HHS Public Access

Author manuscript

Disabil Rehabil. Author manuscript; available in PMC 2019 May 01.

Published in final edited form as:

Disabil Rehabil. 2018 May ; 40(10): 1206–1213. doi:10.1080/09638288.2017.1283712.

Patient reported outcomes in GNE myopathy: Incorporating a valid assessment of physical function in a rare disease

Christina Slota[1,2], **Margaret Bevans**[3], **Li Yang**[3], **Joseph Shrader**[4], **Galen Joe**[4], and **Nuria Carrillo**[1,5]

[1]Therapeutics for Rare and Neglected Diseases, National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD, USA

[2]RTI Health Solutions, Research Triangle Park, NC, USA

[3]National Institutes of Health Clinical Center, Bethesda, MD, USA

[4]Rehabilitation Medicine Department, National Institutes of Health, Bethesda, MD, USA

[5]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

Abstract

BACKGROUND: The aim of this analysis was to evaluate the psychometric properties of three patient reported outcome (PRO) measures characterizing physical function in GNE myopathy: the Human Activity Profile, the Inclusion Body Myositis Functional Rating Scale, and the Activities-specific Balance Confidence scale.

METHODS: This analysis used data from 35 GNE myopathy subjects participating in a natural history study. For construct validity, correlational and known-group analyses were between the PROs and physical assessments. Reliability of the PROs between baseline and 6 months was evaluated using the intra-class correlation coefficient model; internal consistency was tested with Cronbach's alpha.

RESULTS: The hypothesized moderate positive correlations for construct validity were supported; the strongest correlation was between the human activity profile adjusted activity score and the adult myopathy assessment endurance subscale score ($r=0.81$; $p<0.0001$). The PROs were able to discriminate between known high and low functioning groups for the adult myopathy assessment tool. Internal consistency of the PROs was high ($\alpha>0.8$) and there was strong reliability (ICC>0.62).

CONCLUSION: The PROs are valid and reliable measures of physical function in GNE myopathy and should be incorporated in investigations to better understand the impact of progressive muscle weakness on physical function in this rare disease population.

corresponding author Nuria Carrillo, National Institutes of Health, 10 Center Drive, Building 10, Room 10C103, Bethesda, MD 20814, USA, Telephone: +1 (301) 402-2324, Fax: +1 (301) 402-0006, carrilln@mail.nih.gov.

Declaration of Interest Statement: The authors report no declarations of interest

Keywords

psychometrics; quality of life; hereditary inclusion body myopathy; reliability; construct validity; activities of daily living

Introduction

GNE myopathy is a rare genetic muscle disease characterized by slowly progressive muscle atrophy and weakness, ultimately resulting in immobility and dependence on a caregiver. The impact of declining muscle strength on health-related quality of life, specifically physical function, is not well understood in this population. GNE myopathy is caused by mutations in the *GNE* gene, which encodes for a key enzyme in the biosynthesis of sialic acid, resulting in skeletal muscle atrophy [1, 2, 3, 4]. GNE myopathy has an estimated prevalence of ~6 per 1,000,000, with a higher prevalence in the Middle-Eastern Jewish population [5]. The typical clinical presentation begins with foot drop due to distal leg muscle weakness, followed by slowly progressing muscle weakness and atrophy of lower and upper extremities muscles, with relative sparing of the quadriceps [6]. This relentlessly progressive disease ultimately results in wheelchair dependence and requires caregiver support for activities of daily living. There is no approved therapy for GNE myopathy, but clinical trials of candidate pharmacologic therapies are underway (ClinicalTrials.gov Identifiers: NCT02731690, NCT02346461, NCT02736188, NCT0237792, NCT01830972).

Due to the rarity of the disease and its slow progression, it is challenging to evaluate the clinical severity of muscle weakness in GNE myopathy subjects [7]. Established methods, such as Quantitative Muscle Strength Assessment and the six-minute walk test, are used to objectively document changes in peak muscle strength or distance walked, but the relevance of these findings to everyday activity and function remains unknown [8, 9, 10]. The patient's perspective should be taken into consideration for a comprehensive understanding of the disease's impact and for determining the effectiveness of potential therapies [11].

The impact of disease progression on physical functioning and ability to perform activities of daily living have been recommended to be evaluated using patient reported outcome (PRO) measures and other clinical outcome assessments as endpoints in studies of Duchenne muscular dystrophy and rare diseases [12, 13, 14, 15]. The aim of this analysis was to evaluate the psychometric properties of three PROs that have been measured in an ongoing natural history study of GNE myopathy patients, including the human activities profile (HAP), inclusion body myositis function rating scale (IBMFRS), and the Activities-specific Balance Confidence (ABC) scale, in order to better characterize physical function in this rare muscle disease.

Methods

Design

This analysis used baseline and 6 month data from patients that participated on a prospective natural history study of GNE myopathy subjects titled, "A Natural History Study of Patients with GNE Myopathy," (ClinicalTrials.gov; Identifier: NCT01417533) at the National

Institutes of Health (NIH) Clinical Center. The clinical protocol has been approved by the National Human Genome Research Institute Institutional Review Board. Informed consent was obtained from all participants. All participants had a confirmed diagnosis of GNE myopathy by genetic testing. Among other objectives, this natural history study seeks to understand the experience of living with GNE myopathy. Subjects are evaluated at baseline and every 12 months; some subjects were asked to follow-up at 6 months. Subjects completed physical assessments and PRO questionnaires during their visits. Subjects requiring a wheelchair and those with advanced disease are only asked to complete the physical assessments they can comfortably and safely attempt. The use of assistive devices was documented, including braces (ankle-foot orthotics), canes, walkers, and wheelchair.

Patient Reported Outcome Measures

All PRO questionnaires were administered to subjects electronically through a secure web-based application hosted at the NIH after the subjects were given auto-generated usernames and passwords, and were directly entered into the database.

