Long-term Evaluation Parameters in GNE Myopathy: A Five-year Observational Follow-up Natural History Study

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Research Article

Keywords: GNE myopathy, long-term natural history, Gross Motor Function Measure, quality of life

Posted Date: October 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-909985/v1

Abstract

Background

A number of clinical trials targeting GNE myopathy patients have been conducted. However, useful clinical parameters for post-marketing surveillance and long-term clinical observation have not yet been established.

Objective

We conducted a 5-year observational follow-up natural history study to identify evaluation parameters which may be useful for the long-term observation of GNE myopathy patients.

Methods

Thirty-three genetically-confirmed GNE myopathy patients were recruited and evaluated at study entry (baseline) and yearly in a 5-year follow-up. Hand-held dynamometer measurements of knee extension strength, grip power, and pinch power, summed Manual Muscle Testing (MMT) score of 17 muscles, Gross Motor Function Measure (GMFM), 6-minute walk test, percent vital capacity and percent force vital capacity (%FVC), lean body mass (whole body, arms, and legs), creatine kinase (CK), Barthel Index, modified Rankin Scale, and SF-36 national standard scores were examined.

Results

Of the 33 patients, 22 (66%) completed evaluations for the entire 5-year follow-up period. These patients had a significant reduction in summed MMT score (p=0.001), GMFM (p=0.001), grip power (p=0.013), pinch power (p<0.001), CK (p=0.030), %FVC (p<0.001), leg lean body mass (p=0.040), and the Physical Functioning subscale score of the SF-36 (p=0.015) at the 5th year evaluation relative to baseline. Among these parameters, summed MMT score, GMFM, pinch power, and %FVC showed significant changes even in non-ambulant patients.

Conclusions

MMT, GMFM, pinch power, CK, %FVC, lean body mass, and Physical Functioning subscale score of the SF-36 are useful parameters for the long-term evaluation of GNE myopathy patients.

Introduction

GNE myopathy (OMIN 605820), also known as distal myopathy with rimmed vacuoles or Nonaka myopathy, is an early adult-onset myopathy with slow progression that preferentially affects the tibialis anterior muscle and commonly spares the quadriceps femoris muscle [1, 2]. The disease is caused by a mutation in the *GNE* gene, which encodes a bifunctional enzyme (uridinediphosphate-*N*-acetylglucosamine (UDP-GlcNAc) 2-epimerase and N-acetylmannosamine kinase (MNK)) that catalyzes two rate-limiting reactions in cytosolic sialic acid synthesis [3–7].

Oral sialic acid metabolite treatment can prevent muscle atrophy and weakness in a mouse GNE myopathy model [8]. Although a recent clinical trial (Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Sialic Acid; ClinicalTrials.gov; identifier: NCT02377921) failed to demonstrate the efficacy of sialic acid to treat GNE myopathy, another clinical trial is currently underway in the United States to test ManNAc, an uncharged precursor of sialic acid (Multi-Center Study of ManNAc for GNE Myopathy (MAGiNE); ClinicalTrials.gov; identifier: NCT04231266). One of our research interests is the identification of clinically useful parameters for evaluation both in clinical trials and for long-term follow-up after new medications become available for GNE myopathy. We previously published a 1-year natural history study of 27 Japanese GNE myopathy patients and detected significant progression of the disease using Manual Muscle Testing (MMT), grip power, and % forced vital capacity (FVC) [9, 10]. On the other hand, the 6-m walk test (6MWT), Gross Motor Function Measure (GMFM), hand-held dynamometer (HHD) measurements of quadriceps strength, pinch power, lean body mass, creatine kinase (CK), and activities of daily living (ADL) (e.g., as assessed by the modified Rankin scale (mRS) and Barthel Index (BI)) failed to detect significant changes during the 1-year period, possibly due to the small sample size or relatively short observation period.

The present study followed the progress of GNE myopathy patients for a longer period of 5 years to assess changes in clinical parameters with the aim of identifying evaluation parameters which could be useful for post-marketing surveys and long-term clinical observation.

