Patient Preference and Adherence

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ORIGINAL RESEARCH

Impact of Potential Symptoms and Risks Associated with Acid Sphingomyelinase Deficiency on Patients and Caregivers: A Best-Worst Scaling Study

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Purpose: Acid sphingomyelinase deficiency (ASMD) is a rare, progressive, and potentially fatal disease affecting major organs; its symptoms present heterogeneously. Data on the most bothersome symptoms for patients with ASMD types B or A/B and their caregivers or parents are limited. We conducted a survey to quantify the relative impact of potential ASMD symptoms and risks for patients and parents/caregivers.

Patients and Methods: Twenty respondents, recruited via National Niemann-Pick Disease Foundation (United States) and Niemann-Pick United Kingdom, took a preference survey: 11 patients who had a self-reported diagnosis of ASMD types B or A/B and 9 parents who had a child with ASMD types B or A/B. Using object-case best-worst scaling, we explored the most and least bothersome among a set of 15 ASMD symptoms/risks selected based on clinical input and qualitative research with patients and caregivers. In 15 experimentally designed questions containing five items each, respondents ranked the symptoms/risks, irrespective of their experiences with them. Data were analyzed using a conditional multinomial logit model.

Results: Patients reported constant abdominal pain, severe pain in bones and joints, and severe fatigue to be the most bothersome potential symptoms or risks, followed by a chance of bleeding in the spleen. The next most bothersome potential symptom was constant shortness of breath. Easy bruising and noticeable abdominal enlargement were among the least bothersome symptoms. The most bothersome symptom for parents was bleeding in the spleen.

Conclusion: Patients and parents had similar perceptions of the most bothersome potential symptoms/risks. Despite the small sample size typical of rare disease studies, understanding patient preferences is important for such diseases and can inform shared decision-making.

Keywords: best-worst scaling, patient, caregiver, rare disease

Introduction

Acid sphingomyelinase deficiency (ASMD), historically known as Niemann-Pick disease type A, type A/B, and type B, is a rare, progressive, potentially fatal lysosomal storage disease caused by pathogenic variants in the *SMPD1* gene that affect multiple organ systems.[1] ASMD varies in severity, and symptom presentation is heterogeneous.[2] The most severe form of ASMD, type A (infantile neurovisceral ASMD), is characterized by extensive central nervous system (CNS) involvement along with visceral manifestations,[1] whereas ASMD type B (chronic visceral ASMD) has little to no neurological involvement but affects the lungs, liver, spleen, heart, and other organs, potentially leading to serious and life-threatening complications.[2] ASMD type A/B, an intermediate form, involves more significant neurological symptoms than ASMD type B.[2] Historically, patients with ASMD have relied on supplemental breathing aides, occupational and physical therapy, and equipment such as spleen-guards to address the symptoms and risks of the disease. Recently, the first disease-modifying treatment for non-neurologic symptoms of ASMD (olipudase alfa, an acid sphingomyelinase enzyme replacement therapy) was approved in the European Union, the United States (US), and other countries.[3–6]

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No ASMD-specific patient-reported outcome (PRO) measure exists, and limited data exist regarding ASMD-related disease burdens and associated symptoms.[2,7] Research evaluating patient and caregiver (ie, parent, relative, or guardian) experiences has suggested that the most bothersome symptoms of ASMD are fatigue, shortness of breath, bruising/bleeding, lower limb/joint pain, sleep disturbances, headaches, and diarrhea.[7] However, the relative impact of ASMD's symptoms has not been measured. To help fill this knowledge gap, preference surveys, using object-case best-worst scaling (BWS) methodology, were conducted to quantify the relative impact of potential ASMD symptoms and risks among patients and parents of patients with ASMD types B or A/B and inform shared decision-making and treatment improvements. BWS methods are used in a variety of contexts to gather information on the relative importance, burden, or bothersomeness of disease impacts and adverse events.[8–11]

Materials and Methods

Survey Development

Two online surveys containing object-case BWS questions were used to explore the relative importance of 15 actual or potential ASMD symptoms and risks. The symptoms and risks were selected on the basis of qualitative research with patients and caregivers and after consultation with clinical experts.[2,7] The surveys, one for patients and one for parents, contained demographic and background questions about ASMD symptoms and treatments and patient-friendly descriptions of the 15 symptoms and risks. The survey instruments were also reviewed by the panel members of the National Niemann-Pick Disease Foundation, Inc. (NNPDF), and Niemann-Pick United Kingdom (NPUK) advocacy organizations; their input was incorporated into the final surveys.