Human Activity Profile—The Human Activity Profile (HAP) is a 94-item self-report assessment of physical activities that require different degrees of physical fitness [16, 17]. Respondents state for each item whether they are ‘still doing,’ ‘have stopped’ or ‘never did’ this activity. Two scores are calculated: the maximum activity score, which is the number of the highest activity a respondent is “still doing,” and the adjusted activity score, which is calculated by subtracting the number of activities the respondent “stopped doing” that are lower than the maximum activity score. Higher scores indicate greater physical activity. The adjusted activity score is considered a more valid measure of daily activities compared to the maximum activity score, which focuses on maximal energy expenditure [16]. The HAP has been administered in several physically impaired populations as well as in normal healthy adults, and has been found to be a reliable and valid measure of physical activity [16, 18, 19, 20]. Impaired classifications were developed based on an adjusted activity score <53 in healthy respondents, leading to three physical activity levels: impaired (<53), moderately active (53–74) and active (>74) [21].

Inclusion Body Myositis Functional Rating Scale—The Inclusion Body Myositis Functional Rating Scale (IBMFRS) is a 10-item functional rating scale that assesses activities of daily living [22, 23]. Respondents rate their functional ability in 10 areas: swallowing, handwriting, cutting food and handling utensils, fine motor tasks, dressing, hygiene, turning in bed and adjusting covers, sit to stand, walking and climbing stairs. For each area, respondents choose a score between 0 to 4, ranging from ‘unable to perform’ to ‘normal.’ The IBMFRS has been shown to be a reliable and valid measure of disease severity in inclusion body myositis, is sensitive to changes over time, and correlates well with manual muscle testing and strength tests [22, 23, 24].

Activities-specific Balance Confidence Scale—The Activities-specific Balance Confidence (ABC) scale is a 16-item rating scale that assesses an individual’s level of confidence in performing an activity without losing balance. Subjects choose a percentage in intervals of 10 to rate their confidence from 0% (not confident) to 100% (very confident).

The ABC scale has been validated in other physically impaired populations including Huntington's disease, multiple sclerosis, and Parkinson's disease [19, 25, 26, 27]. Discriminative properties of the ABC scale have been reported in older adults, including high, moderate, and low levels of functioning as >80%, 50–80% and <50%, respectively [28]. In addition, fall risk in older adults was reported at a cut-off score of <67% [26].

Clinician Assessed Physical Function

Adult Myopathy Assessment Tool—The Adult Myopathy Assessment Tool (AMAT) assesses functional task performance and sustained or repeated muscle contractions with a composite functional subscale score, endurance subscale score and total score [29, 30]. The AMAT includes 13 tasks: head elevation endurance, supine to prone, modified push-up, repeated modified push-up, sit-up, supine to sit, arm raise, upper extremity endurance, sit to stand, hip flexion endurance, knee extension endurance, repeated heel rise, and step-up. The AMAT has been shown to have good validity and reliability, has been used in clinical trials for similar slowly progressive muscle diseases, and has reported total cut-scores to differentiate between low (0–24), moderate (25–34) and high (35–45) levels of functioning [30, 31].

Quantitative Muscle Strength Assessment—The Quantitative Muscle Strength Assessment (QMA, Aeverl Medical, Gainesville, GA) was previously registered with the FDA as a class II device (Registration number: 3004889973). The Quantitative Muscle Strength Assessment measures the maximal voluntary isometric muscle contraction of different muscles, and has been utilized in several neuromuscular diseases with good to excellent validity and reliability [32, 33, 34]. Ten muscle groups in the upper and lower extremities were tested twice and averaged for a final measured strength (kg) for each muscle. A corresponding percent of predicted strength was calculated based on subjects' age, gender, height and weight utilizing data from the National Isometric Muscle Strength Database Consortium and published literature [35, 36]. The composite upper, lower and total quantitative muscle strength scores are reported.

Functional reach test—The functional reach test is a valid, reliable and age-sensitive measure of postural control [37, 38, 39, 40, 41, 42, 43]. For this test, the subject stands next to a wall and positions the arm closest to the wall at 90 degrees shoulder flexion, then leans forward as far as possible without taking a step. The assessor records the location of the distal tips of the finger at the start position and end position, and the score is the difference between the two is the reach distance measured in inches. Three trials are done and the average of the last two is calculated for the right and left side.

Six-minute walk test—The six-minute walk test is a valid and reliable measure of functional status that has been used in a wide variety of settings and populations [8, 44, 45, 46]. A subject walks for six minutes and tries to cover as much distance as possible, which is measured in meters. The six minute walk test has also been used as a primary or secondary outcome measure in clinical trials for neuromuscular diseases, including Duchenne muscular dystrophy and GNE myopathy [9, 10, 47].

Statistical analysis

Descriptive analysis of the population's disease-related characteristics and outcome measures were performed using baseline data. Data distribution and normality were checked using the Shapiro-Wilk tests and normal QQ plots for all continuous variables. Parametric and non-parametric tests were applied as appropriate.

We followed standards for evaluating the psychometric properties of PRO measures, including construct validity, and reliability: internal consistency and test-retest [48, 49]. For the assessment of construct validity we took two approaches: first, we examined the expected correlation between the PRO measures and clinician assessments of physical function; second, we examined the differences in scores between known-groups. For our sample size of 35 with a power of 0.9, we expected to detect a correlation coefficient of 0.47 or above. We hypothesized a moderate positive correlation between PRO measures, and the six minute walk test, quantitative muscle strength assessment, AMAT and functional reach scores. Pearson or Spearman correlations were performed to check the relationship between the PRO measures and clinician assessments, as well as between the PRO measures themselves using baseline data. One-way analysis of variance (ANOVA) or Kruskal-Wallis tests were performed to compare the PRO scores among the groups previously identified for the AMAT.

Internal consistency was tested using Cronbach's α for the IBMFRS and ABC scale at baseline and 6 months. Since GNE myopathy is a slowly progressive disease, changes were not expected within the 6 month timeframe. For reproducibility, we examined the test re-test reliability of the three PRO scores for patients at baseline and the patients that returned at 6 months using the intra-class correlation coefficient model (ICC 3,1). All statistical tests used a significance level of $p<0.05$. Data were analysed with the Statistical Package for Social Sciences 23.0 (SPSS, Inc., Chicago, IL) and G*Power [50].

Results

Descriptive statistics

Characteristics of GNE myopathy subjects—A total of 35 GNE myopathy subjects completed PRO measures of physical function at baseline and 16 subjects completed the questionnaires at 6 months. Descriptive statistics of the subjects are shown in table 1. The majority of subjects at baseline (91.4%) had a history of falls and used an assistive device (74.3%). Approximately 9% of the subjects at baseline were wheelchair dependent and 20% used a wheelchair only for long distances.

