Complications in GNE myopathy patients: A nationwide repository questionnaire survey in Japan

Wakako Yoshioka
National Center of Neurology and Psychiatry https://orcid.org/0000-0003-0724-0018
Reiko Shimizu
National Center of Neurology and Psychiatry
Yuji Takahashi
National Center of Neurology and Psychiatry
Yuriko Oda
Patient Association for Distal Myopathies
Sumiko Yoshida
National Center of Neurology and Psychiatry
Nahoko Ishihara
National Center of Neurology and Psychiatry
Ichizo Nishino
National Center of Neurology and Psychiatry
Harumasa Nakamura
National Center of Neurology and Psychiatry
Madoka Mori-Yoshimura (yoshimur@ncnp.go.jp)
Department of Neurology, National Center Hospital https://orcid.org/0000-0003-4312-9114

Research

Keywords: muscle disease, immune thrombocytopenia, sleep apnea syndrome, GNE myopathy

Posted Date: January 7th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-139896/v1

Abstract

Background

GNE myopathy is a rare autosomal recessive adult-onset distal myopathy caused by biallelic pathogenic variants in *GNE*. Although some complications associated with GNE myopathy have been reported, little is known about whether they are disease-specific and how often they present. This study aimed to characterize complications of GNE myopathy.

Methods

We conducted a questionnaire survey of GNE myopathy patients registered in a national registry in Japan. The questionnaire requested information regarding immune thrombocytopenia (ITP), cardiac involvement, respiratory involvement, sleep apnea syndrome (SAS), and psychiatric diseases.

Results

The response rate was 62.4% (126/198), yielding a total of 51 male and 75 female participants. Of the participants, 4.1% (5/123) had a diagnosis of ITP, and 16.3% (8/49) of males and 6.6% of females (5/76) had a diagnosis of SAS. In total, 0.8% (1/126) of participants had pervasive developmental disorder and 14.7% (16/109) had a psychiatric disease.

Conclusion

The frequencies of ITP and SAS among Japanese GNE myopathy patients were higher than those observed in the general Japanese population. Routine blood tests and evaluation of sleep-disordered breathing should be considered in order to better manage GNE myopathy patients.

Background

GNE myopathy is a rare adult-onset progressive myopathy caused by biallelic *GNE* pathogenic variants. The disorder is also referred to as distal myopathy with rimmed vacuoles (DMRV), Nonaka myopathy, and hereditary inclusion body myopathy (hIBM), and is now recognized as a global disorder with an estimated frequency of about 1/1,000,000. The frequency is higher in Japan, with a total of about 250–400 Japanese patients. GNE myopathy preferentially affects the tibialis anterior muscles first and slowly progresses to involve proximal leg musculature and the upper limbs, usually sparing the quadriceps femoris muscles even in advanced stages [1]. While recent studies have reported on progression and genotype-phenotype correlations [2, 3, 4], little is known about complications associated with the disorder.

Data from three cohorts of GNE myopathy patients have been published: a data analysis of 269 patients from the patient-reported registry of the GNE Myopathy Disease Monitoring Program (GNEM-DMP; a global registry of GNE myopathy) [2], a data analysis of 121 Japanese patients from Remudy-GNE myopathy (a nationwide registry of Japanese GNE myopathy patients) [3], and a natural history study of 24 Japanese GNE myopathy patients [4]. These studies were focused on progression of the disease and genotype-phenotype correlations, although a limited medical history analysis of concomitant conditions was included. For instance, in the GNE-DMP registry study, several cases of cardiac conduction abnormalities, cardiomyopathy, and respiratory difficulty were reported, with respiratory difficulties observed in advanced stages of the disease [2]. In the Remudy-GNE myopathy study, 34% (26/77) of participants had respiratory dysfunction, and several had a history of immune thrombocytopenia (ITP) and complications of obstructive sleep apnea syndrome (SAS), hypertension, diabetes mellitus, and hyperlipidemia [3]. However, these studies were not focused on complications, and data on complications were obtained by a free description-type question, rendering it difficult to extract information regarding frequency and risk. Accordingly, the present study aimed to collect comprehensive and accurate data regarding complications of GNE myopathy via a questionnaire survey using close-ended questions. Understanding complications of GNE myopathy may allow for early management and intervention in this patient population.

Materials And Methods

Registration

A national registry for neuromuscular diseases in Japan (Remudy; http://www.remudy.jp/) was developed in 2009 and supported by Intramural Research Grants (26 – 7) for Neurological and Psychiatric Disorders from the National Center of Neurology and Psychiatry (NCNP). Patient diagnoses were confirmed genetically based on biallelic *GNE* pathogenic variants or clinically by monoallelic pathogenic variant combined with typical clinical symptoms and pathological findings such as rimmed vacuoles. Details regarding the registry have been described previously [3, 5].

