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Characterization of Strength and Function in Ambulatory Adults With GNE Myopathy

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Abstract

Objective:
To characterize the pattern and extent of muscle weakness and impact on physical functioning in adults with GNEM.

Methods:
Strength and function were assessed in GNEM subjects (n = 47) using hand-held dynamometry, manual muscle testing, upper and lower extremity functional capacity tests, and the GNEM-Functional Activity Scale (GNEM-FAS).

Results:
Profound upper and lower muscle weakness was measured using hand-held dynamometry in a characteristic pattern, previously described. Functional tests and clinician-reported outcomes demonstrated the consequence of muscle weakness on physical functioning.

Conclusions:
The characteristic pattern of upper and lower muscle weakness associated with GNEM and the resulting functional limitations can be reliably measured using these clinical outcome assessments of muscle strength and function.

Key Words: GNE myopathy, hereditary inclusion body myopathy (HIBM), Nonaka disease, distal myopathy with rimmed vacuoles (DMRV), muscle strength, muscle function

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INTRODUCTION

GNE myopathy (GNEM) is a rare, severe, progressive, autosomal recessive myopathy and previously known as hereditary inclusion body myopathy, distal myopathy with rimmed vacuoles, inclusion body myopathy type 2, Nonaka distal myopathy, quadriceps sparing myopathy that leads to marked disability, especially loss of ambulation.[1,2] The disease is associated with a defect in the rate-limiting step of sialic acid biosynthesis due to mutations in the glucosamine (UDP-N-acetyl)-2-epimerase (*GNE*) gene that encodes a bifunctional enzyme (uridinediphosphate-N-acetylglucosamine 2-epimerase and N-acetylmannosamine kinase) in this metabolic pathway.

This disorder was initially described in 1981 in Japanese patients and subsequently in 1984 in a group of Iranian Jews in Israel.[3,4] The disorder is rare, and there is limited accurate information to support the true prevalence, with one report of 1–3/1,000,000 worldwide and a higher prevalence seen in individuals of Middle-Eastern Jewish and Japanese descent.[2,5] Presenting symptoms include foot drop secondary to anterior tibialis muscle weakness, followed by progressive proximal and distal muscle weakness and atrophy in the lower and upper extremities, with symptom onset occurring in the young adult years (mean 26 years, range 15–48 years).[6–9] Magnetic resonance imaging studies have shown fatty and fibrous infiltration or replacement of affected muscles as the

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disease progresses.[7] Early onset weakness of the tibialis anterior muscle with marked sparing of the quadriceps femoris muscle even in the late stages of the disease is a unique feature of this condition that is not well understood.[7,8] The rate of disease progression is gradual and variable over a period of few decades, with most patients eventually requiring the use of a wheelchair (usually between 10–20 years after onset).[7] Although muscle weakness in the upper extremities is noted even in the early stages of the disease, the rate of progression may be slower than in the lower extremities.

Currently, there are no approved treatments for GNEM, although data from a murine model of the disease suggest that sialic acid (and other metabolic intermediates) replacement therapy could be effective in preventing or slowing the rate of decline in muscle function.[5,10,11] Clinical trials are underway to assess the safety and efficacy of long-term exposure to an oral extended release formulation of sialic acid (also known as aceneuramic acid prolonged release) as substrate replacement therapy.

Outcome measures capable of characterizing the pattern and extent of muscle weakness associated with GNEM, functional limitations resulting from this weakness, and relationships between the outcome measures were identified during the study. The reliable and valid assessment of strength and function in adults with GNEM has important clinical implications for disease management and the discovery and development of treatments for patients with this progressive myopathy.

MATERIALS AND METHODS

Study Population and Design

This report presents screening and baseline visit data collected before randomization in a phase 2, placebo-controlled study evaluating extended release sialic acid (aceneuramic acid) in confirmed GNEM patients conducted in the United States and Israel (clinicaltrials.gov: NCT01830972, NCT01517880[12]). This study was approved by the institutional review board or ethics committee at each participating site. Written informed consent was obtained from all participants after explanation of study objectives.

