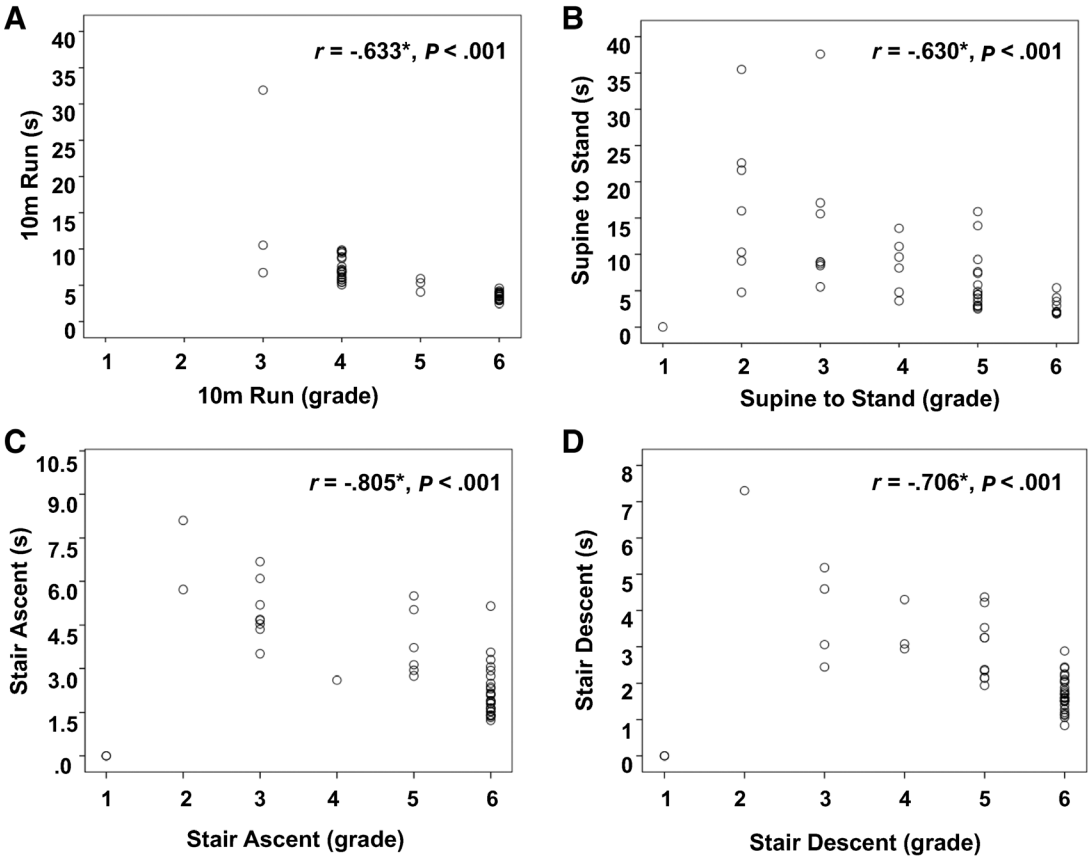

FIGURE 2. Observed relationships between movement pattern (grade) and time to complete 10-m walk/run **(A)**, supine to stand **(B)**, stair ascent **(C)**, and stair descent **(D)**. Each graph illustrates a negative correlation with stair ascent and descent exhibiting the strongest relationships with grade. *.

difficulty performing activities in the standing and transfers domain (D1), whereas axial (D2) and distal (D3) motor functions were mostly preserved. These results are consistent with findings described in a report of a larger study that included individuals with congenital myopathies and congenital muscular dystrophies, in which D1 was also the most affected in congenital myopathies in general.[10,14] This finding contrasted with those of individuals with muscular dystrophy, who presented with a greater mobility limitation, namely 40% of the possible D1 score, and who declined in D1 score over 3 months.[15] In our study, Participants with *RYR1-RM* achieved an average of 71% of the possible D1 score and remained stable over 6 months. An extended longitudinal study including nonambulatory individuals would be informative to determine the rate of decline in motor function in persons with *RYR1*-RM. On the other hand, the current study provides value by showing stability over 6 months; it is not feasible for most intervention trials to be conducted over longer time periods because of burden to participants and the cost of trials.