Participants and questionnaire survey

A questionnaire with a linkable anonymized ID was distributed to 202 GNE myopathy patients (80 males and 122 females) who were registered in the Remudy database as of April 2019. The questionnaire was mailed to the patients, and those who responded did so by postal mail or e-mail (PDF file) via the Remudy homepage. Reminders were sent to those who had not responded. The Patient Association of Distal Myopathies (PADM) also e-mailed their patients to request cooperation with the survey.

The questionnaire requested the following information: muscle symptoms, treatment, and systemic complications. Systemic complications such as ITP, cardiac involvement, respiratory involvement, SAS, and psychiatric diseases were included in the questionnaire, and participants were asked to include any other complications they had (Supplementary Table 1). Information regarding age of disease onset, pathogenic variants, height, body weight, and respiratory function were collected from the Remudy

database. Age of disease onset was defined as the age when participants became aware of GNE myopathy symptoms, rather than the age at diagnosis or when test abnormalities were detected.

Data analysis

Data are presented as mean ± standard deviation (SD), median, range, frequency, and percentage, as indicated. We calculated 95% confidence intervals (CIs) of the frequency of complications and compared them with the frequency reported for the general Japanese population using Fisher's exact test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using EZR on R 3.5.2 and R commander 2.5-1.

Results

Background characteristics

Of the 198 GNE myopathy patients (78 males and 120 females) who received the questionnaire, the 126 (51 males and 75 females) (62.4%) who responded were considered participants of this study (Fig. 1). Mean participant age was 48.9 ± 12.1 years (median, 48 years; range, 25–76 years) and mean age of onset was 29.1 ± 9.4 years (median, 29 years; range, 12–62 years). There were no significant differences in distribution of ages among participants and non-participants (data not shown). Of the participants, 98.4% (124/126) were diagnosed genetically with biallelic *GNE* pathogenic variants, 23.0% (29/126) were homozygotes, and 75.4% (95/126) were compound heterozygotes, while 1.6% (2/126) were diagnosed clinically with a single heterozygous pathogenic variant combined with clinical symptoms and pathological features. Two pathogenic variants were frequent among participants: 88.8% (112/126) carried both or either of c.620A > T (p.D207V) and c.1807G > C (p.V603L). Of those harboring these pathogenic variants, 10.3% (13/126) were able to walk without assistance, 45.2% (57/126) used assistive devices such as sticks or orthoses for walking, and 43.7% (55/126) were unable to walk (Table 1).

Table 1
Participant characteristics

Age		n	Mean age (years) [SD]
	At survey	126	48.9 [12.1]
	Onset	126	29.1 [9.4]
	Assistive device usage *[1]	95	37.4 [12.4]
	Wheelchair usage *[2]	80	37.5 [11.5]
Walking ability at survey		**n**	**% [95% CI]**
	Ambulant without assistance	13	10.3 [5.6–17.0]
	Ambulant with assistive devices	57	45.2 [36.4–54.3]
	Non-ambulant	55	43.7 [34.8–52.8]
	No answer	1	0.8 [0.0- 4.3]
Genetic diagnosis*[3]		**n**	**% [95% CI]**
	Homozygotes	29	23.0 [16.0-31.4]
	p.V603L homozygotes	24	19.0 [12.6–27.0]
	Compound heterozygotes	95	75.4 [66.9–82.6]
	p.D207V / p.V603L	35	27.8 [20.2–36.5]
	p.D207V / other pathogenic variant	33	26.2 [18.8–34.8]
	p.V603L / other pathogenic variant	18	14.3 [8.7–21.6]
	Heterozygotes	2	1.6 [0.2–5.6]
		(All p.V603L heterozygotes)	

*[1] Analyzed 95 participants who currently or previously used assistive devices and responded to the questionnaire.

*[2] Analyzed 80 participants who currently or previously used a wheelchair and responded to the questionnaire.

*[3] Data from the Remudy database. Other data were obtained from the questionnaire.

Immune thrombocytopenia

Among the participants, 4.1% (5/123) had a previous or current diagnosis of ITP (123/126 participants analyzed due to missing data) (Table 2). All five participants who had a diagnosis of ITP were compound heterozygotes carrying c.1807G > C (p.V603L) in one allele. The pathogenic variant of the other allele was

c.131G > C (p.C44S), c.395G > A (p.R132H), c.1351C > T (p.R451*), c.1664C > T (p.A555V), or c.1864G > A (p.A622T). Disease duration and age of onset did not differ between participants with or without ITP (data not shown).

