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Clinical and electrophysiological evaluation of myasthenic features in an alpha-dystroglycanopathy cohort (*FKRP*-predominant)

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Abstract

A postsynaptic dysfunction of the neuromuscular junction has been reported in patients with alpha-dystroglycanopathy associated with mutations in guanosine diphosphate (GDP)-mannose pyrophosphorylase B gene (*GMPPB*), some of whom benefit from symptomatic treatment. In this study, we determine the frequency of myasthenic and fatigue symptoms and neuromuscular junction transmission defects in a fukutin-related protein (*FKRP*)-predominant alpha-dystroglycanopathy cohort. Thirty-one patients with alpha-dystroglycanopathies due to mutations in *FKRP* ($n = 25$), *GMPPB* ($n = 4$), *POMGNT1* ($n = 1$), and *POMT2* ($n = 1$) completed a six-question modified questionnaire for myasthenic symptoms and the PROMIS Short Form v1.0-Fatigue 8a survey, and they underwent 3 Hz repetitive nerve stimulation of spinal accessory nerve-trapezius and radial nerve-anconeus pairs. Results showed that fatigue with activity was common; 63% of the cohort reported fatigue with chewing. A defective postsynaptic neuromuscular junction transmission was not identified in any of the patients carrying *FKRP* mutations but only in one mildly affected patient with *GMPPB* mutations (c.79 G > C, p.D27H and c.402 + 1G > A, splice site variant). We conclude that symptoms of fatigue with activity did not predict abnormal neuromuscular junction transmission on electrodiagnostic studies in this cohort and that, unlike *GMPPB* subgroup, a defective neuromuscular junction transmission does not appear to be present in patients with *FKRP*- associated muscular dystrophies.

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Keywords

Fukutin-related protein (FKRP); Fatigue; Myasthenia; Neuromuscular junction

1. Introduction

Alpha-dystroglycan related muscular dystrophies (or α -dystroglycanopathies) are a heterogenous group of autosomal recessive-inherited muscular dystrophies characterized by hypoglycosylation of alpha-dystroglycan. To date, mutations in 18 genes have been identified to cause, either directly or indirectly, this glycosylation defect [1]. The phenotypic spectrum of this group of muscular dystrophies is strikingly broad ranging from congenital muscular dystrophy (CMD) with severe brain involvement to limb girdle muscular dystrophy (LGMD) [2–5].

The clinical spectrum of α -dystroglycanopathies was recently further expanded by the recognition of a myasthenic-type dysfunction of the neuromuscular junction (NMJ) in patients with guanosine diphosphate (GDP)-mannose pyrophosphorylase B gene (*GMPPB*) mutations, and their potential benefit from symptomatic treatment with pyridostigmine, salbutamol, or 3,4 diaminopyridine [6, 7]. Furthermore, an important role of dystroglycans in both the formation and maintenance of the NMJ, and more specifically in the clustering of the postsynaptic acetylcholine receptors, has been demonstrated [8, 9]. Here, we determine if a neuromuscular transmission defect is unique to those with *GMPPB* mutations or is also seen in a cohort of patients with α -dystroglycanopathies, most of them with *FKRP* mutations. We further investigated whether the presence of myasthenic symptoms and fatigue were associated with electrophysiologic evidence of a NMJ transmission defect in this cohort.

2. Patients and methods

Patient's (or legal guardian's) written consent was obtained in all cases. This study was approved by the University of Iowa institutional review board. All patients enrolled in the Iowa Wellstone Dystroglycanopathy Natural History Study who were seen during a 3-month period were invited to participate in this study. A total of 31 patients from 27 unrelated families agreed to participate. Of these, 25 patients (21 unrelated families) had *FKRP* mutations, four unrelated patients had *GMPPB* mutations, one patient had *POMGNT1* mutations and another patient had *POMT2* mutations. A six-question modified questionnaire to screen for myasthenic symptoms was administered to all participants except to patient#22 [10]; four of these questionnaires were filled in by the patient's caregivers due to the severe intellectual disability of these subjects. In addition, 23 participants completed the Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form v1.0-Fatigue 8a survey. Total raw PROMIS score for each participant was converted to standardized T-score with a mean = 50 (average for US general population) and standard deviation of 10.

