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Patient-Reported Impact of Symptoms in Spinal and Bulbar Muscular Atrophy

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Abstract

Background and Objectives

The aim of this study was to determine the frequency and relative importance of symptoms experienced by patients with spinal and bulbar muscular atrophy (SBMA).

Methods

We conducted a cross-sectional study of 232 participants with SBMA. Participants provided input regarding 18 themes and 208 symptoms that affect patients with SBMA. Participants were asked about the relative importance of each symptom, and analysis was conducted to determine how age, education, disease duration, CAG repeat length, and ambulation status relate to symptom prevalence.

Results

Hip, thigh, or knee weakness (96.5%), fatigue (96.5%), problems with hands and fingers (95.7%), and limitations with walking (95.7%) were the themes with the highest prevalence in the study population. Ambulatory status was associated with the prevalence of 9 of the 14 themes, and CAG repeat length and education were each associated with 4 of 14 themes. The prevalence of fatigue was reduced in those with a lower CAG repeat length and increased with a longer disease duration. Younger patients reported a higher prevalence of emotional issues.

Discussion

There are a diversity of themes that are important to patients with SBMA. These themes have a variable level of importance to the population with SBMA and represent clinically meaningful outcome measures for future therapeutic interventions.

Introduction

Spinal bulbar muscular atrophy (SBMA) or Kennedy disease is an inherited debilitating motor neuron disease caused by a CAG repeat expansion in the androgen receptor gene on the X chromosome.[1,2] The disease has a prevalence of approximately 1–2 per 100,000. Symptoms include muscle twitching (fasciculations), atrophy, tremors, sensory loss, and weakness involving both the proximal and distal limb muscles and bulbar muscles. Nonmotor neuron findings include gynecomastia, erectile dysfunction, testicular atrophy, and metabolic abnormalities.[3,4] The disease onset ranges from 18 to 60 years of age with most presenting in the third to fifth decade.[5] This variation of disease onset and diversity of symptoms results in a complex phenotype and disease burden.

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It is important to understand the symptoms and disease features that have the largest impact on patients with SBMA. Evaluation of the disease burden is necessary for evaluating the clinical efficacy of candidate therapeutics. Patient-reported outcomes are part of the Food and Drug Administration (FDA) medication approval and labeling regulations.[6] In addition, patient-reported outcomes can provide valuable information for improving patient care. In a previous study conducted by our group, 21 patients with genetically confirmed SBMA indicated their symptoms and disease-related difficulties. Using qualitative open-ended interviews, we analyzed 729 quotations and identified 20 symptomatic themes.[7]

In this study, we present the results of a new study, Patient-Reported Impact of Symptoms in SBMA (PRISM-SBMA), an international cross-sectional assessment of patients with SBMA to identify the relative importance and prevalence of the key symptoms in this patient population. In addition, we identified the factors linked to the degree of disease burden in SBMA.

Methods

Study Participants

Participants in this study included individuals with the clinical diagnosis of SBMA. Inclusion criteria included both age of 18 years or older and access to a computer with an internet connection. Participants were encouraged to report their CAG repeat number.

Study Design

We designed a cross-sectional online survey that included questions about symptoms previously reported in 21 patients with SBMA and those previously identified in other neurologic cohorts.[7-12] There were 226 questions and 20 themes. Question selection was based on a consensus among the research team. The approach was to capture as many symptoms and themes as possible while limiting the burden on participants with SBMA and avoiding redundancy.

For each symptom, participants were asked, "How much does the following impact your life now?" Participants were provided a 6-point Likert-type scale to record their responses. The Likert response options included the following: (1) I do not experience this; (2) I experience this, but it does not affect my life; (3) it affects my life a little; (4) it affects my life moderately; (5) it affects my life very much; and (6) it affects my life severely. In addition, participants were given an opportunity to list any other symptoms not included in the survey. This same methodology has been previously reported and used for other neurologic conditions.[8-15] Participants reported their sex, age, CAG repeat number, race, country and state where they reside, employment status, highest level of education, marital status, time since the onset of weakness, location of first weakness, and time since diagnosis. Breathing status was inquired by asking, "How would you describe your breathing?" The response options were as follows: "I breathe without the need for any assisted ventilation"; "I use noninvasive ventilation (Bipap) for SBMA less than 16 hours during a 24-hour day," and "I have a tracheostomy." Speech was inquired about by asking, "How is your speech?" The response options were as follows: "I talk clearly and have no changes in my speech", "I have some speech changes", "I have impaired speech and people occasionally ask me to repeat words or phrases", and "I have impaired speech that is often not understood by others." This methodology has been previously used in other studies of neuromuscular disorders.[9-15]