Materials And Methods

Study population and design

The present study used prospective data from genetically-confirmed Japanese GNE myopathy patients who were evaluated at least twice (at baseline and at least one of the annual follow-up evaluations during the 5 year follow-up period) at the National Center of Neurology and Psychiatry (NCNP) Hospital. Genetic information was acquired from available medical records. Inclusion criteria included the ability to perform repeat testing. Data from patients who were able to attend at least one annual follow-up evaluation were included in the analysis. Patients who attended the 5th year evaluation were requested to answer the 36-item short form survey (SF-36) and provide updates on their ADL and ambulation status. The first patients were enrolled in April 2009, and the last data analyzed were from November 30, 2019.

Evaluation methods (Table 1)

Table 1
Patient characteristics.

	mean +/- SD, max, min, median	n
Age (years)	43.2 +/- 13.4 (23-68, 43)	33
Sex		M:F=11:22
Age at onset (years)	26.6 +/- 11.3 (14-58, 24)	33
Duration from onset of disease to present (years)	17.0 +/- 9.3 (3-34, 15)	33
Age at start using canes/braces (y.o.)	33.7 +/- 13.7 (18-65, 29)	23
Age at start using wheelchair (y.o.)	32.4 +/- 12.9 (18-64, 29)	19
Age at lost ambulation (y.o.)	34.1 +/- 11.7 (22-64, 30)	20

Knee extension (HHD; myu-Tas F-1®, Anima, Japan), grip power (Dynamometer®; TTM Japan), pinch power (PinchTrack^{TM}; JTECH, Japan), and occlusal force (GM10®; NAGANO KEIKI, Japan) were measured three times each for both right and left sides.

Muscle strength tests, including MMT and GMFM (Japanese version; range, 0-100 [%]), were performed [11]. The following 17 muscle parameters were examined: neck flexion, truncal flexion, shoulder abduction, shoulder adduction, shoulder flexion, shoulder extension, elbow flexion, elbow extension, hip flexion, hip extension, thigh adduction, thigh abduction, knee extension, knee flexion, ankle dorsiflexion, and ankle plantarflexion. Right and left MMT scores were averaged, except for those corresponding to neck and truncal flexion. The summed MMT score (range, 0-85) was obtained by adding together scores of the 17 muscle parameters. 6MWT was administered to patients who were able to walk without assistance (including a cane or brace).

Patient condition was assessed by physical examination, pulmonary function tests (percent vital capacity (%VC) and percent force vital capacity (%FVC)), lean body mass (whole body, arms, and legs) as assessed by dual-energy X-ray absorptiometry (DEXA; Discovery bone densitometer, Hologic, Bedford, MA), and skeletal muscle mass index [12]. Blood and urine were collected to measure CK. BI (range, 0-100), mRS (Japanese version; range, 1-5), and SF-36 (Japanese version) national standard scores were used to assess ADL and quality of life (QOL) [13, 14].

Data analysis

Data were summarized using descriptive statistics and presented as mean ± standard deviation (SD), median, range, frequency, or percentage. The Mann-Whitney U test and Kruskal-Wallis test were used for continuous data, and Fisher's exact test was used for binary data. The paired t-test was used to compare differences between baseline and follow-up data. Spearman's rank correlation

coefficients were used to examine correlations between variables. Data of patients for whom meaningful measurements could not be made at baseline were excluded from the analysis. All analyses were performed using SPSS for Macintosh (Version 23; SPSS Inc., Chicago, IL).

Results

General characteristics at study entry

Patient characteristics are summarized in Table 1. A total of 33 Japanese GNE myopathy patients (12 males and 22 females) participated in this study. Two female patients were siblings, and all other patients were unrelated to each other. Mean age at the time of data collection was 43.2 ± 13.4 years (mean ± SD), and mean age at disease onset was 26.6 ± 11.3 years. Thirty percent (11/33) of patients were ambulant and completed the 6MWT without assistance, 18.2% (6/33) required assistance (e.g., cane and/or brace), and 60.6% (20/33) had lost ambulation. Mean age at loss of ambulation was 34.1 ± 11.7 years.