Sleep apnea syndrome and respiratory dysfunction

Respiratory function data of 56 participants who were tested with a spirometer within two years of the questionnaire survey were analyzed. There was no correlation between forced vital capacity (%FVC) and age of onset or disease duration (Figs. 2a, 2b). Mean age of onset and mean disease duration of the seven participants with low %FVC (< 60%) were 17.4±4.6 years (median, 15 years; range, 14–28 years) and 26.3±6.2 years (median, 27 years; range, 17–36 years), respectively, suggesting a younger age of onset and longer disease duration compared to the entire study population.

SAS was diagnosed in 10.4% (13/125) of participants, corresponding to 16.3% (8/49) of males and 6.6% (5/76) of females in the study population. Of these, 4.0% (5/125) were currently using continuous positive airway pressure (CPAP), 1.6% (2/125) previously used CPAP, and 4.8% (6/125) had never used CPAP (125/126 participants analyzed due to missing data). There were no significant differences between participants with and without SAS for disease duration ($p = 0.078$) (Fig. 2c), % forced vital capacity (%FVC) ($p = 0.31$) (Fig. 2d), body mass index (BMI) ($p = 0.07$) (Fig. 2e), and current age ($p = 0.15$).

Cardiac complications

In total, 17.4% (21/125) of participants indicated having a current or past history of cardiac abnormalities: 9.9% (12/125) with arrhythmia, 1.7% (2/125) with valvular heart disease, 1.7% (2/125) with hypertrophic cardiomyopathy, 0.7% (1/125) with coronary artery disease, and 3.3% (4/125) did not know the name or the category of the disease (125/126 participants analyzed due to missing data) (Table 2).

Table 2
Systemic complications

			n	Frequency in GNEM participants % [95% CI]
Immune thrombocytopenia[*1]	Previous / current diagnosis		5	4.1 [1.4–9.4]
	Never diagnosed		118	95.9 [90.6–98.6]
Sleep apnea syndrome[*2]	Previous diagnosis		13	10.4 [5.7–17.1]
	Males		8	16.3 [7.3–29.7]
	Females		5	6.6 [2.2–14.7]
	C	Currently using CPAP	5	4.0 [1.3–9.1]
		Previously used CPAP	2	1.6 [0.2–5.7]
		Never used CPAP	6	4.8 [1.8–10.2]
	Never diagnosed		112	89.6 [82.9–94.3]
Heart complications	Arrhythmia		12	9.9 [5.2–16.7]
	Valvular heart disease		2	1.7 [0.2–5.8]
	Hypertrophic cardiomyopathy		2	1.7 [0.2–5.8]
	Coronary artery disease		1	0.7 [0.0- 4.5]
	Diagnosis unknown		4	3.3 [0.9–8.2]
	No abnormality		100	82.6 [74.7–88.9]

CPAP: continuous positive airway pressure, GNEM: GNE myopathy

[*1] Analyzed 121/126 participants due to missing data (no response) or answer unknown.

[*2] Analyzed 123/126 participants due to missing data (no response) or answer unknown.

Developmental disorders and psychiatric diseases

None of the participants indicated having an intellectual disorder, but 0.8% (1/126) reported having pervasive developmental disorder, in particular, attention deficit hyperactivity disorder (ADHD). In total, 14.7% of participants reported having a psychiatric disease: neurosis (n = 7), depression (n = 4), alcohol abuse (n = 1), and anorexia (n = 1). The breakdown for those with neurosis was as follows: adjustment disorder (n = 4), panic disorder (n = 2), and obsessive-compulsive disorder (n = 1). One participant with

depression also experienced anorexia. Four participants did not know the name of the disorder. The frequency of those who had experienced problematic behavior during school years was 3.2% (4/123): truancy (n = 4), attempted suicide (n = 2), and domestic violence (n = 1) (Table 3).

Table 3
Developmental disorders, psychiatric diseases and problematic behavior

		n	Frequency in GNEM participants % [95% CI]
Developmental disorders	Pervasive developmental disorder	1	0.8 [0.0-4.3]
	Never diagnosed	125	99.2 [9.6–100.0]
Psychiatric diseases*	Neurosis	7	6.4 [2.6–12.8]
	Adjustment disorder	4	3.7 [1.0-9.1]
	Panic disorder	2	1.8 [0.2–6.5]
	Obsessive-compulsive disorder	1	0.9 [0.0–5.0]
	Depression	4	3.7 [1.0-9.1]
	Alcoholism	1	0.9 [0.0–5.0]
	Anorexia	1	0.9 [0.0–5.0]
	Diagnosis unknown	4	3.7 [1.0-9.1]
	Never diagnosed	93	85.3 [77.3–91.4]
Problematic behavior*	Had problematic behavior	4	3.2 [0.9-8.0]
	Truancy	4	3.2 [0.9-8.0]
	Suicide	2	1.6 [0.2–5.7]
	Domestic violence	1	0.8 [0.0-4.4]
	Never had problematic behavior	121	96.8 [92.0-99.1]

GNEM: GNE myopathy

* Multiple answers allowed.