Participants were recruited through the Kennedy's Disease Association (KDA) website and Kennedy's Disease Facebook Group - Raising Awareness, Kennedy's Disease, Kennedy's Disease Patient Group, and through contacting previous National of Institutes of Health (NIH) Neurogenetics Branch SBMA study participants.

The online survey and study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Consulting support was provided by the Biomedical Translational Research Information System (BTRIS). Both NIDDK and BTRIS are part of the NIH. REDCap is a secure web-based application designed to support data capture for research studies. REDCap was developed and licensed by Vanderbilt University.[16,17]

The online self-administered survey link was sent out through social media and emails. Study participation was completely voluntary. No personal identification information was collected. Surveys were conducted from May 2020 to July 2020.

Standard Protocol Approvals, Registrations, and Patient Consents

All study activities were approved by the NIH Neuroscience Institutional Review Board.

Statistical Analysis

We determined the frequency (prevalence) and SD of each symptom and theme in our sample set. We calculated the relative importance and standard deviation of each symptom in the participants who reported that they experienced the individual symptom. For this metric, each participant response was assigned a numerical value as follows: I experience the symptom, but it does not affect my life = 0; it affects my life a little = 1; it affects my life moderately = 2; it affects my life very much = 3; and it affects my life severely = 4. Average life impact scores were calculated for each symptom and theme by summing the impact scores for each and dividing by the number of participants who reported it.

Table 1 Participant Demographics

No. of participants	232
Age in years	
Mean (SD)	59.1 (10.7)
Range	29–83
Sex, n (%)	
Male	227 (97.8)
Female	2 (0.9)
Omitted	3 (1.3)
Race	
American Indian/Alaskan	4 (1.72)
Asian	32 (13.7)
Black/African American	2 (0.9)
White	182 (78.4)
Other	8 (3.4)
Omitted	4 (1.7)
Hispanic	9 (3.9)
Education	
Grade school	2 (0.9)
High school	33 (14.2)
Technical degree	33(14.2)
College	93 (40)
Master's or Doctorate	67 (28.8)
None	2 (0.9)
Omitted	2 (0.9)
Employment status	
Employed—full time	73 (31.4)
Employed—part time	17 (7.3)
On disability	47 (20.2)
Not working/not on disability	4 (1.7)
Retired	83 (35.7)
Other	7 (7.3)
Ambulation status	
Independent	92 (39.6)
Uses a cane or crutches	66 (28.4)
Uses a walker	21 (9)
Wheelchair or scooter	50 (21.5)
Omitted	3 (1.3)
Country	
United States	121 (52.1)
United Kingdom	34 (14.6)
Canada	18 (7.7)
Australia	10 (4.3)
South Korea	11 (4.7)
China	5 (2.1)
Philippines	4 (1.7)
Russia	3 (1.2)
Ireland	3 (1.2)
***Other countries N. of 2 or less**	15
Reported CAG repeat length	129
Mean CAG length (SD)	46 (4)
Range	39–64

List of countries with N of 2 or less: Ecuador, Finland, France, Germany, Greece, Italy, Latvia, Mexico, Netherlands, North Korea, Norway, Siberia, Slovakia, Spain, and Sweden.

Participants' responses were categorized into subgroups based on age (divided into 2 groups based on the median age of the sample), ambulatory status (those who could walk independently vs those who could not walk or required assistive devices), and years since diagnosis (divided into 2 groups based on median years since diagnosis). To use a measure less susceptible to long-tailed distribution and outliers, we divided CAG into 2 groups based on CAG repeats less than or equal to the first quartile vs those that were above the first quartile. We compared the prevalence of symptoms and themes across subgroups using Fisher exact tests. Pairwise comparisons were performed between SBMA groups. The Benjamini-Hochberg procedure was used to correct for multiple comparisons using a false discovery rate of 0.05.