Repetitive nerve stimulation (RNS) using the lowest supramaximal stimulus was performed on two nerve-muscle groups: right radial nerve-anconeus muscle and right spinal accessory nerve-trapezius muscle. The surface stimulating and recording electrodes were placed as

previously reported [11, 12]. These two muscles were selected based on their high sensitivity to detect a neuromuscular transmission defect and to duplicate the approach previously used in patients with *GMPPB* mutations [13]. A train of 7 supramaximal stimuli were delivered at a frequency of 3 Hz at rest, immediately after brief muscle activation of 10 sec, and after muscle activation of 1-minute duration. A 10 or higher percent decrement in the amplitude of the compound muscle action potential (CMAP) between the first and fourth, or first and fifth, responses was considered suggestive of a defect in neuromuscular transmission. All the RNS studies were performed with the same electromyography equipment (9400 Nihon Kohen EMG system) and by the same two trained physicians.

3. Results

A summary of the phenotypic and genotypic characteristics of this α -dystroglycanopathy patient cohort is shown in Table 1.

The six-question modified questionnaire of myasthenic symptoms shows that fatigue with activity is common in this cohort. None of the participants reported diplopia, however, 19 (63.3%) reported fatigue with chewing, 8 (26.7%) fatigue with repeated swallowing, and 4 (13.3%) eyelid drooping. Most of the patients ($n = 24$, 80%) stated that their fatigue worsened in the afternoons or evenings. Of those, 18 (75%) also reported that they felt weaker later in the day. Chewing fatigability was reported in 14 out of 25 (56%) *FKRP* patients, and in all *POMGNT1*, *POMT2*, and *GMPPB* patients who participated in this questionnaire (Table 2). Chewing fatigability was the only symptom reported by Patient #23 whose phenotype was episodic exercise-induced rhabdomyolysis associated with *GMPPB* mutations.

Individual T-scores for the 23 adults who participated in the PROMIS Short Form v1.0-Fatigue 8a scale are represented in Fig. 1 A. Patients #23, #5 and #18 (the phenotype of the latter two was mild LGMD associated with *FKRP* mutations) had the lowest fatigue T-scores. The PROMIS T-score of our α -dystroglycanopathy cohort as a group was comparable to the reported T score for other adult chronic conditions (Fig. 1 B).

Manual muscle testing (MMT) of right elbow extension revealed MRC 3, 4- to 4+, and 5 in 20%, 30%, and 50% of patients, respectively. Likewise, MMT of right elbow flexion showed MRC 3, 4- to 4+, and 5 in 30%, 60%, and 10% of patients, respectively. A total of 30 and 28 patients underwent RNS at rest of the anconeus and trapezius muscles, respectively. The mean CMAP amplitude at baseline of the anconeus and trapezius muscles were 4.624 mV (SD = 3.164) CI (95%) = 3.42–5.827 and 3.353 mV (SD = 1.799) CI (95%) = 2.641–4.065, respectively. A significant decrement (> 10%) in the CMAP amplitude between the first and fourth, and first and fifth, responses was observed in Patient #23 only (Fig. 2) whose baseline CMAP amplitudes for anconeus and trapezius were 4.1 and 7.84 mV, respectively, and within normal range according to reported reference values [11, 14–16]. This patient was treated with pyridostigmine 60 mg twice per day and prn, but he did not experience any significant benefit during two months on treatment and elected to discontinue it. Post-facilitation RNS of the anconeus and trapezius muscles were performed

on 26 and 24 patients, respectively. No significant increment of the CMAP amplitude suggestive of presynaptic neuromuscular transmission defect was identified.

Of note, 3 patients declined RNS of spinal accessory- trapezius pair, a CMAP could not be obtained in one patient on RNS of radial-anconeus pair, 5 patients were not able to perform muscle activation due to intellectual disability or severe muscle weakness, and when patients were not able to maintain muscle activation for 1 min a minimum of 30 sec of exercise was accepted to obtain muscle exhaustion.