Graded Functional Tests. Graded functional tests, including time to run 10-m, time to stand from supine, and the time to ascend/descend stairs, allow for both quantitative (time) and qualitative (grade) assessment of functional ability.[16] In this regard, they complement the MFM-32, especially by adding the dimension of time.[10]

In the current study, the 10-m run test revealed mild to moderate functional motor impairments as determined by recorded grades that ranged from 3 (highly adapted, wide-based lordotic gait, cannot increase walking speed) to 6 (runs with no double leg stance). The observed relationship between 10-m run time and grade suggests that gait abnormality influences walking speed, as expected. In addition, the graded 10-m run test has been validated as a predictor of community ambulation in healthy individuals.[17] A similar study assessing community ambulation based on the 10-m run would be helpful in a larger longitudinal study or individuals with *RYR1*-RM, especially because these individuals often report muscle weakness and fatigue. Muscle weakness and fatigue are common impairments in congenital myopathies that influence quality of life, although research on quality of life in this population is extremely limited.[18,19]

Results of the supine-to-stand GFT ranged in grade from 1 (unable to complete, even with use of a chair) to 6 (stands up without rolling over or using hands on legs). In our study, participants who required assistance

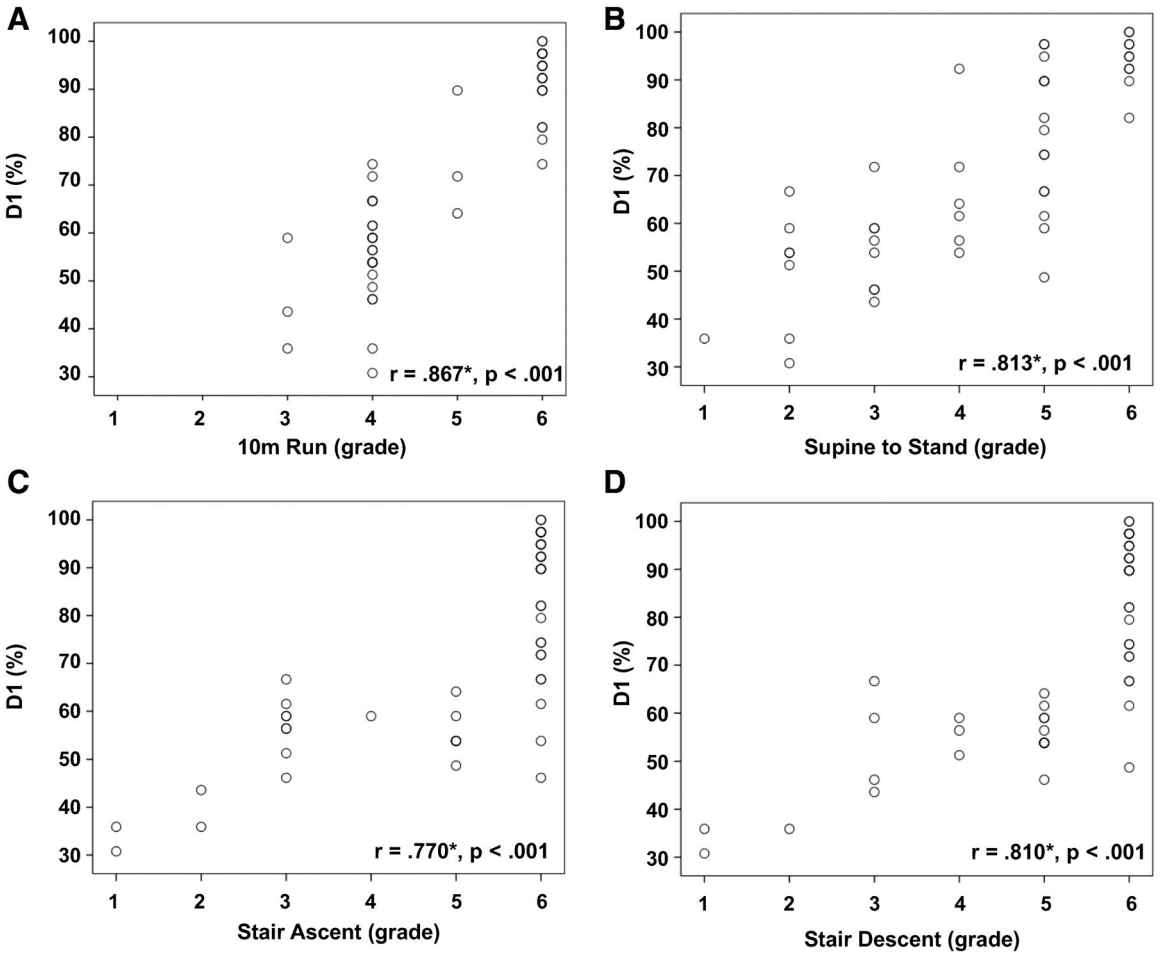

FIGURE 3. Observed relationships between Motor Function Measurement-32 (MFM-32) D1% and the quality of movement (movement pattern) during graded functional tests (grade) including 10-m run **(A)**, supine to stand **(B)**, stair ascent **(C)**, and stair descent **(D)**. Each graph illustrates a strong positive relationship. *<zaq;8>. D1%, motor function performance score for standing and transfers (domain 1) based on the total (maximum) score achieved in the MFM-32.

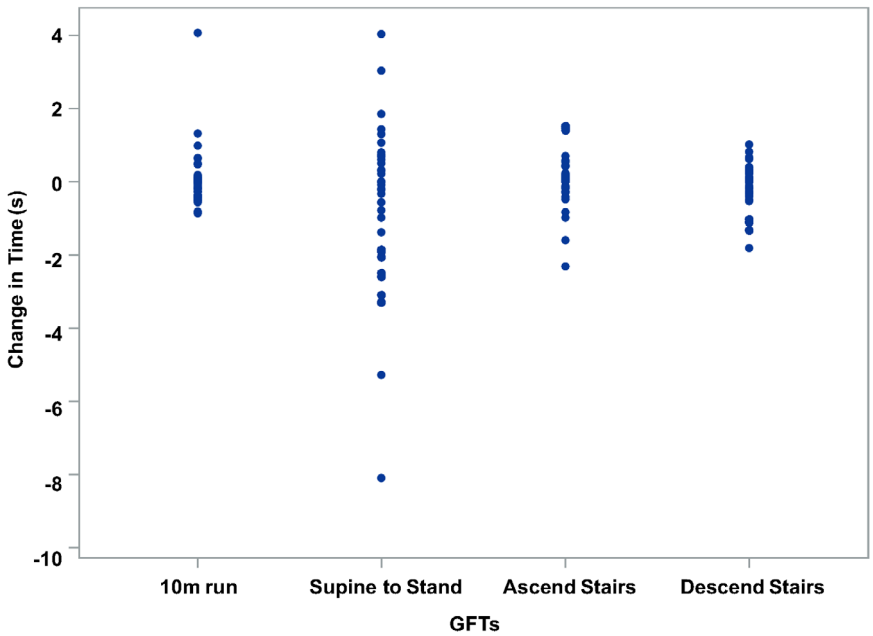

FIGURE 4. Change in time to perform GFTs from baseline to 6 months. There were no significant changes in this time course for any of the following times: 10-m run, $P = 0.585$; supine to stand, $P = 0.159$; ascend stairs, $P = 0.707$; descend stairs, $P = 0.412$. GFT, graded functional test. [Color figure can be viewed at wileyonlinelibrary.com]