GNE mutations (Supplementary Table 1, 2)

Of the 33 patients included in this study, 27% (9/33) harbored the p.V603L homozygous mutation, while 73% (24/33) harbored a compound heterozygous mutation. Of these heterozygotes, 12% (4/33) had the p.D207V/p.V603L genotype. Frequent alleles were V603L (39%, 26/66), D207V (18%, 12/66), and C44S (3%, 2/66).

Patient characteristics during and at end of follow-up period (Table 2)

Table 2
Results of initial and annual evaluations.

			pre		1 year		2 year		3 year		4 year		5 year	
				n		n		n		n		n		n
physical evaluation	summed MMT		38.6 +/- 22.5	33	36.5 +/- 21.7**	29	34.7 +/- 20.3**	23	31.7 +/- 21.4**	21	29.7 +/- 19.0**	13	32.3 +/- 22.1**	21
	GMFM (%)		50.4 +/- 38.4	29	46.3 +/- 38.7	26	42.6 +/- 39.0*	22	41.0 +/- 39.9*	19	28.6 +/- 37.1	11	33.9 +/- 37.1**	18
	6MWT		350.5 +/- 144.4	12	307.5 +/- 134.1	11	307.0 +/- 147.8	8	265.5 +/- 102.9	8	222.0 +/- 130.1**	4	270.8 +/- 112.2	4
	HHD (N)		163.1 +/- 113.0	23	152.0 +/- 145.6	21	132.0 +/- 97.0	15	144.4 +/- 137.1	13	116.3 +/- 161.4	8	130.9 +/- 146.1	12
	Grip power (kg)		9.1 +/- 8.1	23	6.3 +/- 6.4	20	6.4 +/- 7.6	18	7.2 +/- 7.5	15	4.6 +/- 5.6*	10	6.1 +/- 8.2*	16
	Pinch power (N)		26.5 +/- 22.2	27	20.6 +/- 20.3	24	19.7 +/- 21.4**	22	15.0 +/- 15.0**	18	12.1 +/- 12.9*	12	16.3 +/- 20.2**	19
respitaroy function	FVC (%)		87.0 +/- 25.0	33	84.3 +/- 27.6	30	87.4 +/- 25.0*	23	81.2 +/- 26.8**	22	75.0 +/- 24.0**	12	75.8 +/- 31.2**	23
	VC (%)		86.9 +/- 24.2	33	85.5 +/- 27.3	30	88.9 +/- 23.4	23	83.3 +/- 24.8*	22	76.5 +/- 21.5**	12	77.9 +/- 29.7**	23
DEXA	Whole-body lean body mass (kg)		31.1 +/- 7.1	32	30.6 +/- 7.2	29	30.3 +/- 7.3	23	30.0 +/- 6.5	22	27.7 +/- 5.8	14	28.7 +/- 6.2	20
	Arm lean body mass (kg)		2.7 +/- 1.1	32	2.7 +/- 1.1	29	2.6 +/- 0.9	23	2.7 +/- 1.0	22	2.5 +/- 0.8	14	2.6 +/- 0.9	21
	Leg lean body mass (kg)		8.6 +/- 2.6	32	8.5 +/- 2.5	29	8.5 +/- 2.6	23	8.3 +/- 2.2	22	7.3 +/- 1.7	14	7.7 +/- 2.1	21
CK (IU/L)			268.3 +/- 290.8	33	270.1 +/- 336.9	29	203.0 +/- 228.5	24	186.0 +/- 227.8*	21	177.3 +/- 208.4*	13	151.5 +/- 172.6*	23
ADL score	Barthel index		54.8 +/- 39.6	33	50.4 +/- 38.9	28	54.5 +/- 39.0	21	64.6 +/- 44.2	13	38.8 +/- 33.8	12	42.9 +/- 36.8	21
	mRS		3.6 +/- 1.2	33	3.5 +/- 1.1	28	3.6 +/- 1.1	22	3.3 +/- 1.2	15	3.9 +/- 0.7	12	3.8 +/- 1.1	22
QOL score	SF36	Pyshical functioning	0.0 +/- 19.3	33	-4.9 +/- 15.4	27	1.2 +/- 21.3	16	0.8 +/- 16.3*	14	-2.5 +/- 13.9*	14	-5.1 +/- 16.8*	21
		Role physichal	35.4 +/- 19.1	33	30.7 +/- 17.9	27	30.6 +/- 20.5	16	31.8 +/- 16.0	14	25.1 +/- 18.2	14	27.1 +/- 18.8	21