4. Discussion

We investigated an alpha-dystroglycanopathy cohort (*FKRP*-predominant) for electrophysiologic evidence of neuromuscular transmission defects and myasthenic and fatigue symptoms. We identified a single subject (Patient #23), with *GMPPB* mutations (c.79 G > C, p.D27H and c.402 + 1G > A, splice site variant) who had electrophysiologic evidence of postsynaptic NMJ dysfunction on 3 Hz RNS studies of spinal accessory and radial nerves, however, none of *FKRP* patients presented such defect. While NMJ transmission on RNS was normal in most of this cohort, symptoms of fatigue with activities and even eyelid drooping were surprisingly common; fatigue with chewing was reported in more than half of patients. These symptoms that are often associated with myasthenic syndromes did not predict electrophysiologic evidence of NMJ transmission defect in our study. On the other hand, patient #23 who did have a defective NMJ transmission on RNS reported chewing fatigability as only symptom on myasthenic questionnaire, his PROMIS T-score for fatigue was comparable to the average T-score for the US population, and his neurologic exam was normal between his episodes of exercise-induced rhabdomyolysis.

In our series, 80% of patients reported fatigue at the end of the day and most of these also reported worsened muscle weakness later in the day (although that was not reported by our single patient with postsynaptic NMJ impairment on RNS studies). Fatigue is a complex symptom that not only refers to subjective physical tiredness but also intellectual exhaustion. Muscle fatigue is defined by loss of muscle force that is restored by rest; whereas muscle weakness is the loss of muscle force that is not reversible by rest. Determining the degree of muscle fatigue in patients with muscle weakness due to muscular dystrophy is challenging for the clinician.

Our series shows that electrophysiological evidence of defective neuromuscular transmission is not likely to be seen in patients with *FKRP* mutations and might be absent or rare in α -dystroglycanopathy patients with congenital muscular dystrophy. Together with previous reports, our work suggests that the myasthenic phenotype might be uniquely associated with *GMPPB* mutations. We note that we did not perform single fiber-electromyography but limited RNS studies to increase subject participation and tolerance, and that it is possible that minor defects in the neuromuscular transmission are present more commonly than we detected here. On the other hand, single fiber-electromyography, although it is very sensitive, is not specific and abnormal results may be secondary to the myopathic process these patients have rather than a superimposed NMJ transmission defect.

We found, as others have reported, that not all patients with *GMPPB* mutations have abnormal neuromuscular transmission on electrodiagnostic studies and that those with abnormal neuromuscular transmission have relatively mild or fluctuating skeletal muscle phenotypes [6, 7]. The phenotype of *GMPPB*-associated dystroglycanopathies is strikingly broad [17–19]. It has been suggested that there is a continuum of *GMPPB*-associated phenotypes with myasthenic syndrome at the mild end and congenital muscular dystrophy involving eye and brain at the more severe end. Some genotype-phenotype correlations are apparent [19], but exactly how these relate to the presence of electrophysiological neuromuscular transmission dysfunction is still unclear [20]. More than 20 patients with *GMPPB* mutations and associated myasthenic syndrome (with or without electrophysiologic evidence of abnormal neuromuscular transmission) have been reported [6, 7, 20–24]. Of those, five belong to a Chinese cohort with the most frequent mutation being c.1070G > A (p.R357H) [20]. Up to 10 of the remaining patients (including Patient #23 in this cohort) have at least one copy of the c.79G > C variant (p.D27H) [6, 21–24].

There is growing and compelling evidence to support the role of glycosylated dystroglycan in the formation and maintenance of the NMJ [8, 9, 25–27]. *GMPPB* acts very early in the process of glycosylation, catalyzes the formation of GDP-mannose, and contributes to both O-type and N-type glycosylation pathways. Thus, it is possible that *GMPPB* plays a specific role in dystroglycan glycosylation at the NMJ that is not shared by proteins more distal in the glycosylation pathway, which would support that a defective neuromuscular transmission had been identified only in patients with α -dystroglycanopathy associated with mutations in *GMPPB* gene. Another possibility is that *GMPPB* is involved in the glycosylation of key proteins that maintain the normal function of NMJ such as acetylcholine receptor (AChR), agrin, low-density lipoprotein receptor-related protein 4 (LRP4) or muscle-specific kinase (MusK); which are well known targets of the autoimmune response in myasthenia gravis [28]. Furthermore, it is plausible that the defect in neuromuscular transmission associated with *GMPPB* mutations is detected by electrodiagnostic studies in early stage of the disease and dissipates as the muscle becomes more dystrophic; this would explain why such defect is mostly found in mildly affected *GMPPB* patients.