Data Availability

Anonymized data will be provided on request.

Results

Our online survey was distributed worldwide. The target number of responders was approximately 200 participants. We believe a sample of this size is sufficient for the primary outcome measure in this relatively rare neuromuscular disorder. We received 232 survey responses. Participants answered approximately 63,280 questions. Participants' ages ranged from 29 to 83 years, with a mean age of 59.1 years (Table 1). The participants in this study represented 26 countries and 33 US states. The mean number of years since the onset of the first weakness was 18.5 years (SD 10.1) and 12.5 years (SD 8.6) since diagnosis. Approximately 75% of

Table 2 Clinical Information

No. of participants	232
Years since first weakness was noticed	
Mean (SD)	18.5 (10.1)
Range	0–53
Years since diagnosis	
Mean (SD)	12.5 (8.6)
Range	0–50
Location of first weakness	N, (%)
Lower limbs	172 (75)
Upper limbs	23 (10)
Swallowing	14 (6)
Speech	4 (17)
Breathing	1 (0.4)
Other	16 (6.9)
Omitted	2
Breathing	
Breathe without the need for any assisted ventilation	207 (89.6)
Use noninvasive ventilation for SBMA less than 16 h during a 24-h day	22 (0.5)
Tracheostomy	2 (0.8)
Speech	N, (%)
No speech changes	49 (21)
Some speech changes	122 (53)
Impaired speech (people occasionally ask me to repeat words or phrases)	51 (22)
Impaired speech that is often not understood by others	8 (3.5)
Omitted	2

our sample reported leg weakness as an initial motor symptom (Table 2), and 53% reported some speech changes.

Prevalence of Symptoms and Themes

Fourteen of the 18 themes were selected based on the following criteria: (1) high prevalence in our current sample, (2) precise meaning with no redundancy, and (3) identified as potentially responsive to future therapeutics. The most prevalent 2 themes were hip, thigh, or knee weakness and fatigue experienced by 96.5%, followed by limitations in walking and problems with hands and fingers, each reported by 95.7% of our study participants (Figure). Of the 208 symptoms, the most prevalent were muscle fatigue reported by 98.6%, followed by difficulty running and loss of muscle both reported at 98.1%.

Average Impact of Symptoms and Themes

The average impact of each theme is demonstrated in the Figure. The themes with the highest average life impact scores (0–4) were (1) limitation of walking (2.53), (2) fatigue (2.20), and (3) inability do activities (2.19). Of the 208 symptoms, difficulty running (3.25), difficulty walking long distance (3.22), and difficulty going up stairs (3.18) had the highest average impact. Details regarding individual prevalence and impact of symptoms are summarized in the eTable (links.lww.com/CPJ/A476).