P-values are calculated relative to baseline data. *: p<0.05, **: p<0.01

		pre		1 year		2 year		3 year		4 year		5 year	
			n		n		n		n		n		n
	Bodily pain	45.1 +/- 11.3	33	42.0 +/- 9.7	27	47.6 +/- 9.7	16	42.5 +/- 11.1	14	43.4 +/- 10.7	14	41.5 +/- 11.7	21
	Social functioning	38.1 +/- 13.9	33	38.6 +/- 15.0	27	35.7 +/- 15.0	16	30.3 +/- 9.4	14	31.7 +/- 19.1	14	34.9 +/- 17.3	21
	General health perceptions	40.0 +/- 9.3	33	39.2 +/- 9.1	27	40.8 +/- 6.8	16	37.0 +/- 7.1	14	35.8 +/- 9.7	14	37.1 +/- 9.0	21
	Vitality	44.5 +/- 10.8	33	42.0 +/- 10.2	27	43.8 +/- 10.5	16	41.4 +/- 8.7	14	39.5 +/- 11.1	14	39.6 +/- 14.8	21
	Role emotinoal	41.8 +/- 16.6	33	40.4 +/- 18.0	27	41.3 +/- 18.9	16	46.3 +/- 8.9	14	38.2 +/- 18.9	14	34.3 +/- 19.9	21
	Mental health	46.0 +/- 11.2	33	47.2 +/- 8.9	27	47.5 +/- 10.2	16	46.7 +/- 7.8	14	43.6 +/- 10.3	14	43.0 +/- 12.6	21
P-values are calculated relative to baseline data. *: p<0.05, **: p<0.01													

Follow-up was disrupted for 5 ambulant patients due to their participation in Phase II/III clinical trials of SA, and 9 patients due to personal reasons (mainly difficulty visiting the hospital due to disease progression). The remaining 22 patients were followed for 5 years, although 9 of these patients missed some of the annual visits. For patients unable to attend all annual visits, we requested that they prioritize attending the 1st year and 5th year evaluations. Of patients who completed the 5th year evaluation, only 4 were able to complete the 6MWT. Two patients lost ambulation, and one patient newly developed multiple sclerosis and nephrotic syndrome, during the follow-up period.

Annual changes in physical status and measurements (Table 2)

Measurement results are shown in Table 2. A total of 30 patients participated in the 1st year follow-up visit. For physical evaluation, 2, 21, 10, 10, and 5 patients were unable to complete the GMFM, 6MWT, HHD, grip power, and pinch power tests at baseline and thus were excluded from the analysis. For 6MWT, HHD, grip power, and pinch power tests, 1, 2, 2, and 6 patients, respectively, scored 0 for these measurements during the 5-year follow-up period. Summed MMT score, 6MWT, GMFM, %FVC, %VC, and grip power significantly differed at the 1st year evaluation compared to baseline.

At the 5th year evaluation, significant reductions in summed MMT (p=0.003), GMFM (p=0.007), grip power (p=0.038), pinch power (p<0.001), %FVC (p=0.001), and %VC (p=0.002) were observed compared to baseline (Table 2, Figure 1). Two patients received non-invasive positive pressure ventilation (NPPV) due to severe nocturnal respiratory failure.