Outcomes summary statistics—A summary of the baseline HAP maximum and adjusted activity scores, IBMFRS and ABC scale scores are shown in table 2. The HAP subscale raw scores of 'self-care' had the highest score (91.8 ± 21.6) while 'independent exercise' (43.1 ± 28) had the lowest score in GNE myopathy subjects (table 2). We compared the limitations of this population to those of more common conditions. The reported HAP scores from GNE myopathy subjects had a significantly higher maximum activity score (69.3 ± 20) than other impaired (61.8 ± 14.8), COPD (58.8 ± 13.2), and

dialysis (55.2 ± 14.9) subjects, and a significantly lower maximum activity score than the healthy (85.3 ± 7) and older adults (75.7 ± 6.2) [20, 21, 51, 52, 53] (table 3). GNE myopathy subjects had a significantly lower adjusted activity score (51.4 ± 22.7) than older adults (71.6 ± 7.1) and arthritic subjects (67.5 ± 12.3); there was no significant difference in adjusted activity scores compared to the other impaired populations [21, 52].

Construct validity

Table 4 shows the correlation coefficients of the PRO measures of physical function and the clinician assessments at baseline. As hypothesized, construct validity of the HAP adjusted activity score was supported with a moderate to large positive correlation with the six-minute walk test and AMAT total score and subscale scores ($p<0.0001$). The HAP adjusted activity score had stronger correlations with physical assessments than the HAP maximum activity score. The strongest relationship was with the HAP adjusted activity score and the AMAT endurance subscale score ($r=0.81$; $p<0.0001$) followed by the HAP adjusted activity score and the AMAT total score ($r=0.78$; $p<0.0001$). Table 5, presents the correlations of the HAP subscale scores with the physical assessments, as well as with the IBMFRS and ABC scores. The personal/household work and hand use were the two HAP subscales that had the strongest correlations with the physical assessments and other PRO measures ($p<0.001$).

As hypothesized, construct validity of the IBMFRS was supported by moderate to large positive correlations ($p<0.0001$) with all the physical assessments except the functional reach test (right and left) (table 4). The IBMFRS had the strongest correlation with the AMAT functional ($r=0.75$; $p<0.0001$) and total score ($r=0.70$; $p<0.0001$). The ABC scale was also significantly correlated to the AMAT, six-minute walk, lower extremity quantitative muscle strength and the left functional reach test. However, the significantly correlated relationships were small in effect ($r=0.44–0.69$) compared to the two HAP scores and IBMFRS score. The highest correlation for the ABC scale score with a physical assessment was with the AMAT endurance subscale score ($r=0.69$; $p=0.0002$). Together, the PROs correlated strongly between one another ($r=0.64–0.84$; $p<0.0001$); the HAP adjusted activity score and IBMFRS had the strongest correlation ($r=0.84$; $p<0.0001$).

A one-way ANOVA was conducted to examine the ability of the PROs to discriminate between subjects with high, moderate and low functional abilities, as previously defined with cut-scores from the AMAT (table 6). Subjects in the AMAT ‘high functioning’ group had significantly higher ABC [$F(2, 29) = 11.7$, $p<0.0001$] and HAP adjusted activity [$F(2, 32) = 15.8$, $p<0.0001$] scores than individuals in the low and moderate functioning groups. There was no significant difference detected between the low and moderate AMAT groups for the IBMFRS [$F(2, 32) = 7.3$, $p=0.002$]. There was also no significant difference in the low and moderate functioning groups for the HAP maximum activity score (Chi-square: 13.11; $p<0.001$).

Reliability

Internal Consistency—We examined the internal consistency of the PRO measures at baseline and 6 months. The Cronbach’s alpha value was consistency strong for the ABC scale (baseline $\alpha=0.94$; 6 months $\alpha=0.9$) and IBMFRS total score (baseline $\alpha=0.87$; 6

months α=0.8). Internal consistency reliability is not appropriate for the HAP measure due to categorical scoring.

Reproducibility—Forty-six percent (16/35) of the patients at baseline completed the PROs at the 6 month visit. We examined test-retest reliability and found there was substantial agreement, as demonstrated by the ICCs (3,1) among the ABC scale (ICC=0.89), IBMFRS (ICC=0.87), and HAP maximum activity (ICC=0.75) and adjusted activity scores (ICC=0.62) between baseline and 6 months.

Discussion

In this analysis, we aimed to evaluate the psychometric properties, including construct validity, internal consistency and test-retest reliability of three PRO measures assessing physical function in an ongoing natural history study of GNE myopathy in order to better characterize physical function in GNE myopathy patients.

These findings demonstrate good construct validity, internal consistency and reproducibility of the HAP, IBMFRS, and ABC scale in a diverse cohort of GNE myopathy subjects. In terms of construct validity, the PROs had moderate to high correlations with the physical assessments and between each other. However, in terms of known-groups validity, all of the PROs were able to discriminate between the high and the low functioning groups based on AMAT cut scores. The ABC scale and the HAP further discriminated between those with high and moderate functional capacity. The PROs were unable to discriminate between subjects with low and moderate function. We suspect this has more to do with the mean total AMAT scores of those in the low functioning group as they were at the high end of the 0–24 point cut score, which nearly places them in the moderate functioning group. Furthermore, the GNE myopathy subjects had significantly lower HAP scores than healthy adults, and were not significantly different in terms of their adjusted activity score from other impaired populations as shown in table 3 [16, 20, 21, 51, 52, 53, 54]. GNE myopathy subjects tended to have higher maximum activity scores compared to the other impaired populations, which was expected since GNE myopathy patients display greater impairment when performing activities of daily living rather than activities that require short bursts of strength. The HAP adjusted activity score has been reported to be a more valid measure of activities of daily living and daily physical function than the HAP maximum activity score, and thus better illustrates the impairment in physical function of GNE myopathy subjects [16]. Previous authors offer the HAP subscale scores, however the limited psychometric properties of the HAP subscale scores narrowed their application beyond research purposes [54].

The IBMFRS and ABC scales performed well at both baseline and 6 months. The test-retest reliability of the three PROs was also good, and the reproducibility of the HAP was similar to other studies that reported the test-retest of the HAP maximum activity score and adjusted activity score in different populations [20, 51, 53]. All of the PROs had low levels of burden, with the HAP being the longest questionnaire to complete at an estimated time of 10 minutes [21].