Object-case BWS has been used extensively in healthcare settings.[8–14] Prior studies have used object-case BWS to assess the potential benefits and risks of treatments, rank the relative importance of adverse events that patients might experience from treatments, and rank preferences for different modes of treatment administration.[11–13] In object-case BWS, respondents answer a series of questions, each question presenting a subset of features or outcomes from a longer list of such items. Respondents identify the best or most preferred item and the worst or least preferred item in each subset. This yields the relative importance of each item included in the BWS exercise.

Table 1 lists the 15 items (symptoms and risks) included in the BWS exercise, some of which are different levels of severity of the same symptom. Respondents were shown a series of 15 questions, each question containing a varying subset of five items from the complete list of 15 items shown in Table 1. Figure 1 presents an example question. In each question, respondents were asked to rank the symptom or risk from most bothersome to least bothersome, even if the respondents had not experienced the symptom or risk. The BWS method requires all respondents to rank all 15 items, and each respondent expresses preferences based on their own experience and circumstances.

A total of 30 BWS questions each containing 5 items were created using a balanced incomplete block design created in SAS.[14–17] The questions were split into 2 blocks of 15 questions, and respondents were randomly assigned to view one block of 15 questions. Appendix A presents the 5 specific items that appeared in each of the 30 questions.

For the four symptoms with multiple levels of severity, the surveys first described each of the four symptoms and provided definitions of the levels of severity (eg, constant, frequent, occasional) in patient-friendly language, followed by questions about the respondents' experiences with each of the symptoms (Table 2).

To test the language and questions in the surveys, four pretest interviews were completed (two interviews were with caregivers who have a child of any age diagnosed with chronic ASMD, and the remaining two interviews were with adult ASMD patients aged ≥18 years). One patient and one parent each were recruited from the US (NNPDF) and the UK (NPUK).

Sample

The study sample was recruited from the memberships of two advocacy organizations: NNPDF, based in the US with a membership of 450 families, and NPUK, based in the UK with approximately 500 members. Recruitment was conducted via emails, social media, and publicity at conferences. To be eligible to complete the survey, individuals were required to be a resident of the US or UK, be aged 18 years or older, have a self-reported diagnosis of ASMD types B or A/B or have a child diagnosed with ASMD types B or A/B, and not be using an investigational therapy as part of

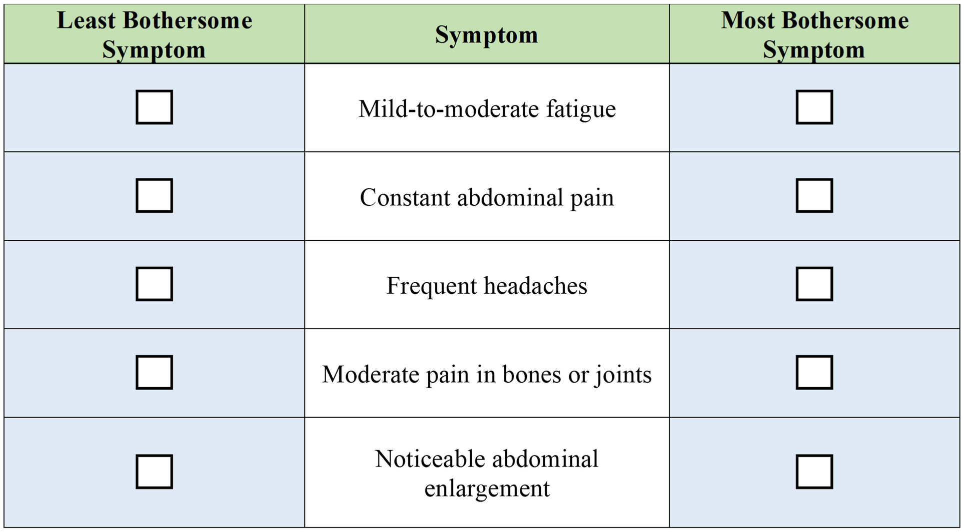
Table 1 Best-Worst Scaling Symptoms and Risks and Number of Times Each Symptom or Risk Selected as Most or Least Bothersome