Among the muscle parameters assessed, shoulder extension, shoulder flexion, shoulder abduction, elbow extension, hip flexion, and knee extension showed significant changes at the 5th year evaluation compared to baseline.

Annual changes in parameters among non-ambulant patients (supplementary table3, Figure 2)

We also analyzed the data of non-ambulant participants. At the 5th year evaluation, significant reductions in summed MMT (p=0.006), GMFM (p=0.047), pinch power (p=0.026), %FVC (p=0.001), and %VC (p=0.005) compared to baseline were observed among 20 non-ambulant patients. On the other hand, no significant change in grip power (p=0.185) was observed in comparison with the baseline evaluation, which were significantly reduced among entire population. No significant changes were detected of SF-36 (Supplementary table 3).

ADL and QOL scores (Table 2, Table 3)

Table 3
Correlations between SF-36 and other parameters at initial visit.

		n	physical functioning	Role physical	Bodily Pain	General Health	Vitality	Social Functioning	Role emotional	Mental Health
mean+/- SD		33	-0.039	35.39	45.10	38.07	45.97	39.97	41.827	45.97
SD			19.26	19.13	11.34	13.94	11.21	9.32	16.57	11.21
significance to national standard scores (*p*)			<0.001**	<0.001**	0.019*	<0.001**	0.047*	<0.001**	0.008**	0.041**
correlation (ρ)	Summed MMT	33	0.898**	0.100	0.313	-0.279	0.003	0.089	0.07	-0.013
	GMFM	29	0.928**	0.182	0.459*	-0.195	0.075	0.077	0.054	0.051
	6MWT	12	0.731**	0.396	0.102	-0.173	-0.289	0.363	-0.107	-0.301
	HHD	23	0.592**	-0.019	0.003	-0.346	0.015	-0.014	-0.106	-0.206
	Grip power	23	0.738**	-0.159	-0.248	-0.409	-0.439	-0.122	-0.369	−0.427*
	Pinch power	27	0.637**	0.310	0.205	-0.022	0.199	-0.011	0.199	-0.011
	%FVC	33	0.638**	0.105	0.422*	−0.488**	0.004	0.14	0.144	0.038
	%VC	33	0.674**	0.091	0.386*	−0.465**	0.011	0.122	0.163	0.067
	CK (IU/L)	33	0.583**	0.060	0.301	−0.377*	0.059	0.219	-0.001	0.049
	DEXA whole body	32	0.434*	-0.191	-0.010	-0.464**	-0.113	-0.116	-0.26	-0.229
	DEXA arm	32	0.315	-0.207	-0.159	-0.393*	-0.161	-0.124	-0.305	-0.319
	DEXA legs	32	0.524**	-0.144	-0.024	-0.416**	-0.063	-0.079	-0.180	-0.162
	BI	33	-0.742**	-0.119	-0.285	0.214	0.009	-0.157	-0.13	-0.016
	mRS	33	0.902**	0.199	0.342	-0.226	0.086	0.147	0.146	0.109

*: p<0.05, **: p<0.01. All assessed subscales had significantly lower scores than the national standard index (score=50). Motor function measures, respiratory function, whole body and leg lean body mass, and ADL scores were significantly correlated with the Physical Functioning subscale.

No significant changes were observed in mRS and BI during the 5-year follow-up period. Among the subscales of SF-36, only scores for Physical Functioning were significantly reduced at the 3rd, 4th, and 5th year evaluations compared to baseline (Table 2).

National standard scores for SF-36 were used to evaluate QOL. All assessed subscales had significantly lower scores than the national standard index (score=50). Motor function measures (summed MMT, GMFM, 6MWT, grip power, and pinch power), respiratory function (%VC and FVC), whole body and leg lean body mass, and ADL scores (BI and mRS) were significantly correlated with the Physical Functioning subscale (Table 3).

Correlation between quantitative items and simplified items, DEXA, and CK (Supplementary table 4)

Summed MMT and GMFM were well correlated with pinch power, grip power, %VC or %FVC, CK, and DEXA (legs). These items were also correlated with certain muscle MMT scores (e.g., elbow flexion and knee extension).