Patients and Methods

Ambulatory patients with GNEM between the ages of 18 and 65 years with a confirmed molecular diagnosis were enrolled and participated in a screening visit to confirm eligibility. At the screening visit, subjects were required to walk a minimum of 20 meters independently (allowing for the use of orthoses and an assistive walking device if needed) to be eligible for randomization.

Muscle strength and functional capacity were assessed by trained physical therapists at both the screening and baseline visits, which were conducted no more than 28 days apart. Physical therapists participated in a 2-day on-site training session to standardize administration of the tests and to minimize interrater variability of the measurements. Assessments included hand-held dynamometry (HHD), manual muscle testing (MMT), a 6-minute walk test (6MWT), a gait speed (GS) test, a modified 30-second sit-to-stand (STS) test, a 1 kg weighted arm lift (WAL) test, and a timed stair climb (SC) test.

Dynamometry provides a quantitative measure of skeletal muscle force production generated during a maximal voluntary isometric contraction. Dynamometry has been used extensively to document muscle weakness, disease progression, and treatment outcomes in various neuromuscular diseases.[13–17] The microFET2 dynamometer (Hoggan Scientific, St Lake City, UT) used within this study is capable of measuring in 0.1 kg increments from 0.4 to 136 kg of force. This allows for quantitative measurement of strength in severely affected muscle groups with limited residual healthy muscle tissue, such as those commonly observed in GNEM. Muscle groups assessed with the microFET2 device included shoulder abductors, elbow flexors, and elbow extensors in the upper extremities and hip adductors, hip abductors, hip flexors, hip extensors, knee flexors, and

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knee extensors in the lower extremities. Isometric grip strength was assessed using a hydraulic grip dynamometer (B&L Engineering, Santa Ana, CA). The highest value obtained from 3 reproducible efforts (within 15%) was recorded in kilograms for each muscle group tested, and the percent of normal predicted value was calculated based on age, sex, height, and weight using published normative data.[12,18–21] A composite score of LE strength was calculated by summing HHD bilateral mean raw scores for hip flexors, hip extensors, hip abductors, hip adductors, and knee flexors. Knee extensors were excluded from this composite score because of the unique relative sparing of this muscle group in GNEM. A composite score of UE strength was also computed by summing HHD bilateral mean raw scores for grip, shoulder abductors, elbow flexors, and elbow extensors.

MMT was performed bilaterally for the ankle dorsiflexors and ankle plantarflexors. Modified Medical Research Council (MRC) scoring was used with grades ranging from 0 (no palpable muscle activity) to 5 (normal strength).[22]

The 6MWT has been used to assess endurance and walking ability in many conditions (including cardiopulmonary disease, stroke, and osteoarthritis), and has normative data available to allow for comparison of walking ability to healthy age-matched peers. Administration of the 6MWT for the evaluation of walking capacity and endurance was standardized in accordance with the American Thoracic Society (ATS) guidelines with a modification made to the course length.[23–26] A 20-m course (40 m/lap) was available and used at all sites. Subjects were permitted to use their usual orthoses and assistive devices. The total distance walked in a 6-minute period was recorded in meters, and reference equations were used to calculate the percent of normal predicted distance based on age and sex.[23,27,28]

A GS test measures the time taken to walk short distances and has been used in studies of rheumatoid arthritis and osteoarthritis.[24] The GS test was administered at a maximum pace along a 7.62-m walking course with additional distance added to the course length for acceleration and deceleration. Subjects were permitted to use their usual orthoses and assistive devices. The time required to walk the course was recorded in seconds. The percent of normal predicted speed was calculated based on normative data that considers age, height, and sex.[29]

The 30-second STS test is a valid and reliable measure of proximal LE strength in older adults and patients with idiopathic inflammatory myositis.[24,30–32] A modified version of the test was administered to determine the number of times the subject could rise from a seated position in a chair to a standing position in a 30-second period. The standard administration requires that the person's arms be folded across the chest for the duration of the test. In an effort to minimize the floor effects associated with the testing of weaker subjects, use of the chair armrests and assistive devices were permitted during the stand maneuver.