The available data here and in prior reports indicate that clinicians should consider screening individuals with mutations in *GMPPB*, and relatively mild muscle weakness, with or without symptoms of fluctuating weakness, for a neuromuscular transmission defect. Although our patient did not benefit from symptomatic treatment, benefit has been previously reported [6, 7]. On the other hand, we do not consider necessary to perform such screening in patients with *FKRP* mutations since we could not identify any with a defective NMJ transmission defect in this study. Whether patients with other α -dystroglycanopathies may benefit from NMJ assessments is uncertain and requires further investigations. Our clinical impression is that muscle fatigue is common and multifactorial in patients with severe muscular dystrophy. Thus, to better determine the presence and contributory role of a defective neuromuscular junction transmission as independent factor to account for patient's muscle fatigue we favor to perform clinical and electrical longitudinal studies in patients with mild phenotypes (even pre-symptomatic patients when possible) in whom muscles are at early dystrophic stage.

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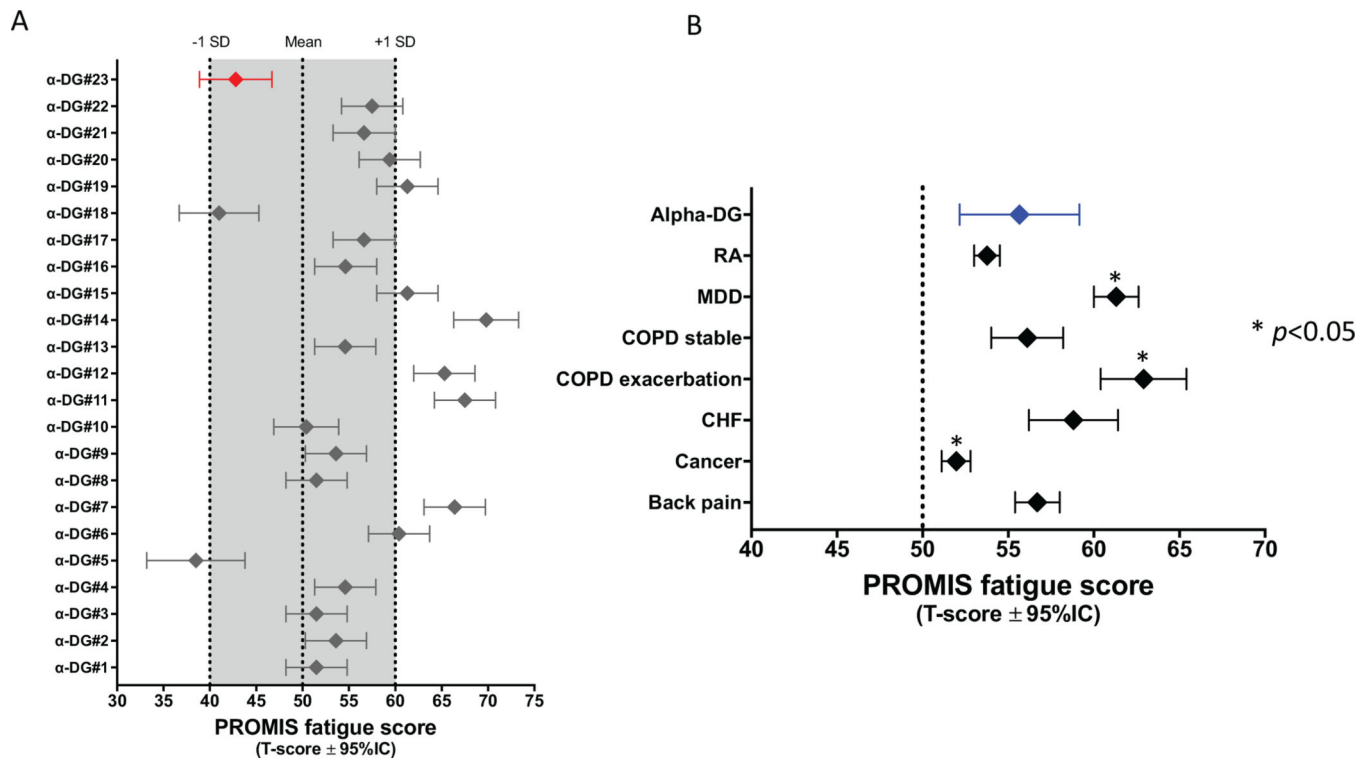


Fig. 1. PROMIS fatigue score in α -dystroglycanopathy cohort.