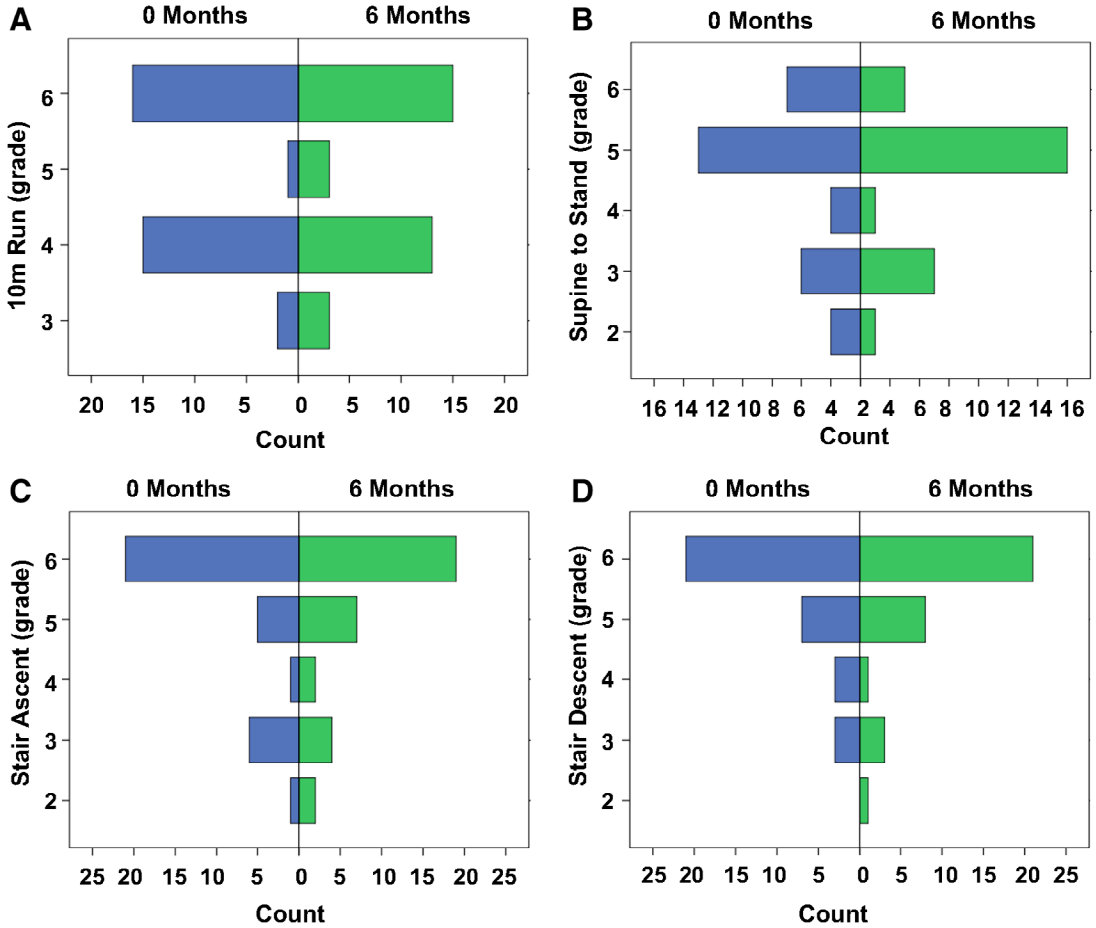

FIGURE 5. Observation of graded functional test performance movement pattern (grades) between baseline (blue) and 6-month (green) visits. There were no significant changes in this time course for any of the following grades: **(A)** 10-m run, $P = 0.705$. **(B)** Supine to stand, $P = 0.963$. **(C)** Ascend stairs, $P = 0.720$. **(D)** Descend stairs, $P = 0.763$. [Color figure can be viewed at wileyonlinelibrary.com]

from an external support (chair/railing; 12.9 s) or used the Gowers' maneuver (14.3 s) required the greatest amount of time to transfer from supine to stand. Transitioning from supine to stand is a functional activity important for physical independence[20] and maintaining mobility through adulthood.[21] The observed range of grades for this test reflects that independence and mobility characteristically become important concerns to this population.

Stair ascent and descent are commonly performed daily activities that require greater lower extremity range of motion and muscle strength compared with level walking. Similarly to the other graded functional tests, the more assistance required to ascend or descend stairs (based on GFT grade) the longer it took to complete the tests. On the basis of the average time to complete stairs, individuals with *RYR1*-RM have more difficulty ascending stairs compared with descending. Stair climbing requires greater strength in the hip, knee, and ankle musculature.[22] Some of the most commonly reported affected muscles in patients with *RYR1*-RM include musculature activated during stair ascent–hip flexion (sometimes rectus femoris, vastus intermedius, vastus lateralis, adductor magnus), knee flexion (semimembranosus), and ankle dorsiflexion (soleus, lateral gastrocnemius).[23–25] Overall, ability to ascend and descend stairs is considered an important functional measure because of its relevance to activities of daily living, independence, and community involvement.[26] Therefore, graded timed stair tests can serve as a clinical yet functional test for assessment of motor impairment in people with *RYR1*-RM and may demonstrate improvement after therapeutic intervention, as seen in other NMD trials.[13,27]