Discussion

To our knowledge, we describe the first comprehensive survey of complications among GNE myopathy patients. This survey will contribute to better manage GNE myopathy patients and help physicians provide early diagnosis and treatment.

Previous studies have reported thrombocytopenia in three Japanese GNE myopathy patients [6], two Chinese siblings with GNE myopathy [7], and a Caucasian woman with GNE myopathy [8], but no study had assessed its frequency in a larger cohort of GNE myopathy patients. In the present study, 4.1% (5/123) of participants had a diagnosis of ITP. However, given the lack of data on the frequency of ITP collected in the same manner for the general Japanese population, the risk is difficult to evaluate. Nonetheless, based on the reported frequency of ITP for the general Japanese population of 2.16/100,000/yr[1)][9], about 0.2% of Japanese people are estimated to have ITP, suggesting that the frequency of ITP among GNE myopathy patients is much higher than that of the general Japanese population.

Pathogenic *GNE* variants lead to decreased enzymatic activities of UDP-N-acetylglucosamine 2-epimerase (UDP-GlcNAc 2-epimerase) / N-acetylmannosamine kinase (ManNAc kinase), the rate-limiting enzyme of sialic acid biosynthesis encoded by the *GNE* gene [10]. UDP-GlcNAc 2-epimerase was reported to regulate cell surface sialylation in human hematopoietic cell lines and the function of specific cell surface adhesion molecules [11]. Moreover, a correlation between the shortening of mean platelet life span after removal of sialic acid and an increase in platelet-associated IgG has been reported [12]. These results suggest that pathogenic *GNE* variants may lead to cell surface hyposialylation and impair cell surface adhesion molecules in platelets, inducing antigens that bind to IgG on the platelet membrane, ultimately leading to thrombocytopenia. The high incidence of ITP observed in GNE myopathy patients in our survey suggests a potential relationship between pathogenic *GNE* variants and ITP, highlighting the importance of conducting routine blood tests in these patients. Further studies on this topic, such as a matched cohort study comparing GNE myopathy patients with the general population, are warranted.

The frequency of SAS in the general Japanese population is estimated to be about 3.3% in males and 0.5% in females [13]. In the present survey, 16.3% of males and 6.6% of females had a diagnosis of SAS. Although those who indicated having SAS in our survey might include those whose SAS had been cured, overall the results point to Japanese GNE myopathy patients having a higher frequency of SAS than the general Japanese population. SAS is reportedly associated with many muscle diseases, such as acid maltase deficiency [14, 15], Duchenne muscular dystrophy [16], myotonic dystrophy [17], oculopharyngeal muscular dystrophy [18], facioscapulohumeral muscular dystrophy [19], and inflammatory myopathy [20]. Specific features of neuromuscular diseases, such as pharyngeal weakness, macroglossia, bulbar manifestations, and low lung volume, might increase the susceptibility of patients to sleep-disordered breathing. To our knowledge, no study has reported on the association between SAS and GNE myopathy. The main risk factor for obstructive SAS is obesity and BMI [21]. Therefore, we compared BMI between participants with and without SAS, but found no significant difference between the two groups (data not shown). In addition, no correlation was observed between the frequency of SAS and %FVC, indicating that diaphragm weakness is unlikely to be a major cause of SAS among GNE myopathy patients. Muscle weakness of the upper airway muscles could contribute to SAS, however, they are not evaluated in majority of GNE myopathy patients. Upper airway muscle function had better be examined among GNE myopathy patients. Since SAS is considered to pose a greater risk for death than diabetes mellitus and

stroke [22], screening for SAS in GNE myopathy patients will be important for early diagnosis and therapeutic intervention.

Frequencies of valvular heart disease, hypertrophic cardiomyopathy, and coronary artery disease in the general Japanese population have been reported to be 20%, 0.02%, and 0.8%, respectively [23–25]. Frequencies of valvular heart disease and coronary artery disease did not significantly differ between our study population and the general Japanese population. Hypertrophic cardiomyopathy was observed in 1.7% (2/125) of participants, although the number of the affected individuals are so small and difficult to glean useful comparison. Two GNE myopathy siblings with cardiomyopathy have been reported previously [26]. In contrast, disease-specific cardiac involvement was not observed in the present survey and the previous GNEM-DMP survey [2]. While it is possible some patients may not be regularly monitoring cardiac function, prospective data collection will be necessary to draw conclusions.