Discussion

To our knowledge, this study is the first to assess the 5-year natural history of GNE myopathy. In our previous 1-year observational study, not all parameters assessed at the 1st year evaluation were significantly different compared to baseline [8]. Thus, in the present study, the follow-up period was extended to 5 years. MMT, GMFM, grip power, pinch power, %FVC, %VC, leg lean body mass, CK, and the Physical Functioning subscale of the SF-36 showed significant changes at the 5th year evaluation compared to baseline. On the other hand, no significant changes were observed for 6MWT, HHD, arm and truncal body mass, BI, mRS, and other SF-36 subscales. The lack of change in the 6MWT during the follow-up period could be explained by the small number of patients who could be tested and the exclusion of patients due to their participation in clinical trials. Among the muscles evaluated by MMT, shoulder girdle muscles showed continuous significant changes, even as early as at the 1st year evaluation, suggesting that MMT of shoulder girdle muscles may be useful to include in evaluations for clinical trials and natural history studies.

While a previous observational study of GNE myopathy patients assessed HHD over the course of 3 years [15], the quantitative measurement of many muscles is not realistic for routine clinical visits. In contrast, our study clearly demonstrated the utility of summed MMT score as well as shoulder muscle MMT scores, in addition to other laboratory parameters. Importantly, these items are easy to measure during clinical visits and do not overly burden evaluators and patients.

For severely affected, non-ambulant patients, walking parameters and grip power are not always useful. We evaluated clinical parameters in non-ambulant patients and found significant reductions in all items, except for grip power, which showed significant reductions in the analysis of the entire population at the 5th year evaluation. As 43% of the Japanese patients were non-ambulant, items for non-ambulant patients were quite important. Although we did not analyze data from ambulant patients due to the small sample size, the simplified items identified in the present study may be useful in clinical practice, even in outpatient settings with limited labor force.

Physical functioning subscales of SF-36 were significantly correlated to other evaluation items. Therapeutic approach could be ameliorate QOL of GNE myopathy patients, and SF-36 physical functioning can be useful for self-reporting evaluation.

This study has some limitations. First, the small number of patients, especially ambulant patients, did not allow us to draw conclusions regarding the utility of 6MWT. Second, the evaluation of ADL was limited to the use of mRS and BI, which are not sensitive enough to detect temporal disease progression. Using disease-specific scales, such as the GNE Myopathy Functional Activity Scale, may be an alternative, but it was not used from the beginning of our study period.

In conclusion, MMT, GMFM, pinch power, CK, %FVC, %VC, DEXA lean body mass, and the Physical Functioning subscale of the SF-36 may be useful for the long-term evaluation of GNE myopathy patients.

Abbreviations

ADL: ability of daily living

BI: Barthel Index

CK: creatine kinase

DEXA: dual-energy X-ray absorptiometry

ECG: electrocardiography

FVC: forced vital capacity

GMFM: Gross Motor Function Measure

HHD: hand-held dynamometer of quadriceps

MAGiNE : Multi-Center Study of ManNAc for GNE Myopathy

MMT: manual muscle testing

MNK: N-acetylmannosamine kinase

mRS: modified Rankin scale

6MWT: 6-minute walk test

NCNP: National Center of Neurology and Psychiatry, Japan

QOL: quality of life

SD: standard deviation

SF-36: 36-item short form survey national standard score

UDP-GlcNAc: uridinediphosphate-*N*-acetylglucosamine

Declarations

Ethics approval and consent form

This study have been performed in accordance with the Declaration of Helsinki ,and was approved by the Medical Ethics Committee of the NCNP (20-9-Ji6 and A2018-024). Study objectives, design, risks, and benefits of participation were explained to all patients, and their written informed consent was obtained prior to enrollment.

Consent for publication

Not applicable

Availability of data and materials

This study included articles which are available via PubMed. All information analyzed in this study was collected in a dataset, which is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was partly supported by Research on Intractable Diseases of Health and Labour Sciences Research Grants and and Intramural Research Grants (2-4, 2-6) for Neurological and Psychiatric Disorders from the National Center of Neurology and Psychiatry.