Motor Function Measure-32 and Graded Functional Tests. The ability of our *RYR1*-RM cohort to complete the motor tasks on the MFM-32 assessment translated to how these individuals performed the timed functional tests. The more assistance (1 vs. 2 handrails) required and/or compensatory movements (lower grades) used to transition from supine to stand or complete the 10-m run the lower the achieved percentage of the maximum score in D1 (Fig. 3) and D2. When ascending and descending stairs, individuals who did not use a reciprocal gait (grades 2–4) or require the use of railings (grades

2, 3, 5) also demonstrated a lower D1 (Fig. 3) and D2 percentage. Therefore, D1 of the MFM and graded functional tests are collectively informative of functional ability in people with *RYR1*-RM. We would expect therapeutic intervention, if successful, to demonstrate parallel improvements in these measures (D1 of MFM and GFTs).

Disease Progression. In support of previous anecdotal reports of clinically observed stable disease presentation in *RYR1*-RM-affected individuals, we found no significant changes in 6-month motor function-related abilities in an ambulatory subset of this population. Furthermore, these findings were not affected by age. In addition, we learned that the MFM-32 D1 and GFTs were able to detect motor function deficits in this *RYR1*-RM subset and, thus, may serve as assessments of interventions in future studies. It is important to note that, although GFTs are not attainable in nonambulatory individuals, the MFM-32 assesses motor function in nonambulatory as well as ambulatory individuals and may be an optimal assessment for motor performance in nonambulatory *RYR1*-RM individuals; however, additional studies are required.[10]

RYR1-RM comprises a group of NMDs that have been suggested to be nonprogressive (stable)[4,28] or slowly progressive.[4] We also found that there was no change in mean score or time for MFM and GFTs, respectively, over a 6-month period. No change was observed in the GFT grade for 10-m run, supine to stand, and stair ascent/descent. Taken together, comparative results from these assessments support clinical reports of *RYR1*-RM as a stable or slowly progressive disease. For future studies, the demonstration of 6-month stability in motor function in ambulatory individuals with *RYR1*-RM suggests that therapeutic intervention-based studies could use D1 of the MFM as well as GFTs to assess improvement in motor function. However, a longer study would be beneficial to determine when changes occur in patients with *RYR1*-RM.

Limitations. The inclusion criterion requiring individuals to be ambulatory for the latter clinical trial portion of this study limited these natural history results to individuals with *RYR1*-RM who are mildly to moderately affected. The small sample, number of individuals lost to follow-up, wide age range of participants, and the 6-month time frame for assessing functional abilities and performance were additional limitations. Because *RYR1*-RM-affected individuals remained stable for the 6 months of this study, the time point at which the disease would show decline remains unclear. A longer, prospective, longitudinal study including ambulatory and nonambulatory individuals could allow determination of the rate of functional motor decline. It would also enable categorization of motor function and decline by levels of disease severity. For example, nonambulatory participants may score lower on MFM D1 and D2 than the average score of >90% observed for these 2 domains in this study. The use of quality of life assessments in such a study could further inform the effect of the disease on quality of life over time.

In conclusion, our results provide evidence that the natural history of ambulatory individuals affected with *RYR1*-RM is that of a stable disease over 6 months, based on motor function measures. Motor Function Measure-32 and GFTs are useful measures for detecting motor impairment in this population. The use of assistance (railings/furniture) or compensatory movements (i.e., Gowers' maneuver) was associated with slower times to complete tasks, showing greater impairment. Domain 1 score from the MFM-32 was related to level of functional performance and length of time during graded functional tests. Domain 2 was moderately correlated with quality of movement (grade on GFT), suggesting that motor impairments in this domain may be more apparent in more severe cases. Because the MFM-32 D1 and GFTs identified functional deficits in *RYR1*-RM and were stable over a 6-month time frame, they may serve as acceptable functional outcome measures to assess changes in motor function in response to a therapeutic intervention.

Presented at the World Muscle Society Conference, October 2017, St Malo, France.

The authors thank Carmel Nichols, BS and Janvi Raichura for assistance with data collection and storage; Fatou Tounkara, BS for assisting with participant enrollment; and the patients and families for their involvement in this study.

Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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