Frequencies of developmental disorders, psychiatric diseases, and problematic behaviors were not significantly higher in the present study population compared to the general Japanese population [5, 27–30], suggesting that GNE myopathy may not impact central nervous system development and may not be associated with psychiatric diseases. Interestingly, our previous Remudy-questionnaire survey conducted among Becker muscular dystrophy patients revealed that 7.2% and 12.0% of participants had developmental disorders and problematic behavior, respectively [31]. These frequencies are higher than that observed in our present study population. Psychiatric diseases observed among physically disabled patients tend to be lumped together, but it is important to be aware that the risk of developing a psychiatric disease differs by underlying disease.

This study has some limitations. First, the range of 95% CIs was wide and thus may have hindered the detection of significant differences due to the small sample size. Nonetheless, it is difficult to secure a large sample size with this very rare disease, and the present study represents one of the largest surveys of complications in GNE myopathy patients conducted to date. Second, self-reported data are not objective and it was difficult to obtain details of the disease for some of the questions as the patients did not remember the name of the disease. Third, there may have been selection bias, as those with severe phenotypes may have been more willing to participate in the national registry. Fourth, we did not adopt a matched case-control design, therefore, other factors such as age or frequency of medical examination might have affected the frequency. Notwithstanding these potential limitations, we believe that this first and largest survey of complications in GNE myopathy patients will raise awareness among physicians which could potentially lead to early diagnosis and early therapeutic invention.

In conclusion, GNE myopathy was found to be associated with ITP and SAS. For better management of GNE myopathy patients, physicians should be mindful of these complications and test for blood cell counts and sleep-disordered breathing in routine clinical assessments. A natural history study of a large GNE myopathy patient cohort, including an assessment of these complications, would be highly informative.

Abbreviations

ADHD
attention deficit hyperactivity disorder
BMI
body mass index
CI
confidence interval
CPAP
continuous positive airway pressure
DMRV
distal myopathy with rimmed vacuoles
FVC
forced vital capacity
GNEM-DMP
GNE Myopathy Disease Monitoring Program
hIBM
hereditary inclusion body myopathy
ITP
immune thrombocytopenia
ManNAc
UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine
NCNP
National Center of Neurology and Psychiatry
PADM
Patient Association of Distal Myopathies
Remudy
national registry for neuromuscular diseases in Japan
SAS
sleep apnea syndrome
SD
standard deviation
UDP-GlcNAc
UDP-N-acetylglucosamine

Declarations

Ethics approval and consent to participate: All patients registered in Remudy were informed that their data would be removed from the registry or shared with them immediately upon request. The registration process was approved by the Medical Ethics Committee of the NCNP (A2011-079). The present study

was also approved by the same committee (A2018-105), and patients were informed that refusal to participate would not affect their medical care and that their consent would be confirmed by the return of their questionnaires.

Consent for publication: All patients were provided with an explanation of the objectives, design, benefits, and risks of the study, and that their responses would be published. Consent for publication was considered to have been provided upon receipt of a response to the questionnaire.

Availability of data and material: Any data that support the findings of this study are available from the corresponding author, Madoka Mori-Yoshimura, upon reasonable request.

Competing interests: The authors have no conflicts of interest to report.

Funding: This work was partly supported by Research on Intractable Diseases of Health and Labor Sciences Research Grants, Comprehensive Research on Disability Health and Welfare Grants, Research and Development Grants for Comprehensive Research for Persons with Disabilities and Practical Research Project for Rare / Intractable Diseases from the Japan Agency for Medical Research and Development, AMED, Health and Labor Science Research Grants, and an Intramural Research Grant (29-3, 29-4) for Neurological and Psychiatric Disorders from the NCNP.

Authors contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Wakako Yoshioka and Madoka Yoshimura-Mori. The first draft of the manuscript was written by Wakako Yoshioka and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements: We are grateful to the members of Remudy and the members of the Patient Association for Distal Myopathies in Japan (PADM) for their collaboration.