Subgroup Analysis

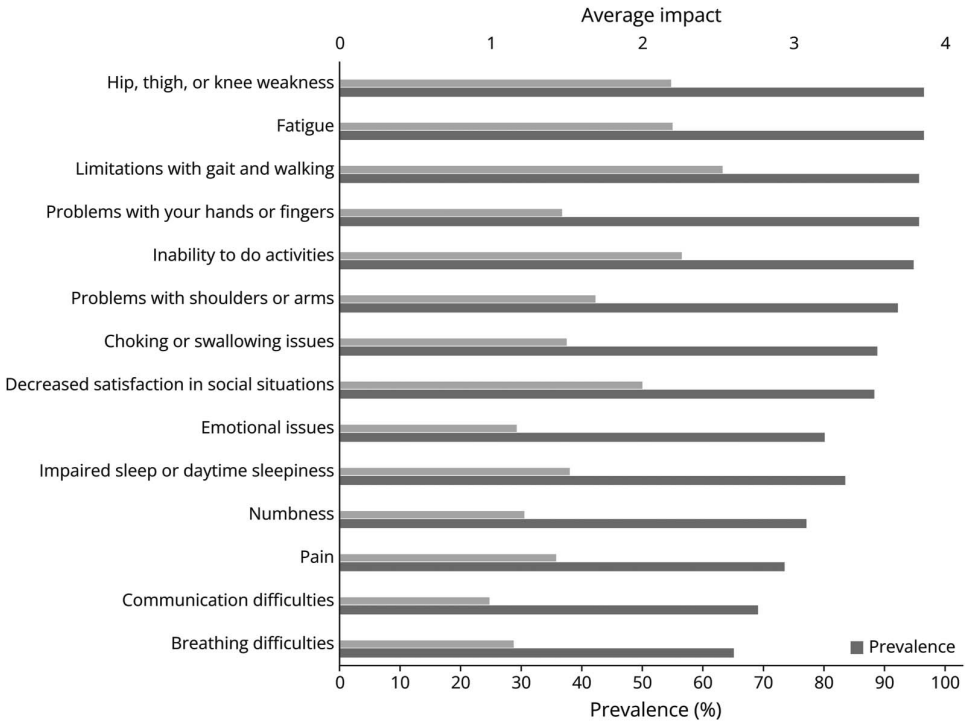
The prevalence of each theme was subgrouped by age, education level, disease duration, CAG repeat length, and ambulation status (Table 3). Younger patients reported a higher prevalence of emotional issues. Ambulatory status was associated with 9 of the 14 themes, and lower (≤Q1) CAG repeat length and education were each associated with 4 of 14 themes. The prevalence of fatigue was lower in those with a lower CAG repeat length and increased disease duration. Increased CAG repeat length was associated with increased prevalence of emotional issues and communication difficulties and reduced satisfaction in social situations.

Of the 208 symptoms, the most prevalent symptoms were leg weakness and decreased ability to carry a heavy load with arms, each experienced by 99.2% of participants with SBMA. Of the least experienced symptoms, less than 40% reported difficulties with comprehension or controlling laughter or crying and autonomic symptoms such as nausea, diarrhea, and excessive sweating.

Discussion

In this study, we present results from an international study designed to document the most prevalent and clinically important SBMA themes and symptoms. SBMA is a slowly progressive disease, and an array of symptoms and themes result in the increasing disease burden. These features vary in prevalence and importance in this population. Patients with SBMA are often misdiagnosed early in their disease, for example, as experiencing amyotrophic lateral sclerosis, spinal muscular atrophy, or muscular dystrophy.[18,19] Similar to prior studies, our data show a delay in the average time between a patient's first symptom and diagnosis.[5] Most of our participants reported that their weakness first started in the lower limbs. Muscle symptoms were more prevalent in our sample than tremors, sensory changes, or nonneurologic manifestations. Although additional research is needed, we believe the symptoms identified by our participants to be similar to those that motivate a patient with SBMA to seek medical care. Data provided in this study can be used in clinical care to identify the features of SBMA, limit the delay in diagnosis, and monitor clinical status. In addition, researchers and regulatory agencies can use this

Figure 1 Prevalence and Average Impact of Symptomatic Themes, With Prevalence (%) on the Lower X-Axis (Dark Bars) and Average Impact Ranging From 0 to 4 on the Upper X-Axis (Light Bars)



information in developing therapeutic trials that target the most common and important symptoms in this population.

Patient-reported impact of symptoms in SBMA (PRISM) builds on a previous study of disease burden in a smaller number of patients with SBMA with limited demographics. In this larger international study, we found that the prevalence of symptomatic themes was high in the population with SBMA. Of the 208 symptoms, the top 5 most prevalent symptoms were all related to physical function. When we ranked all the symptoms based on the population impact score, which considers the effect of symptoms on participants' lives, the top 5 were all related to lower limb physical function (difficulty running, difficulty walking long distance, difficulty going upstairs, difficulty walking up hills or inclines, and difficulty getting up from the floor or ground).

Nine of the 14 themes had a prevalence of 90% or greater. Despite the high disease burden, 39% of our sample were employed during this study and 69% had a college degree or graduate education.[20] This is perhaps due to the disease's natural history, which is characterized by adult onset in cases, slow progression, and lack of cognitive involvement. In addition, it demonstrates the educational resilience in this sample.