This analysis is based on a diverse cohort compared to other GNE myopathy studies, which does not tend to focus on one ethnicity or a narrow degree of impairment [55, 56, 57, 58, 59, 60, 61]. In addition, only one natural history study incorporated a quality of life assessment, the SF-36 [55], while we analysed several PROs that were more disease-specific. There were a few limitations to our analysis. First, the sample size used for this analysis was limited because GNE myopathy is a rare genetic disease with a prevalence of approximately 30,000 patients worldwide, making it difficult to perform studies with larger sample sizes [62]. There may be some sample bias in the 6 month sample since some patients missed their visit and were seen at a 12 month visit, or we were unable to follow-up. More studies should be performed using these PROs and clinician assessments of physical function to provide further support for the validity and reliability of these PRO measures in GNE myopathy. A second limitation of this study was that only participants who could travel were eligible, thus potentially excluding severely impaired GNE myopathy subjects as evidenced by the higher mean AMAT scores in the low functioning group. There was also missing data related to advanced GNE myopathy subjects being unable to perform these tests. Thus, it is unknown whether these PROs are valid for severely limited GNE myopathy subjects. Furthermore, the high correlation between the PROs and the six minute walk test should be interpreted with caution since there may be a floor effect, as 31.4% (11/35) of GNE myopathy subjects were unable to complete the six minute walk test; thus, it is unclear if these PROs are appropriate measures of physical function in advanced GNE myopathy subjects that are wheelchair dependent and cannot complete the sit minute walk test which may have influenced the findings. Many more subjects were able to complete the Quantitative Muscle Strength Assessment and AMAT (94% and 100%, respectively) than the six minute walk test. Furthermore, correlations were weaker with physical assessments that focused on a limited number of muscles (e.g. functional reach test, upper quantitative muscle strength and lower quantitative muscle strength) rather than tests that incorporated the majority of muscles impacted by GNE myopathy (e.g. AMAT and total quantitative muscle strength). With advanced disease, there are also inherent limitations in performing physical assessments thereby limiting the spectrum of disease severity in this cohort. As a result, we are unable to conclude whether these PROs are valid in advanced GNE myopathy subjects.

Clinical Implications

Since this is the first analysis of PRO measures related to physical function in GNE myopathy, several interesting clinically relevant findings were identified. First, the majority of subjects (74.3%) reported using an ambulatory device at their baseline visit. The ABC scale has been validated as a good questionnaire for assessing fall risk with a threshold of <67% [63, 64]; our subjects were below this threshold. Assessing fall risk is especially important in GNE myopathy subjects, since falls are one of the first signs of the disease, and the majority of our subjects reported a history of falls. Furthermore, it is thought that fractures resulting from falls can be devastating to GNE myopathy patients as it can result in faster muscle atrophy and disease progression. Thus, while the ABC scale had weakest correlations with the physical assessments compared to the other PROs, it is a clinically important questionnaire to assess fall risks in this population. In addition to addressing fall risk, GNE myopathy subjects may benefit from attending physical therapy or occupational therapy services to help maintain their functional capacity. Incorporating PROs along with

physical performance assessments may assist clinicians in understanding the GNE myopathy patients' limitations in activities of daily living.

Because of the small number of non-ambulant patients, comparisons on PRO scores between ambulant and non-ambulant patients was not performed, but should be evaluated in future studies.

Research Implications

Research involving PROs and quality of life is scarce in rare diseases. This was the first analysis of the psychometric properties of three PROs assessing physical function in GNE myopathy subjects. Our findings suggest these PROs are appropriate to use in GNE myopathy in order to gain a better understanding of how slow progressive muscle atrophy impacts activities of daily living and physical function. However, a further ongoing assessment of the validity and reliability of these PROs in GNE myopathy should be performed. Although muscle groups had only modest correlations with the PROs, the total strength composites demonstrated robust correlations with all the PROs. The IBMFRS appeared to be the most appropriate PRO of the ones used in this analysis for the GNE myopathy population since it took into account ambulatory device use (the HAP and ABC scale do not), had the lowest burden, and was moderately to highly correlated with the other PROs and physical assessments. However, a disease-specific PRO for GNE myopathy would be beneficial to develop and utilize in future studies in order to detect functional changes over time and identify responders to treatment in clinical trials. It is important for future studies to assess the changes over time in strength and PRO scores to capture minimally important differences and clinically meaningful changes in GNE myopathy subjects. Incorporation of disease-specific PRO endpoints is of growing importance in drug development. Detecting a clinically meaningful treatment effect that also results in a meaningful effect on quality of life is necessary to allow for adequate review of promising drug therapies [12, 13, 15]. The patient-centred nature of PROs are especially important in rare disease clinical trials as they provide direct insight to the disease process.

Acknowledgements:

We would like to thank John Perreault and Vandana Singhal for their roles in coordinating the natural history study and the nurses at the NIH Clinical Center for providing care to our participants during their visits. We would especially like to thank the participants of the natural history study for their participation and important role in improving our understanding of GNE myopathy.

Funding: This work was supported by the Intramural Research Programs of the National Human Genome Research Institute (no grant number associated), and the National Center for Advancing Translational Sciences (no grant number associated), National Institutes of Health, Bethesda, Maryland, United States.

REFERENCES

1. Huizing M, Malicdan MV, Krasnewich DM, Manoli I, Carrillo-Carrasco N. GNE Myopathy In: Scriver CR, Childs B, Sly WS, Valle D, Beaudet AL, Vogelstein B, Kinsler KW, editors. Scriver's Online Metabolic and Molecular Bases of Inherited Disease. http://www.ommbid.com. New York: McGraw-Hill; 2014.
2. Huizing M, Carrillo-Carrasco N, Malicdan MC, Noguchi S, Gahl WA, Mitrani-Rosenbaum S, Argov Z, Nishino I. GNE myopathy: new name and new mutation nomenclature. Neuromuscul Disord. 2014;24:387–9. [PubMed: 24685570]