References

1. Nishino I, Carrillo-Carrasco N, Argov Z. GNE myopathy: current update and future therapy. J Neurosurg Psychiatry 2015;86:385-392.
2. Pogoryelova O, Gonzalez Coraspe JA, Nikolenko N, Lochmuller H, Roos A. GNE myopathy: from clinics and genetics to pathology and research strategies. Orphanet J Rare Dis 2018;13:70.
3. Mori-Yoshimura M, Hayashi YK, Yonemoto N, Nakamura H, Murata M, Takeda S, et al. Nationwide patient registry for GNE myopathy in Japan. Orphanet J Rare Dis 2014;9:150.
4. Mori-Yoshimura M, Oya Y, Yajima H, Yonemoto N, Kobayashi Y, Hayashi YK, et al. GNE myopathy: a prospective natural history study of disease progression. Neuromuscul Disord 2014;24:380-386.
5. Nakamura H, Kimura E, Mori-Yoshimura M, Komaki H, Matsuda Y, Goto K, et al. Characteristics of Japanese Duchenne and Becker muscular dystrophy patients in a novel Japanese national registry of muscular dystrophy (Remudy). Orphanet J Rare Dis 2013;8:60.

6. Izumi R, Niihori T, Suzuki N, Sasahara Y, Rikiishi T, Nishiyama A, et al. GNE myopathy associated with congenital thrombocytopenia: a report of two siblings. Neuromuscul Disord 2014;24(12):1068-1072.
7. Zhen C, Guo F, Fang X, Liu Y, Wang X. A family with distal myopathy with rimmed vacuoles associated with thrombocytopenia. Neurol Sci 2014;35(9):1479-1481.
8. Paul P, Liewluck T. Distal myopathy and thrombocytopenia due to a novel GNE mutation. J Neurol Sci 2020;415:116954.
9. Kurata Y, Fujimura K, Kuwana M, Tomiyama Y, Murata M. Epidemiology of primary immune thrombocytopenia in children and adults in Japan: a population-based study and literature review. Int J Hematol 2011;93(3):329-335.
10. Hinderlich S, Weidemann W, Yardeni T, Horstkorte R, Huizing M. UDP-GlcNAc 2-Epimerase/ManNAc Kinase (GNE): A Master Regulator of Sialic Acid Synthesis. Top Curr Chem 2015;366:97-137.
11. Keppler OT, Hinderlich S, Langner J, Schwartz-Albiez R, Reutter W, Pawlita M. UDP-GlcNAc 2-epimerase: a regulator of cell surface sialylation. Sci 1999;284(5418):1372-1376.
12. Kotzé HF, van Wyk V, Badenhorst PN, Heyns AD, Roodt JP, Lötter MG. Influence of platelet membrane sialic acid and platelet-associated IgG on ageing and sequestration of blood platelets in baboons. J Thromb Haemost 1993;70(4):676-680.
13. Society. TJC. Guidelines for Diagnosis and Treatment of Sleep Disordered Breathing in Cardiovascular Disease（JCS 2010）. Circ J 2010;74(Suppl.11):1053-1084.
14. Margolis ML, Howlett P, Goldberg R, Eftychiadis A, Levine S. Obstructive sleep apnea syndrome in acid maltase deficiency. Chest 1994;105(3):947-949.
15. Mellies U, Ragette R, Schwake C, Baethmann M, Voit T, Teschler H. Sleep-disordered breathing and respiratory failure in acid maltase deficiency. Neurology 2001;57(7):1290-1295.
16. Suresh S, Wales P, Dakin C, Harris MA, Cooper DG. Sleep-related breathing disorder in Duchenne muscular dystrophy: disease spectrum in the paediatric population. J Paediatr Child Health 2005;41(9-10):500-503.
17. Quera Salva MA, Blumen M, Jacquette A, Durand MC, Andre S, De Villiers M, et al. Sleep disorders in childhood-onset myotonic dystrophy type 1. Neuromuscul Disord 2006;16(9-10):564-570.
18. Dedrick DL, Brown LK. Obstructive sleep apnea syndrome complicating oculopharyngeal muscular dystrophy. Chest 2004;125(1):334-336.
19. Della Marca G, Frusciante R, Dittoni S, Vollono C, Buccarella C, Iannaccone E, et al. Sleep disordered breathing in facioscapulohumeral muscular dystrophy. J Neurol Sci 2009;285(1-2):54-58.
20. Selva-O'Callaghan A, Sampol G, Romero O, Lloberes P, Trallero-Araguás E, Vilardell-Tarrés M. Obstructive sleep apnea in patients with inflammatory myopathies. Muscle Nerve 2009;39(2):144-149.
21. Hannon TS, Rofey DL, Ryan CM, Clapper DA, Chakravorty S, Arslanian SA. Relationships among obstructive sleep apnea, anthropometric measures, and neurocognitive functioning in adolescents with severe obesity. J Pediat 2012;160(5):732-735.

22. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. NEJM 2005;353(19):2034-2041.
23. Doi K, Ogawa H, Ishigami K, Ikeda S, Aono Y, Hamatani Y, et al. Impact of Valvular Heart Disease on Mortality, Thromboembolic and Cardiac Events in Japanese Patients With Atrial Fibrillation- The Fushimi AF Registry. Circ J 2020;84(5):714-722.
24. Miura K, Nakagawa H, Morikawa Y, Sasayama S, Matsumori A, Hasegawa K, et al. Epidemiology of idiopathic cardiomyopathy in Japan: results from a nationwide survey. Heart 2002;87(2):126-130.
25. Yatsuya H, Iso H, Li Y, Yamagishi K, Kokubo Y, Saito I, et al. Development of a Risk Equation for the Incidence of Coronary Artery Disease and Ischemic Stroke for Middle-Aged Japanese- Japan Public Health Center-Based Prospective Study. Circ J 2016;80(6):1386-1395.
26. Chai Y, Bertorini TE, McGrew FA. Hereditary inclusion-body myopathy associated with cardiomyopathy: report of two siblings. Muscle Nerve 2011;43(1):133-136.
27. Ministry of Health and Welfare. Our mental health. 2011. http://www.mhlw.go.jp/kokoro/speciality/detail.html. Accessed 20 June 2020.
28. Inagaki M. Ministry of Health and Weflare Intellectual disorder. https://www.e-healthnet.mhlw.go.jp/information/heart/k-04-004.html. Accessed 20 June 2020.
29. The Nippon Foundation. Fact-finding investigation of truancy. 2018. https://www.nippon-foundation.or.jp/app/uploads/2019/01/new_inf_201811212_01.pdf. Accessed 20 June 2020.
30. Hattori S. Survey of suicide conducted by The Nippon Foundation in 2016: Results and suicide prevention. Mind Soc 2017;48(1):52-57.
31. Mori-Yoshimura M, Mizuno Y, Yoshida S, Minami N, Yonemoto N, Takeuchi F, et al. Social involvement issues in patients with Becker muscular dystrophy: A questionnaire survey of subjects from a patient registry. Brain Dev 2018;40(4):268-277.

Figures

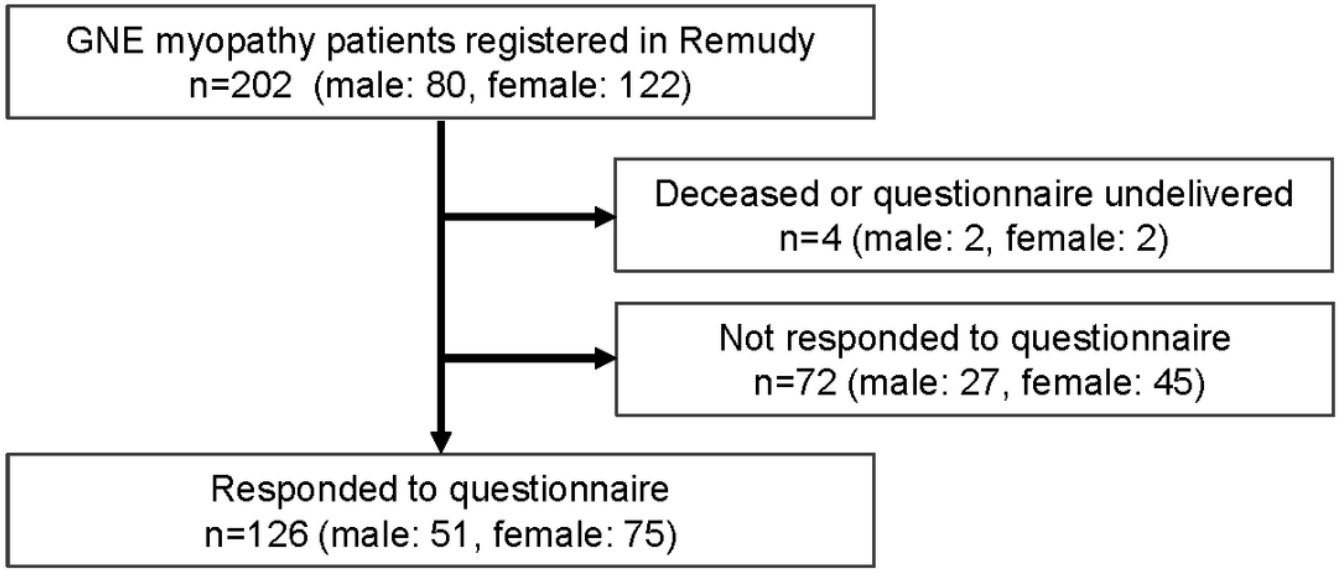

Figure 1

Participant recruitment Questionnaires were sent to 198 Japanese GNE myopathy patients registered in a national registry for neuromuscular diseases in Japan (Remudy), and 126 (62.4%) responded.