The WAL test has been demonstrated to be reliable and a valid measure of UE strength in the elderly and in patients with idiopathic inflammatory myositis.[32,33] The test was administered bilaterally to determine the number of times the subject could raise a 1 kg weight above the head in a 30-second period. The number of repetitions completed with each arm was recorded.

The SC test is a well-established assessment of functioning in patients with neuromuscular disorders.[34] The test measures the time required to ascend 4 standard stairs. Use of the handrail and an assistive device was permitted while climbing. The time required to complete the test was recorded in seconds.

The ability to perform activities of daily living was assessed with a clinician-reported functional activity scale developed for GNEM. The GNEM Functional Activity Scale (GNEM-FAS) is a 25-item scale administered by a physical therapist based on patient response and clinical observation. The items are divided into 3 domains: mobility, upper

extremity function, and self-care. All 25 items are scored from 0 to 4 based on the level of independence, the use of assistive devices, and compensations with lower scores associated with greater disability and dependence. A total score and 3 domain subscores were calculated.

Data Analysis

Screening and baseline visit values for measures of strength and function were summarized descriptively. In addition, percent of normal predicted values based on normative data was calculated for the individual HHD muscle groups, 6MWT distance, and GS.[12,18–21,28] Patients were randomized for study purposes to groups based on the ability to walk 200 or more meters on the 6MWT at the screening visit. As a result, the 200-m cutoff was used to distinguish weaker from stronger study subjects. Test–retest reliability was assessed for HHD and the functional capacity measures using intraclass correlation coefficients calculated from the screening and baseline visit observations.[35] The reliability of MMT was assessed by the percent agreement in the scores from repeated measures. Correlation coefficients were calculated to examine the relationships between the measures using the statistical program SAS9.4.

RESULTS

Patient Characteristics

Fifty-four subjects were screened for participation in a phase 2 clinical study of aceneuramic acid for the treatment of GNEM. Forty-seven qualifying subjects returned for repeat testing at baseline. Subject demographics and baseline characteristics are presented in Table 1.

TABLE 1. GNE Myopathy Demographic and Baseline Characteristics (n = 47)

Demographic and Baseline Characteristics	Statistic
Female % (n)	62 (29)
Male % (n)	38 (18)
Mean age (range), y	40 (18–64)
Mean age at symptom onset (range), y	28 (13–50)
Mean symptom duration (±SD), y	12 ± 8
Ethnic descent: % (n)	
Persian Jewish	60 (28)
Indian subcontinent	15 (7)
European	13 (6)
Other	13 (6)
% (n) Use of orthoses for foot drop support	60 (28)
% (n) Use of assistive device for walking	51 (24)
% (n) Use of wheelchair or scooter for mobility	23 (11)

Reliability of Measures of Strength and Function

Test–retest reliability was assessed using data collected from screening and baseline visits conducted 1–4 weeks apart. ICCs for individual HHD measures and functional tests ranged from 0.814 to 0.987 (Table 2). HHD mean raw values for the group are also presented in Table 2, where high reliability is seen for both weaker and stronger muscle groups. A difference of no more than 1 MMT grade (eg, −4 to 4) was observed in the ankle dorsiflexor and ankle plantarflexor scores for the vast majority of patients (96% and 94%, respectively).

Characterization of Strength and Function

Baseline UE and LE strength, as measured by HHD, is presented as a percent of the normal predicted value for each muscle group for the full cohort (Fig. 1). LE weakness is more pronounced in the hip flexors, hip adductors, and knee flexors (all ≤25% of the normal predicted values) relative to the hip extensors and hip abductors (29% and 51% of normal predicted values, respectively). The knee extensors are the strongest muscle group tested in this cohort (58% of normal predicted values), which is consistent with the relative quadriceps sparing feature of this disease.[1,4] The UE muscle groups tested range from 41% to 46% of normal predicted values.