3. Nishino I, Carrillo-Carrasco N, Argov Z. GNE myopathy: current update and future therapy. J Neurol Neurosurg Psychiatry. 2014.
4. Eisenberg I, Avidan N, Potikha T, Hochner H, Chen M, Olender T, Barash M, Shemesh M, Sadeh M, Grabov-Nardini G, Shmilevich I, Friedmann A, Karpati G, Bradley WG, Baumbach L, Lancet D, Asher EB, Beckmann JS, Argov Z, Mitrani-Rosenbaum S. The UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase gene is mutated in recessive hereditary inclusion body myopathy. Nature genetics. 2001;29:83–7. Epub 2001/08/31. [PubMed: 11528398]
5. Celeste FV, Vilboux T, Ciccone C, de Dios JK, Malicdan MC, Leoyklang P, McKew JC, Gahl WA, Carrillo-Carrasco N, Huizing M. Mutation update for GNE gene variants associated with GNE myopathy. Hum Mutat. 2014;35:915–26. [PubMed: 24796702]
6. Argov Z, Yarom R. "Rimmed vacuole myopathy" sparing the quadriceps. A unique disorder in Iranian Jews. J Neurol Sci. 1984;64:33–43. Epub 1984/04/01. [PubMed: 6737002]
7. Nishino I, Carrillo-Carrasco N, Argov Z. GNE myopathy: current update and future therapy. J Neurol Neurosurg Psychiatry. 2015;86:385–92. [PubMed: 25002140]
8. Bennell K, Dobson F, Hinman R. Measures of physical performance assessments: Self-Paced Walk Test (SPWT), Stair Climb Test (SCT), Six-Minute Walk Test (6MWT), Chair Stand Test (CST), Timed Up & Go (TUG), Sock Test, Lift and Carry Test (LCT), and Car Task. Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S350–70. Epub 2012/05/25. [PubMed: 22588756]
9. Merlini L, Sabatelli P. Improving clinical trial design for Duchenne muscular dystrophy. BMC Neurol. 2015;15:153 Epub 2015/08/27. [PubMed: 26306629]
10. Hoffman EP, Connor EM. Orphan drug development in muscular dystrophy: update on two large clinical trials of dystrophin rescue therapies. Discovery medicine. 2013;16:233–9. Epub 2013/11/16. [PubMed: 24229740]
11. Guyatt GH, Ferrans Ce Fau - Halyard MY, Halyard My Fau - Revicki DA, Revicki Da Fau - Symonds TL, Symonds Tl Fau - Varricchio CG, Varricchio Cg Fau - Kotzeva A, Kotzeva A Fau - Valderas JM, Valderas Jm Fau - Alonso J, Alonso J. Exploration of the value of health-related quality-of-life information from clinical research and into clinical practice.
12. McLeod LD, Coon CD, Martin SA, Fehnel SE, Hays RD. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. Expert Rev Pharmacoecon Outcomes Res. 2011;11:163–9. Epub 2011/04/12. [PubMed: 21476818]
13. FDA. Guidance for Industry: Patient Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims. Silver Spring, MD 2009.
14. FDA. Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment: Draft Guidance for Industry Rockville, MD 6 2015.
15. FDA. Rare Diseases: Common Issues in Drug Development: Draft Guidance for Industry Rockville, MD 8 2015.
16. Davidson M, de Morton N. A systematic review of the Human Activity Profile. Clin Rehabil. 2007;21:151–62. [PubMed: 17264109]
17. Daughton DM, Fix AJ, Kass I, Bell CW, Patil KD. Maximum oxygen consumption and the ADAPT quality-of-life scale. Arch Phys Med Rehabil. 1982;63:620–2. Epub 1982/12/01. [PubMed: 7149948]
18. Anand S, Chertow GM, Johansen KL, Grimes B, Kurella Tamura M, Dalrymple LS, Kaysen GA. Association of self-reported physical activity with laboratory markers of nutrition and inflammation: the Comprehensive Dialysis Study. J Ren Nutr. 2011;21:429–37. Epub 2011/01/18. [PubMed: 21239185]
19. Brouwer B, Musselman K, Culham E. Physical function and health status among seniors with and without a fear of falling. Gerontology. 2004;50:135–41. Epub 2004/04/29. [PubMed: 15114034]
20. Herzberg PY, Heussner P, Mumm FH, Horak M, Hilgendorf I, von Harsdorf S, Hemmati P, Rieger K, Greinix H, Freund M, Lee SJ, Holler E, Wolff D. Validation of the human activity profile questionnaire in patients after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2010;16:1707–17. Epub 2010/06/15. [PubMed: 20541028]
21. Fix AJ, Daughton DM. Human Activity Profile professional manual. Lutz, FL: Psychological Assessment Resources; 1998.

22. Amato AA, Barohn RJ. Inclusion body myositis: old and new concepts. J Neurol Neurosurg Psychiatry. 2009;80:1186–93. Epub 2009/10/30. [PubMed: 19864656]

23. Jackson CE, Barohn RJ, Gronseth G, Pandya S, Herbelin L. Inclusion body myositis functional rating scale: a reliable and valid measure of disease severity. Muscle Nerve. 2008;37:473–6. Epub 2008/02/01. [PubMed: 18236463]

24. Rider LG, Werth VP, Huber AM, Alexanderson H, Rao AP, Ruperto N, Herbelin L, Barohn R, Isenberg D, Miller FW. Measures of adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis: Physician and Patient/Parent Global Activity, Manual Muscle Testing (MMT), Health Assessment Questionnaire (HAQ)/Childhood Health Assessment Questionnaire (C-HAQ), Childhood Myositis Assessment Scale (CMAS), Myositis Disease Activity Assessment Tool (MDAAT), Disease Activity Score (DAS), Short Form 36 (SF-36), Child Health Questionnaire (CHQ), physician global damage, Myositis Damage Index (MDI), Quantitative Muscle Testing (QMT), Myositis Functional Index-2 (FI-2), Myositis Activities Profile (MAP), Inclusion Body Myositis Functional Rating Scale (IBMFRS), Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), Cutaneous Assessment Tool (CAT), Dermatomyositis Skin Severity Index (DSSI), Skindex, and Dermatology Life Quality Index (DLQI). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S118–57. Epub 2012/05/25. [PubMed: 22588740]

25. Powell LE, Myers AM. The Activities-specific Balance Confidence (ABC) Scale. J Gerontol A Biol Sci Med Sci. 1995;50A:M28–34. Epub 1995/01/01. [PubMed: 7814786]