Fatigue was highly prevalent in our sample and higher than previously reported.[21] The frequency of fatigue was also higher than has been reported in other inherited neuromuscular disorders.[8,9] Fatigue is an important and likely underaddressed clinical symptom in SBMA. Given its prevalence and relative burden in SBMA, it is worthwhile to consider future therapeutics for this key symptom and to develop appropriate outcome measures to serially quantify changes in this symptom in response to treatments. This symptom was more prevalent in those with a shorter disease duration and a longer CAG repeat length. The association with disease duration could be due to an association with overall activity. Those with a shorter disease duration may be more active and experience this symptom more frequently. In addition, previous studies have shown that those with a longer CAG repeat length develop the disease earlier.[22] Additional studies are warranted to further investigate the relationship between CAG repeat length and fatigue in this population and to explore potential interventions to mitigate this common life-altering symptom.

Emotional issues have been identified as a major and significant factor that affects the quality of life.[23] The burden of this theme not only affects the mental well-being but extends to affect functional, social, and physical functions. The prevalence of emotional issues was high in our sample. This

Table 3 Prevalence of Symptomatic Themes by Subgroup Categories

	Mean age = 59 y			Educational level			Disease duration (DD) mean = 18.5 y		
	Age > the mean	Age ≤ the mean		College+	Other		DD > the mean	DD ≤ the mean	
Total no. of responses (232)	121	111		160	68		96	133	
	Theme prevalence, %		*p* Value	Theme prevalence, %		*p* Value	Theme prevalence, %		*p* Value
1. Hip and thigh weakness	95	96	1	96	95.5	1	94	97.7	0.28
2. Fatigue	94.2	95.5	0.4	93.7	97	0.1	94.7	98.4	0.02[a]
3. Limitations with your mobility or walking	97.5	93.7	0.2	95	98.5	0.28	95.8	95.4	1
4. Problems with your hands or fingers	94.5	96.6	0.5	96.25	94.1	0.4	95.8	95.4	1
5. Inability to do activities	97.5	89	0.01[a]	91.8	98.5	0.04[a]	94.7	92.4	0.76
6. Problems with shoulders and arms	90	92.8	0.47	91.2	97.2	0.15	92.7	91.7	1
7. Choking or swallowing issues	90	86.4	0.3	85	98.5	<0.001[a]	92.7	86.4	0.16
8. Decreased satisfaction in social situations	86	89	0.5	86.2	91.1	0.1	84.3	90	0.2
9. Impaired sleep or daytime sleepiness	83.5	86.5	1	80	89.7	0.05[a]	81.2	85	0.5
10. Emotional issues	74.3	85.5	0.04[a]	79.3	80	0.7	80.2	80.4	0.8
11. Numbness	82.6	71.2	0.05[a]	75.6	82	0.2	79	75	0.42
12. Pain	73.7	72.9	0.88	66.8	86.7	0.001[a]	68.75	75.9	0.28
13. Communication difficulties	72.7	63.9	0.25	67.5	70	0.6	66.6	69.9	0.66
14. Breathing issues	69.4	58.5	0.12	56.8	80	<0.001[a]	66.6	63	0.6

	Ambulatory status			CAG repeats		
	Independent	Requires any type of assistive device		>43[b]	≤43[b]	
Total no. of responses	92	137		96	32	
Theme prevalence, %	Theme prevalence, %		*p* Value	Theme prevalence, %		*p* Value
1. Hip and thigh weakness	91.3	98.5	<0.001[a]	98.9	96.9	0.4
2. Fatigue	91.3	97	0.06	97.8	90.6	0.01[a]
3. Limitations with your mobility or walking	90.2	99.2	<0.001[a]	95.8	93.9	0.64
4. Problems with your hands or fingers	93.4	97	0.2	95.8	95.8	1
5. Inability to do activities	85.8[c]	99.2	<0.0001[a]	95.7	94.9	0.64
6. Problems with shoulders and arms	86.9	94.1	0.02[a]	93.7	93.9	1
7. Choking or swallowing issues	80.4	94.8	<0.001[a]	90.6	84.6	0.3
8. Decreased satisfaction in social situations	81.5[c]	91.2	0.02[a]	93.6	78.7	0.005[a]
9. Impaired sleep or daytime sleepiness	83.6	83.2	1	79.1	75.7	0.8
10. Emotional issues	80.4	80.2	1	85.4	61.6	<0.001[a]
11. Numbness	68.4[c]	83.2	<0.001[a]	78.9	69.2	0.1
12. Pain	67.3[c]	76.6	0.16	70.8	65.6	0.6
13. Communication difficulties	66.5	76.6	<0.001[a]	77	56.4	0.02[a]
14. Breathing issues	48.9[c]	74.4	<0.0001[a]	64.2	46.8	0.09