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TABLE 2. Reliability of Measures of Muscle Strength and Function (n = 47)

	Intraclass Correlation Coefficient (ICC)	95% Confidence Interval (CI)	Mean Value for All Subjects (SD) Units, n = 47
Grip	0.974	0.955–0.986	16.2 (10.2) kg
Shoulder abduction	0.959	0.928–0.977	7.7 (5.2) kg
Elbow flexion	0.978	0.960–0.987	10.0 (5.9) kg
Elbow extension	0.985	0.974–0.992	6.8 (3.9) kg
Knee extension	0.814	0.689–0.892	23.3 (6.7) kg
Knee flexion	0.968	0.943–0.982	3.7 (4.9) kg
Hip flexion	0.949	0.911–0.971	4.1 (5.3) kg
Hip abduction	0.904	0.834–0.945	12.7 (6.5) kg
Hip adduction	0.930	0.878–0.961	5.0 (4.3) kg
Hip extension	0.953	0.918–0.974	10.4 (7.3) kg
6MWT	0.987	0.977–0.993	273.3 (134.4) m
Maximum GS test	0.961	0.931–0.978	106.3 (45.8) cm/s
SC test	0.876	0.786–0.930	8.8 (10.3) s
STS test	0.906	0.837–0.946	10.0 (4.7) repetitions
WAL Test	0.930	0.868–0.963	22.8 (11.6) repetitions

Foot drop and tripping during walking are the most common presenting symptoms for patients with GNEM due to weakness of the tibialis anterior.[1,4] MMT results for ankle dorsiflexion detected this feature with 81% of subjects lacking full antigravity motion and no subject having residual strength in the normal (5 or −5) range. MMT grades for ankle plantar flexion were more varied and distributed from 0 (no palpable muscle activity) to 5 (normal).

The mean 6MWT distance for all subjects at baseline was 278 m (39% of the normal predicted value). Fourteen subjects (3 men, 11 women) walked <200 m. These short-distance walkers averaged 128 m (19% of the normal predicted

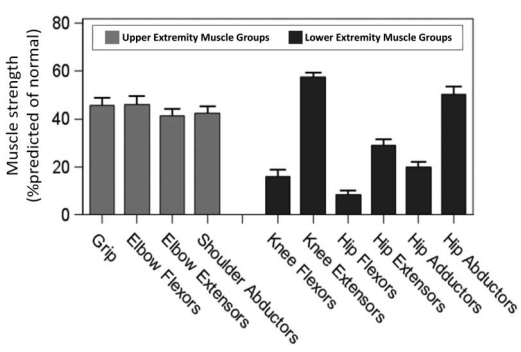

FIGURE 1. Muscle strength profile of subjects with GNEM using HHD measurements (Mean ± SEM, n = 47)

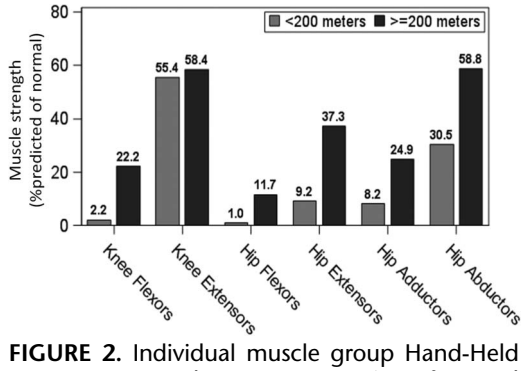

FIGURE 2. Individual muscle group Hand-Held Dynamometry values as a proportion of normal predicted, stratified by 6MWT distance at the Screening visit (Mean; n = 47)

TABLE 3. Relationship Between Lower and Upper Extremity Composite Scores and Measures Functional Capacity (Pearson Correlation Coefficient)

	6MWT	Maximum GS	SC	STS	WAL
Lower extremity composite (LEC)	0.92	0.64	0.58	0.81	
Upper extremity composite (UEC)					0.71

values). Thirty-three subjects (15 men, 18 women) walked ≥200 m. These long-distance walkers averaged 339 m (47% of the normal predicted values).