26. Lajoie Y, Gallagher SP. Predicting falls within the elderly community: comparison of postural sway, reaction time, the Berg balance scale and the Activities-specific Balance Confidence (ABC) scale for comparing fallers and non-fallers. Arch Gerontol Geriatr. 2004;38:11–26. Epub 2003/11/06. [PubMed: 14599700]

27. Ganesan M, Kanekar N, Aruin AS. Direction-specific impairments of limits of stability in individuals with multiple sclerosis. Ann Phys Rehabil Med. 2015;58:145–50. Epub 2015/05/12. [PubMed: 25960358]

28. Myers AM, Fletcher PC, Myers AH, Sherk W. Discriminative and evaluative properties of the activities-specific balance confidence (ABC) scale. J Gerontol A Biol Sci Med Sci. 1998;53:M287–94. Epub 2008/03/05. [PubMed: 18314568]

29. Harris-Love MO, Joe G, Davenport TE, Koziol D, Abbett Rose K, Shrader JA, Vasconcelos OM, McElroy B, Dalakas MC. Reliability of the adult myopathy assessment tool in individuals with myositis. Arthritis Care Res (Hoboken). 2015;67:563–70. Epub 2014/09/10. [PubMed: 25201624]

30. Harris-Love MO, Fernandez-Rhodes L, Joe G, Shrader JA, Kokkinis A, La Pean Kirschner A, Auh S, Chen C, Li L, Levy E, Davenport TE, Di Prospero NA, Fischbeck KH. Assessing function and endurance in adults with spinal and bulbar muscular atrophy: validity of the adult myopathy assessment tool. Rehabil Res Pract. 2014;2014:873872 Epub 2014/05/31. [PubMed: 24876969]

31. Shrader JA, Kats I, Kokkinis A, Zampieri C, Levy E, Joe GO, Woolstenhulme JG, Drinkard BE, Smith MR, Ching W, Ghosh L, Fox D, Auh S, Schindler AB, Fischbeck KH, Grunseich C. A randomized controlled trial of exercise in spinal and bulbar muscular atrophy. Ann Clin Transl Neurol. 2015;2:739–47. Epub 2015/08/15. [PubMed: 26273686]

32. Visser J, Mans E, de Visser M, van den Berg-Vos RM, Franssen H, de Jong JM, van den Berg LH, Wokke JH, de Haan RJ. Comparison of maximal voluntary isometric contraction and hand-held dynamometry in measuring muscle strength of patients with progressive lower motor neuron syndrome. Neuromuscul Disord. 2003;13:744–50. Epub 2003/10/17. [PubMed: 14561498]

33. Andres PL, Hedlund W, Finison L, Conlon T, Felmus M, Munsat TL. Quantitative motor assessment in amyotrophic lateral sclerosis. Neurology. 1986;36:937–41. Epub 1986/07/01. [PubMed: 3714055]

34. Brussock CM, Haley SM, Munsat TL, Bernhardt DB. Measurement of isometric force in children with and without Duchenne's muscular dystrophy. Phys Ther. 1992;72:105–14. [PubMed: 1549631]

35. NIMS. Muscular weakness assessment: use of normal isometric strength data. The National Isometric Muscle Strength (NIMS) Database Consortium. Arch Phys Med Rehabil. 1996;77:1251–5. Epub 1996/12/01. [PubMed: 8976307]

36. Andrews AW, Thomas MW, Bohannon RW. Normative values for isometric muscle force measurements obtained with hand-held dynamometers. Phys Ther. 1996;76:248–59. Epub 1996/03/01. [PubMed: 8602410]
37. Duncan PW, Weiner DK, Chandler J, Studenski S. Functional reach: a new clinical measure of balance. J Gerontol. 1990;45:M192–7. Epub 1990/11/01. [PubMed: 2229941]
38. Behrman AL, Light KE, Flynn SM, Thigpen MT. Is the functional reach test useful for identifying falls risk among individuals with Parkinson's disease? Arch Phys Med Rehabil. 2002;83:538–42. Epub 2002/04/05. [PubMed: 11932858]
39. Duncan PW, Studenski S, Chandler J, Prescott B. Functional reach: predictive validity in a sample of elderly male veterans. J Gerontol. 1992;47:M93–8. Epub 1992/05/01. [PubMed: 1573190]
40. Maranesi E, Ghetti G, Rabini RA, Fioretti S. Functional reach test: movement strategies in diabetic subjects. Gait Posture. 2014;39:501–5. Epub 2013/10/01. [PubMed: 24074730]
41. Lynch SM, Leahy P, Barker SP. Reliability of measurements obtained with a modified functional reach test in subjects with spinal cord injury. Phys Ther. 1998;78:128–33. Epub 1998/02/25. [PubMed: 9474105]
42. Weiner DK, Duncan PW, Chandler J, Studenski SA. Functional reach: a marker of physical frailty. J Am Geriatr Soc. 1992;40:203–7. Epub 1992/03/01. [PubMed: 1538035]
43. Hasmann SE, Berg D, Hobert MA, Weiss D, Lindemann U, Streffer J, Liepelt-Scarfone I, Maetzler W. Instrumented functional reach test differentiates individuals at high risk for Parkinson's disease from controls. Front Aging Neurosci. 2014;6:286 Epub 2014/11/12. [PubMed: 25386137]
44. Casanova C, Celli BR, Barria P, Casas A, Cote C, de Torres JP, Jardim J, Lopez MV, Marin JM, Montes de Oca M, Pinto-Plata V, Aguirre-Jaime A, Six Minute Walk Distance P. The 6-min walk distance in healthy subjects: reference standards from seven countries. Eur Respir J. 2011;37:150–6. [PubMed: 20525717]
45. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. Am J Respir Crit Care Med. 1997;155:1278–82. [PubMed: 9105067]
46. Wise RA, Brown CD. Minimal clinically important differences in the six-minute walk test and the incremental shuttle walking test. COPD. 2005;2:125–9. Epub 2006/12/02. [PubMed: 17136972]
47. Lu QL, Cirak S, Partridge T. What Can We Learn From Clinical Trials of Exon Skipping for DMD? Mol Ther Nucleic Acids. 2014;3:e152 Epub 2014/03/13. [PubMed: 24618851]
48. Mokkink LB, Prinsen CA, Bouter LM, Vet HC, Terwee CB. The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) and how to select an outcome measurement instrument. Brazilian journal of physical therapy. 2016;20:105–13. Epub 2016/01/21. [PubMed: 26786084]
49. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, Bouter LM, de Vet HC. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007;60:34–42. Epub 2006/12/13. [PubMed: 17161752]
50. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behavior research methods. 2009;41:1149–60. Epub 2009/11/10. [PubMed: 19897823]
51. Stuifbergen AK. Physical activity and perceived health status in persons with multiple sclerosis. J Neurosci Nurs. 1997;29:238–43. Epub 1997/08/01. [PubMed: 9307926]
52. Bilek LD, Venema DM, Camp KL, Lyden ER, Meza JL. Evaluation of the human activity profile for use with persons with arthritis. Arthritis Rheum. 2005;53:756–63. Epub 2005/10/07. [PubMed: 16208665]
53. Johansen KL, Painter P, Kent-Braun JA, Ng AV, Carey S, Da Silva M, Chertow GM. Validation of questionnaires to estimate physical activity and functioning in end-stage renal disease. Kidney Int. 2001;59:1121–7. Epub 2001/03/07. [PubMed: 11231369]
54. Farrell MJ, Gibson SJ, Helme RD. Measuring the activity of older people with chronic pain. Clin J Pain. 1996;12:6–12. Epub 1996/03/01. [PubMed: 8722729]
55. Mori-Yoshimura M, Oya Y, Yajima H, Yonemoto N, Kobayashi Y, Hayashi YK, Noguchi S, Nishino I, Murata M. GNE myopathy: a prospective natural history study of disease progression. Neuromuscul Disord. 2014;24:380–6. [PubMed: 24656604]