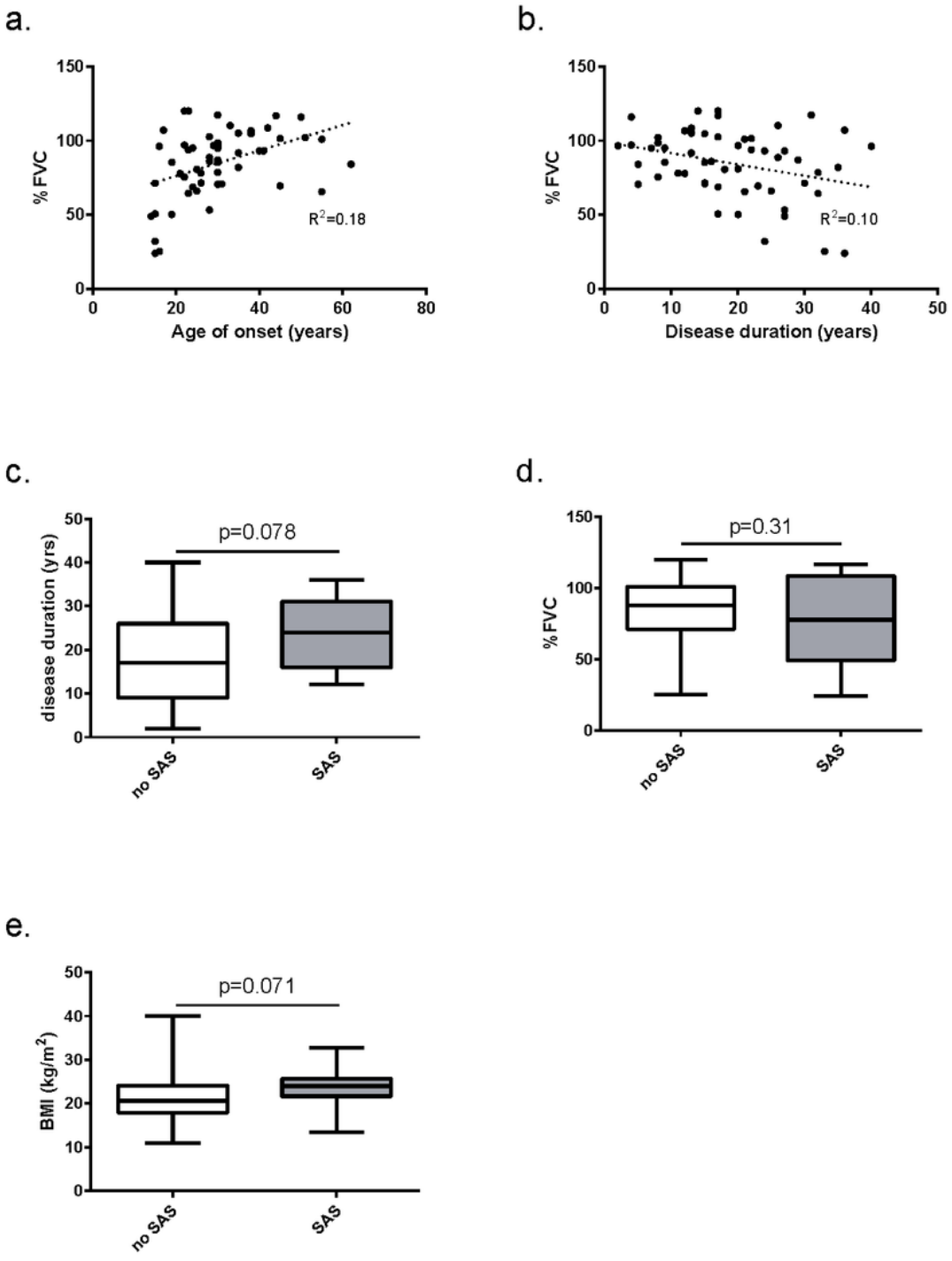

Figure 2

Participant recruitment There was no correlation between %FVC and (a) age of onset or (b) disease duration. (c) Disease duration was significantly longer among patients with a diagnosis of SAS compared to those without. No difference was observed in (d) %FVC or (e) BMI among patients with and without SAS.

Supplementary Files

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

- SupplementaryTable1.pdf