A) Representation of the individual standardized T-scores of the PROMIS Short Form v1.0-Fatigue 8a scale for the 23 adult α -dystroglycanopathy patients. Patient #23 presents a comparable T-score with the average US population. B) The mean T-score of the α -dystroglycanopathy cohort as a group is comparable with other reported adult chronic conditions such as rheumatoid arthritis (RA), stable chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and back pain. Major depressive disorder (MDD) and COPD exacerbation demonstrated significantly higher mean T-score whereas cancer significantly lower mean T-score than α -dystroglycanopathy group [29]. One-way Anova and ad hoc T-test analyses were the statistics methods used.

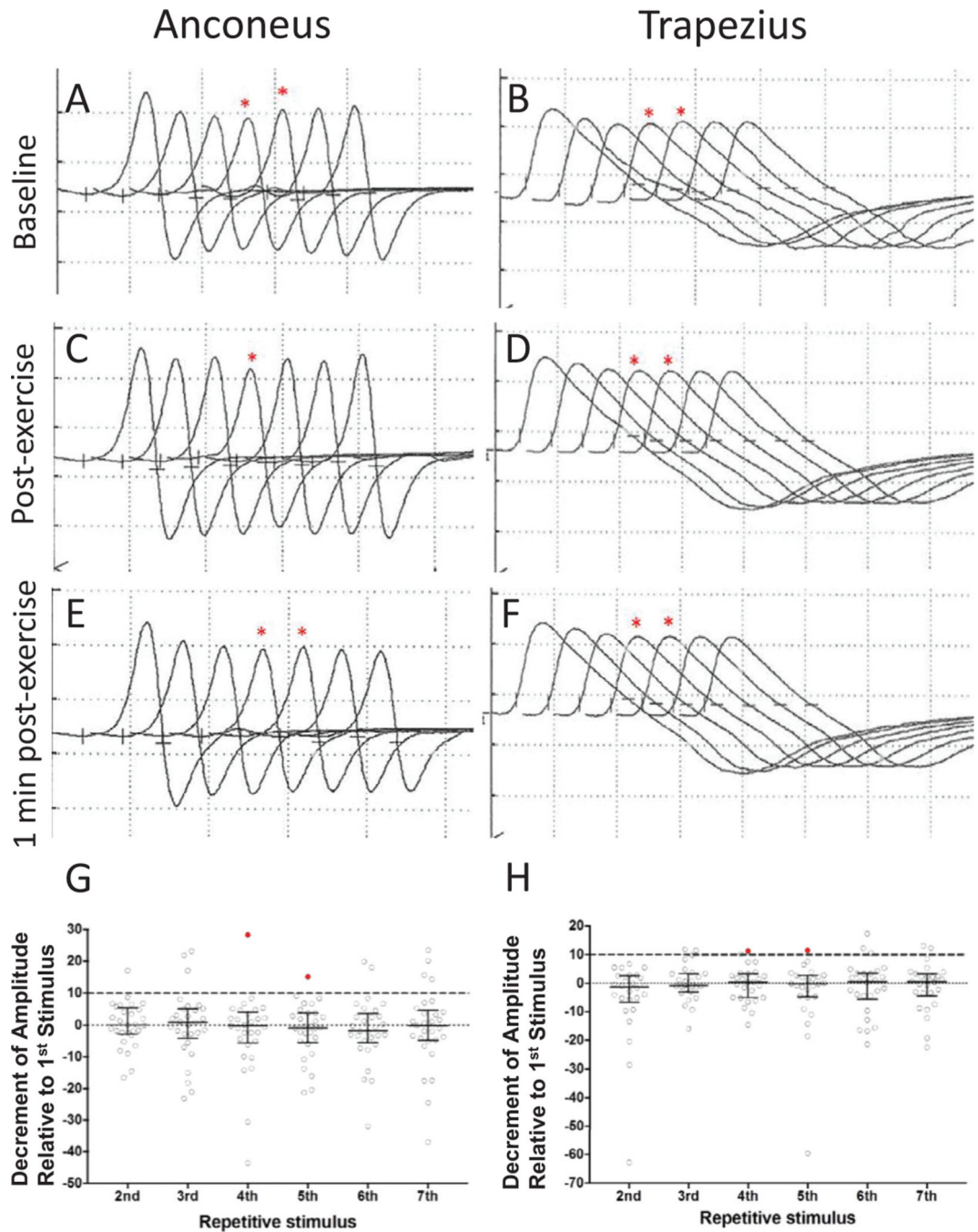


Fig. 2. RNS on anconeus and trapezius muscles in α -dystroglycanopathy cohort.

A > 10% decrement between the first and fourth (and first and fifth) responses were obtained at baseline (A and B) and 1 min after exercise (E and F), and partially corrected immediately after exercise (C and D) in patient#23 who has *GMPPB* mutations. The relative decrement of amplitude between the first stimulus and the subsequent 6 stimuli (2–7) for each patient in this cohort is represented in G (for anconeus) and H (for trapezius). Red dot represents Patient #23 as the only patient who had higher than 10% decrement in the amplitude between the 1st and 4th (and 1st and 5th) responses in both anconeus and trapezius muscles.

Of note, RNS that showed decrement or increment of CMAP at baseline due to technical factors (i.e.; movement) was repeated when affecting 1st, 4th and 5th responses, or minimize after brief and prolonged exercises.

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Table 1