Author's contributions

M.MY designed the study, conducted the literature search, collected, analyzed and interpreted the data, and drafted the first manuscript. H.Y. collected and interpreted the data and drafted the manuscript. Y.O. and S.N collected and interpreted the data and revised the manuscript for intellectual content. I.N. and Y.T. drafted the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank all participants and members of the Patients Association for Distal Myopathies in Japan (PADM).

References

[1] Nonaka I, Sunohara N, Satoyoshi E, Terasawa K, Yonemoto K. Autosomal recessive distal muscular dystrophy: a comparative study with distal myopathy with rimmed vacuole formation. Ann Neurol. 1985;17(1):51-9.

[2] Argov Z, Yarom R. “Rimmed vacuole myopathy” sparing the quadriceps. A unique disorder in Iranian Jews. J Neurol Sci. 1984;64(1):33-43.

[3] Nishino I, Noguchi S, Murayama K, Driss A, Sugie K, Oya Y, et al. Distal myopathy with rimmed vacuoles is allelic to hereditary inclusion body myopathy. Neurology. 2002;59(11):1689-93.

[4] Eisenberg I, Avidan N, Potikha T, Hochner H, Chen M, Olender T, et al. The UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase gene is mutated in recessive hereditary inclusion body myopathy. Nat Genet. 2001;29(1):83-7.

[5] Kayashima T, Matsuo H, Satoh A, Ohta T, Yoshiura K, Matsumoto N, et al. Nonaka myopathy is caused by mutations in the UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase gene (GNE). J Hum Genet. 2002;47(2):77-9.

[6] Keppler OT, Hinderlich S, Langner J, Schwartz-Albiez R, Reutter W, Pawlita M. UDP–GlcNAc 2-epimerase: a regulator of cell surface sialylation. Science. 1999;284(5418):1372-6.

[7] Malicdan MC, Noguchi S, Nishino I. Recent advances in distal myopathy with rimmed vacuoles (DMRV) or hIBM: treatment perspectives. Curr Opin Neurol. 2008;21(5):596-600.

[8] Malicdan MC, Noguchi S, Hayashi YK, Nonaka I, Nishino I. Prophylactic treatment with sialic acid metabolites precludes the development of the myopathic phenotype in the GNE myopathy mouse model. Nat Med. 2009;15(6):690-5.

[9] Mori-Yoshimura M, Oya Y, Yajima H, Yonemoto Y, Kobayashi Y, Hayashi YK, et al. GNE myopathy: a prospective natural history study of disease progression. Neuromuscul Disord. 2014;24(5):380-6.

[10] 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(1):84-8.

[11] Kondo I, Fukuda M. Gross motor functional measure manual. 2nd ed. Tokyo, Japan: Igaku-Shoin; 2000. p. 1-124. (in Japanese)

[12] Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147(8): 755-63.

[13] Hosoda T, Yanagisawa K. Handbook of Physiotherapy. 3rd ed. Tokyo, Japan: Igaku-Shoin; 2000. p. 675-7. (in Japanese)

[14] Fukuhara S, Suzukamo U. Manual of SF-36v2 Japanese version. 2009 ed. Kyoto, Japan: Institute for Health Outcomes & Process Evaluation Research; 2000. p. 1-127. (in Japanese)

[15] Lochmüller H, Behin A, Tournev I, Tarnopolsky M, Horváth R, Pogoryelova O, et al. Results from a 3-year Non-interventional, Observational Disease Monitoring Program in Adults with GNE Myopathy. J Neuromuscul Dis. 2021;8(2):225-234.