56. Mori-Yoshimura M, Hayashi YK, Yonemoto N, Nakamura H, Murata M, Takeda S, Nishino I, Kimura E. Nationwide patient registry for GNE myopathy in Japan. Orphanet J Rare Dis. 2014;9:150 Epub 2014/10/12. [PubMed: 25303967]
57. Mori-Yoshimura M, Monma K, Suzuki N, Aoki M, Kumamoto T, Tanaka K, Tomimitsu H, Nakano S, Sonoo M, Shimizu J, Sugie K, Nakamura H, Oya Y, Hayashi YK, Malicdan MC, Noguchi S, Murata M, Nishino I. Heterozygous UDP-GlcNAc 2-epimerase and N-acetylmannosamine kinase domain mutations in the GNE gene result in a less severe GNE myopathy phenotype compared to homozygous N-acetylmannosamine kinase domain mutations. J Neurol Sci. 2012;318:100–5. Epub 2012/04/18. [PubMed: 22507750]
58. Mori-Yoshimura M, Oya Y, Hayashi YK, Noguchi S, Nishino I, Murata M. Respiratory dysfunction in patients severely affected by GNE myopathy (distal myopathy with rimmed vacuoles). Neuromuscul Disord. 2013;23:84–8. Epub 2012/11/07. [PubMed: 23127962]
59. Argov Z, Eisenberg I, Grabov-Nardini G, Sadeh M, Wirguin I, Soffer D, Mitrani-Rosenbaum S. Hereditary inclusion body myopathy: the Middle Eastern genetic cluster. Neurology. 2003;60:1519–23. Epub 2003/05/14. [PubMed: 12743242]
60. Broccolini A, Pescatori M, D'Amico A, Sabino A, Silvestri G, Ricci E, Servidei S, Tonali PA, Mirabella M. An Italian family with autosomal recessive inclusion-body myopathy and mutations in the GNE gene. Neurology. 2002;59:1808–9. Epub 2002/12/11. [PubMed: 12473780]
61. Chaouch A, Brennan KM, Hudson J, Longman C, McConville J, Morrison PJ, Farrugia ME, Petty R, Stewart W, Norwood F, Horvath R, Chinnery PF, Costigan D, Winer J, Polvikoski T, Healy E, Sarkozy A, Evangelista T, Pogoryelova O, Eagle M, Bushby K, Straub V, Lochmuller H. Two recurrent mutations are associated with GNE myopathy in the North of Britain. J Neurol Neurosurg Psychiatry. 2014.
62. Huizing M, Malicdan MC, Celeste F, Vilboux T, Ciccone C, Gahl WA, Carrillo N, Genetic Analysis Reveals that GNE Myopathy is an Underdiagnosed Neuromuscular Disorder. 2015; Washington, DC: Publisher.
63. Botner EM, Miller WC, Eng JJ. Measurement properties of the Activities-specific Balance Confidence Scale among individuals with stroke. Disabil Rehabil. 2005;27:156–63. Epub 2005/04/13. [PubMed: 15824045]
64. Talley KM, Wyman JF, Gross CR. Psychometric properties of the activities-specific balance confidence scale and the survey of activities and fear of falling in older women. J Am Geriatr Soc. 2008;56:328–33. Epub 2008/01/09. [PubMed: 18179492]

Implications for Rehabilitation

- GNE myopathy is a rare muscle disease that results in slow progressive muscle atrophy and weakness, ultimately leading to wheelchair use and dependence on a caregiver.
- There is limited knowledge on the impact of this disease on the health-related quality of life, specifically physical function, of this rare disease population.
- Three patient reported outcomes have been shown to be valid and reliable in GNE myopathy subjects and should be incorporated in future investigations to better understand how progressive muscle weakness impacts physical functions in this rare disease population.
- The patient reported outcome scores of GNE myopathy patients indicate a high risk for falls and impaired physical functioning, so it is important clinicians assess and provide interventions for these subjects to maintain their functional capacity.

Table 1.

GNE myopathy subjects' characteristics at baseline and 6 months. Data presented as n (%) unless otherwise indicated.

	Baseline (n=35)
Mean age, years (range)	41 (25–65)
Gender, n	
Male	15 (42.9)
Female	20 (57.1)
Ethnicity	
Middle Eastern	6 (17.1)
Asian	11 (31.4)
Caucasian	16 (45.7)
Other	2 (5.7)
History of falls	32 (91.4)
Use of ambulatory device	26 (74.3)
Braces	24 (68.4)
Cane	18 (51.4)
Walker	8 (22.9)
Wheelchair use	
Dependent	3 (8.6)
Subjects reported for long distances only	7 (20)

Table 2.

