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

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Research

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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

| 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

| Genetic diagnosis            | 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

| Complication                                | n     | Frequency in GNEM participants % [95% CI] |
|---------------------------------------------|-------|-----------------------------------------|
| **Immune thrombocytopenia**                 |       |                                         |
| Previous / current diagnosis                | 5     | 4.1 [1.4–9.4]                           |
| Never diagnosed                             | 118   | 95.9 [90.6–98.6]                       |
| **Sleep apnea syndrome**                    |       |                                         |
| 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

| Developmental disorders | n  | Frequency in GNEM participants |
|-------------------------|----|--------------------------------|
|                         |    | % [95% CI]                     |
| Pervasive developmental disorder | 1  | 0.8 [0.0-4.3]                  |
| Never diagnosed         | 125| 99.2 [9.6–100.0]               |

| Psychiatric diseases*   | n  | Frequency in GNEM participants |
|-------------------------|----|--------------------------------|
|                         |    | % [95% CI]                     |
| 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*   | n  | Frequency in GNEM participants |
|-------------------------|----|--------------------------------|
|                         |    | % [95% CI]                     |
| 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.

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**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.

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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.

a. 

\[
\begin{align*}
\text{% FVC} & \quad \text{Age of onset (years)} \\
\text{0} & \quad 20 & \quad 40 & \quad 60 & \quad 80
\end{align*}
\]

\[R^2 = 0.18\]

b. 

\[
\begin{align*}
\text{% FVC} & \quad \text{Disease duration (years)} \\
\text{0} & \quad 10 & \quad 20 & \quad 30 & \quad 40 & \quad 50
\end{align*}
\]

\[R^2 = 0.10\]

c. 

\[
\begin{align*}
\text{p=0.078} & \quad \text{disease duration (years)} \\
\text{no SAS} & \quad \text{SAS}
\end{align*}
\]

d. 

\[
\begin{align*}
\text{p=0.31} & \quad \text{% FVC} \\
\text{no SAS} & \quad \text{SAS}
\end{align*}
\]

e. 

\[
\begin{align*}
\text{p=0.071} & \quad \text{BMI (kg/m^2)} \\
\text{no SAS} & \quad \text{SAS}
\end{align*}
\]

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](#)