Lower Extremity Strength and 6MWT

Individual LE muscle strength, as measured by HHD, showed a positive relationship to performance in the 6MWT, with stronger subjects walking longer distances. The mean percent of predicted normal value for each lower extremity muscle group is shown for subjects walking < 200 and ≥200 m during the screening visit 6MWT; it is depicted in Figure 2. Pearson correlation coefficients for the lower extremity muscle groups tested ranged from 0.60 to 0.85 (data not shown). The weakest correlation of 0.60 was observed for the knee extensors, which is consistent with the relative sparing of this muscle group even in more severely affected patients. For this reason, the calculated LEC includes all muscle groups tested except for the knee extensors.

Muscle Strength and Function

LE and UE strength, as measured by HHD, shows a positive relationship to the functional tests administered with stronger subjects, demonstrating better performance. A similar relationship between strength and function was observed for the upper extremities.

Pearson correlation coefficients comparing lower extremity composite (LEC) score and 6MWT, maximum GS, SC, and STS tests are presented in Table 3 along with correlation results for upper extremity composite (UEC) score and the WAL test.

Relationships between the performance-based outcome measures and the GNEM-FAS total and domain scores (Table 4) support the meaningfulness of the functional outcome measures. The highest correlations were seen between those assessments that are expected to be more closely related, such as the mobility score and 6MWT (0.83). Similarly, lower correlations were seen among those assessments that are expected to be related to a lesser degree, such as the correlations of the GNEM-FAS upper extremity score with the 6MWT (0.52) and HHD lower extremity composite (0.50).

DISCUSSION

This is the largest study conducted to date to assess clinical outcome measures in

TABLE 4. Relationship Between GNEM-FAS Scores and Measures of Strength and Functional Capacity (Pearson Correlation Coefficient)

GNEM Functional Activity Scale (GNEM-FAS) Score	6MWT	LEC	UEC	STS	WAL	SCT
Mobility	0.83	0.86	0.62	0.73	0.63	−0.54
Upper extremity	0.52	0.50	0.66	0.47	0.46	−0.53
Self-care	0.51	0.55	0.60	0.52	0.51	−0.69
GNEM-FAS total	0.71	0.73	0.70	0.66	0.65	−0.68

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adults with GNEM. The data collected during this study demonstrate that dynamometry administered using a hand-held device provides reliable, reproducible, and quantifiable measures of strength in various muscle groups in the upper and lower extremities of affected patients, replicates the pattern of weakness previously identified with MMT, and differentiates between stronger patients and those with more profound weakness. Composite measures of UE strength and LE strength showed that HHD can be used to predict performance on functional measures. The functional performance measures used in this study included the 6MWT, GS, SC, STS, and WAL tests and were demonstrated reliable and capable of quantifying limitations in critical motor activities, such as walking distances with acceleration and deceleration, stair climbing, standing, and reaching.

Analysis of the GNEM-FAS data revealed moderate to high correlations with logical patterns of association between total and individual domain scores and HHD and functional tests. This suggests that the GNEM-FAS adequately measures constructs relevant to the daily function of patients with GNEM and can be used to provide support for the clinical meaningfulness of observed changes in HHD and functional performance tests.

Despite recent progress in understanding the molecular genetics of GNEM and development of treatment strategies such as substrate replacement therapies, inhibitors of degenerative processes, and gene-based or cell-based therapies, there is currently no approved treatment for GNEM.[1,2] The outcome measures included in this study are well suited to characterize not only the nature and extent of upper and lower muscle weakness, but also the resulting functional limitations seen in adults with GNEM. As a result, these measures show promise as appropriate endpoints for use in clinical trials of investigational therapies in GNEM or to document progression of the disease in the absence of treatment.

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