College+: college education or higher.
[a] Significant after a Benjamini-Hochberg analysis.
[b] CAG repeat of 43 indicates the Q1 value.
[c] One participant did not answer the questions.

finding was not captured in prior work with generic surveys.[5] We believe this example emphasizes the importance of designing future disease-specific patient-reported outcome measures that are capable of addressing the issues that are most relevant to a particular population.

In our subgroup analysis, we found that ambulatory status was associated with the prevalence of the symptomatic themes. Nine of the 14 themes were more prevalent in those who were unable to walk independently without the need of an assistive device. Gait dysfunction has important implications for function in everyday life and for the overall quality of life. This shows that interventions targeting ambulatory status may affect the overall burden of disease in patients with SBMA. On the contrary, participants' age and disease duration showed fewer statistically significant differences in symptomatic themes, suggesting that these variables are less refined markers of disease burden in the population with SBMA.

Comparing our data with patient-reported impact of symptoms studies involving other neuromuscular disorders,[8-13] the patient-reported impact of symptoms in spinal bulbar muscular atrophy (PRISM-SBMA) showed an overlap with some of its most prevalent symptomatic themes. For example, hand and finger weakness overlapped with Charcot-Marie-Tooth (CMT) disease and hip and thigh or knee weakness was shared with spinal muscular atrophy (SMA). Although these themes overlapped, the prevalence varied across populations. SBMA shared the lack of cognitive difficulties with both SMA and CMT. Alternatively, our sample did not report gastrointestinal issues, contrary to what was observed in HD, SMA, DM1, DM2, and CMT. These data show the phenotypic heterogenicity and distinctive pattern of disease burden in these different neuromuscular disorders.

We recognize that our study has several limitations. Our sample is not a true cross-sectional representation of the population with SBMA. This is due to multiple reasons. Our questions were in English and required access to the internet to capture responses. Those with limited access to the internet or with English language barriers were underrepresented in this study. Participants were not incentivized to participate. Completing more than 270 questions may be challenging for some participants and may have contributed to the number of participants who did not complete all responses. In addition, participants with SBMA who are advanced in disease burden or not intersected in research may have been underrepresented. Most of the participants were from the United States and the United Kingdom, and most of them were highly educated. This pattern was seen in the study evaluating the impact of symptoms in patients with the related condition SMA.[11] Despite these limitations, we believe our sample represents participants who are willing to participate in future clinical trials.

PRISM-SBMA adds to our existing knowledge of the burden of disease in the population with SBMA. This study shows that despite the overlap in disease burden among neuromuscular disorders, the prevalence of symptoms varies by disease. The knowledge obtained here is relevant to clinical care providers and facilitates shared decision-making. Understanding the most prevalent and impactful symptoms allows for a holistic approach to patient care. For example, the study improves our awareness of symptoms that may be overlooked. Evaluation of these disease-specific symptoms allows for a more accurate assessment of the disease burden during longitudinal follow-up and clinical trials. Patient-reported measures create a common and consistent language between patients and providers. Incorporating such measures in clinical care was viewed favorably and has led to improved communication.[24-26] In addition, understanding the impact of symptoms is important for the planning and implementation of future SBMA research. These symptoms can be targets of therapeutic interventional trials and can serve as primary or secondary endpoints in clinical trials.

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Disclosure

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