Figures

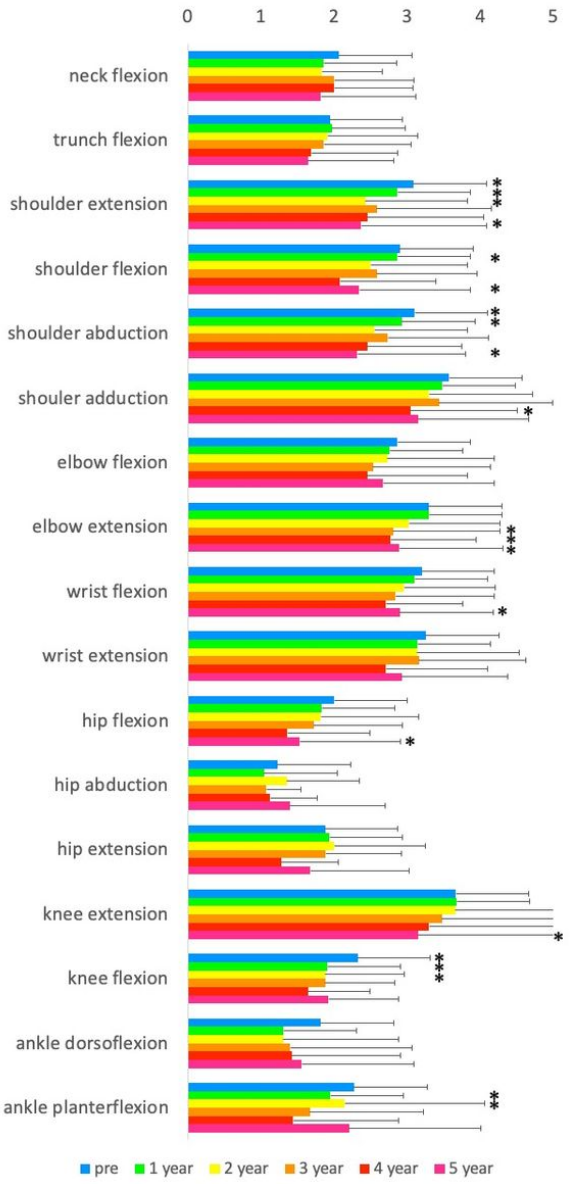

Figure 1

Annual changes in assessed parameters Manual muscle testing at baseline and annual follow-ups. *p < 0.05

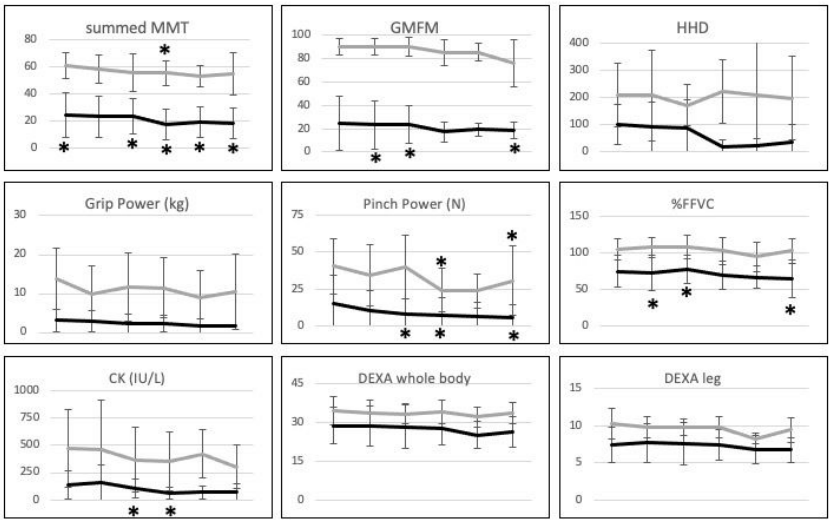

Figure 2

Annual changes in summed MMT, GMFM, Hand-Held Dinamomator (HHD) of knee extension, grip power, pinch power, %FVC, CK, DEXA whole body and DEXA lages of ambulant (gray line) and non-ambulant (black line) participants. *p < 0.05 of baseline.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1genotype.docx
- Supplementaytable2.docx
- supplementarytable3.docx
- Supplementarytable4.docx