Summary of the phenotypic-genotypic spectrum of this α -dystroglycanopathy cohort.

<i>n</i> = 31	CMD	LGMD	Exercise-induced rhabdomyolysis	Genotype
<i>FKRP</i> (<i>n</i> = 25)	—	25	—	c.826 C>A (hm) (<i>n</i> = 17)
	—	—	—	c.826 C>A/c.1073 C>T (<i>n</i> = 2)
	—	—	—	c.826 C>A/1050_1027delins TCAA (<i>n</i> = 2)
	—	—	—	c.826C>A/p.948_949delC (<i>n</i> = 1)
	—	—	—	c.826C>A/c.586 G>C (<i>n</i> = 1)
<i>GMPPB</i> (<i>n</i> = 4)	2	1	1	c.826 C>A/? (<i>n</i> = 1) ^a
	—	—	—	c.860 G>A/c.859C>T, c.1069 G>A/c.931 C>T
	—	—	—	c.79G>C/c.760G>A
<i>POMT2</i> (<i>n</i> = 1)	1	—	—	c.79G>C/c.402 + 1G>A
	—	—	—	c.1997A>G/c.1116 + 1G>A
<i>PMGNT1</i> (<i>n</i> = 1)	1	—	—	c.1895 + 1 G>T/c.626C>T

CMD, congenital muscular dystrophy; LGMD, limb-girdle muscular dystrophy; hm, homozygous.

Three out of the four patients with *GMPPB* mutations were previously reported as patient P8 (CMD), P3 (LGMD), and P4 (exercise-induced rhabdomyolysis) [16].

^a A second *FKRP* mutation was not detected in this patient despite clinical diagnosis being consistent with α -dystroglycanopathy. Genetic testing for one *FKRP* patient was not available at the time of this manuscript.

Table 2

Six-question modified questionnaire of myasthenic symptoms.

	<i>FKRP</i> (n = 25)	<i>GMPPB</i> (n = 3)	<i>POMGNNTI</i> (n = 1)	<i>POMT2</i> (n = 1)	Total (%)
1) Have you ever noticed one or both eyelids drooping?	YES 2	1	1	0	4 (13.3%)
2) Have you ever had double vision?	YES 0	0	0	0	0 (0%)
3) Do you tire with repeated swallowing?	YES 5	1	1	1	8 (26.6%)
4) Does your jaw tire from chewing?	YES 14	3	1	1	19 (63.3%)
5) Is your weakness worse in the afternoons/evenings?	YES 14	2	1	1	18 (60%)
6) Is your fatigue worse in the afternoon/evenings?	YES 20	2	1	1	24 (80%)