Summary of patient reported outcome scores at baseline (n=35)

	Mean ± SD	Range of scores	Possible range	Standardized mean (SD)
HAP maximum activity score	69.3 ± 20	15 – 94	0 – 94	
HAP adjusted activity score	51.4 ± 22.7	7 – 90	0 – 94	
HAP subscales				
Self-care	7.3 ± 1.7	0 – 8	0 – 8	91.8 ± 21.6
Personal/household work	16.7 ± 7.1	1 – 25	0 – 25	66.9 ± 28.3
Entertainment/social	10.2 ± 2.7	6 – 16	0 – 16	63.6 ± 17
Independent exercise	12.1 ± 7.8	0 – 27	0 – 28	43.1 ± 28
Hand use	20.1 ± 6.9	2 – 28	0 – 28	71.8 ± 24.8
Leg effort	24.8 ± 12.9	0 – 50	0 – 50	49.7 ± 25.8
Back effort	7.3 ± 2.9	0 – 12	0 – 12	61 ± 24.3
IBMFRS	29.4 ± 8.1	9 – 40	0 – 40	
ABC scale	48.4 ± 25.7	0 – 100	0 – 100	

Table 3.

Comparison HAP scores (maximum activity score and adjusted activity score) in different populations to GNE myopathy subjects [20, 21, 51, 52, 53]. Scores presented as mean (SD).

Sample	N	Age Range (years)	Maximum activity score*	Adjusted activity score*
Healthy adults	477	20–79	85.3 (7)	83.2 (7.8)
Multiple Sclerosis	37	23–77	61.2 (19.3)	43.4 (21.5)
Older adults	102	60–88	75.7 (6.2)	71.6 (7.1)
Impaired	162	16–83	61.8 (14.8)	50.7 (17.6)
COPD	30	37–77	58.8 (13.2)	48.7 (14.2)
Dialysis	39	22–83	55.2 (14.9)	43.6 (19.1)
Allogeneic hematopoietic stem cell transplant	176	18–72	73.25 (17.7)	56.39 (20.63)
Arthritis	28	24–69	74.6 (9.2)	67.5 (12.3)
GNE myopathy	35	25–65	69.3 (20)	51.4 (22.7)

Table 4.

Correlations of patient reported outcomes and physical assessments at baseline[#]

	HAP adjusted activity score	HAP maximum activity score[a]	IBMFRS	ABC Scale
Upper quantitative muscle strength	0.37* (n=33)	0.18 (n=33)	0.58** (n=33)	0.20 (n=30)
Lower quantitative muscle strength	0.43* (n=33)	0.19 (n=33)	0.52** (n=33)	0.44* (n=30)
Total quantitative muscle strength	0.44** (n=33)	0.23 (n=33)	0.58** (n=33)	0.36 (n=30)
Six minute walk test	0.69** (n=24)	0.62** (n=23)	0.55** (n=23)	0.55** (n=21)
AMAT Functional subscale	0.71** (n=35)	0.58** (n=35)	0.75** (n=35)	0.63** (n=32)
AMAT Endurance subscale	0.81** (n=35)	0.65** (n=35)	0.70** (n=35)	0.69** (n=32)
AMAT Total score	0.78** (n=35)	0.66** (n=35)	0.75** (n=35)	0.68** (n=32)
Functional reach- right	0.26 (n=25)	0.53* (n=25)	0.18 (n=24)	0.38 (n=22)
Functional reach- left	0.36 (n=25)	0.29** (n=25)	0.34 (n=24)	0.47* (n=22)
HAP adjusted activity score		0.82** (n=35)	0.84** (n=34)	0.79** (n=32)
HAP maximum activity score[a]			0.63** (n=34)	0.53** (n=32)
IBMFRS				0.77** (n=32)

*p<0.05

**p<0.001. Values are Pearson's correlation coefficient r.

[a]Spearman correlation performed and Spearman rho reported

[#]n values differ because the ABC questionnaire was implemented later in the natural history study. In addition, some participants were unable to complete the functional performance tests.

Table 5.

Human Activity Profile subscale items correlation to other PROs and physical assessments. Values are Pearson's correlation coefficient r.

	Self-care	Personal/house work	Entertain/social	Indep. exercise	Hand use	Leg effort	Back effort
Upper quantitative muscle strength (n = 33)	0.35	0.48**	0.24	0.27	0.47**	0.38*	0.33
Lower quantitative muscle strength (n = 33)	0.25	0.5**	0.23	0.16	0.41*	0.35	0.32
Total quantitative muscle strength (n = 33)	0.32	0.53**	0.26	0.23	0.48**	0.4*	0.35
Six minute walk test (n = 24)	0.5	0.58**	0.69**	0.63**	0.63**	0.7**	0.77**
AMAT Functional subscale (n = 35)	0.50**	0.64**	0.43*	0.3	0.62**	0.52**	0.57**
AMAT Endurance subscale (n = 35)	0.47**	0.75**	0.64*	0.54**	0.7**	0.74**	0.67**
AMAT Total score(n = 35)	0.5**	0.72**	0.54**	0.43*	0.68**	0.64**	0.64**
Functional reach- right (n = 25)	-0.15	0.19	0.31	0.28	0.2	0.25	0.53**
Functional reach- left (n = 25)	-0.17	0.31	0.34	0.31	0.32	0.31	0.55**
ABC scale	0.46**	0.72*	0.58**	0.34	0.72**	0.58**	0.65**
IBMFRS	0.71**	0.81**	0.35	0.49**	0.85**	0.70**	0.68**

* $p<0.05$

** $p<0.001$

Table 6.

Patient reported outcome scores by level of impairment as defined by the AMAT cut-scores (low: 0–24, moderate: 25–34, high: 35–45).

Variables	AMAT		
	Low (n=15)	Moderate (n=9)	High (n=11)
ABC	36.9 (15.7)	39.8 (20.1)[c]	75.3 (25.1)[d**]
IBMFRS	25.1 (8.7)[b#]	29.9 (5.3)	35.8 (4.6)[e]
HAP maximum activity score[a]	11.73[#]	11.69	24.33
HAP adjusted activity score	38.3 (17.6)	45.2 (19.1)	74.3 (12.3)[**]

[a] Kruskal-Wallis performed and mean rank presented. Chi-square = 13.11

[b] n=16

[c] n=8

[d] n=9

[e] n=10

with missing/incomplete scores excluded.

[**] p<0.001 compared to low and moderate functioning AMAT groups

[#] p<0.001 compared to high AMAT group