Item	Parents			Patients		
	Number of Times Selected		No. of Times Seen	Number of Times Selected		No. of Times Seen
	Most Bothersome	Least Bothersome		Most Bothersome	Least Bothersome	
Chance of bleeding in your spleen from a light hit in the abdomen	26	6	45	22	7	55
Severe pain in bones or joints	21	2	45	27	1	55
Constant abdominal pain	15	1	46	27	0	56
Constant moderate shortness of breath	12	1	43	11	2	53
Severe fatigue	14	4	46	24	0	56
Frequent abdominal pain	11	3	46	13	4	56
Frequent moderate shortness of breath	8	3	43	4	5	53
Moderate pain in bones or joints	6	4	46	6	5	56
Frequent diarrhea	8	9	44	9	7	54
Very noticeable abdominal enlargement	7	12	43	3	21	53
Frequent headaches	0	6	45	11	8	55
Difficulty sleeping	3	11	45	4	13	55
Noticeable abdominal enlargement	4	18	46	0	29	56
Mild-to-moderate fatigue	0	23	46	4	17	56
Easy bruising	0	32	46	0	46	56i

a clinical trial for ASMD. The study design was reviewed by RTI International's institutional review board (IRB) and determined to be exempt from full review (IRB ID STUDY00020258). All pretest participants and survey respondents were required to provide informed consent; participation in the survey was voluntary.

Analysis

Responses to all questions in the survey were summarized using descriptive statistics, except for the BWS questions. The patient sample was analyzed separately from the parent sample.



Least Bothersome Symptom	Symptom	Most Bothersome Symptom
☐	Mild-to-moderate fatigue	☐
☐	Constant abdominal pain	☐
☐	Frequent headaches	☐
☐	Moderate pain in bones or joints	☐
☐	Noticeable abdominal enlargement	☐

Figure 1 Example Best-Worst Scaling Question. Respondents were shown the following prompt: "For the next 15 questions, we will show you sets of five symptoms. For each set, please select the symptom that would bother you the most if [you/your child] experienced it by checking the box to the right of the symptom. Then, please select the symptom that would bother you the least if [you/your child] experienced it by checking the box to the left of that symptom. Please choose only one symptom as the most bothersome and one symptom as the least bothersome. Imagine that you have experienced the symptoms when answering the questions".

Table 2 Symptoms/Risks and Levels of Severity

Symptom/Risk	Description in the Survey	Levels Presented in the Survey
Moderate shortness of breath	ASMD can lead to shortness of breath or the feeling of being winded. The shortness of breath can be mild to severe. In addition to the severity of the shortness of breath, some [people/children] experience shortness of breath more often and some experience it less often. For this survey, we are going to ask you to think about how often [you/your child] experiences moderate shortness of breath. When your child has moderate shortness of breath: ● [You/He/she] becomes short of breath after minimal physical activity. ● [You/He/she] may have trouble with daily activities like activities at school, playing, or doing chores at home. Later in this survey, we will ask you to think about hypothetical treatments that have different effects on how often [you/your child] experiences moderate shortness of breath. There are 3 possibilities.	Occasional: ● [You/Your child] experiences occasional moderate shortness of breath. ● [You/Your child] can do all his/her usual school and social activities. Frequent: ● [You/Your child] experiences moderate shortness of breath on most days. ● [You/Your child] may have trouble doing some of his/her usual school and social activities on days when he/she experiences shortness of breath. Constant: ● [You/Your child] experiences moderate shortness of breath every day. ● [You/Your child] has trouble doing all his/her usual school and social activities.
Abdominal enlargement	For people who have ASMD, enlargement of the liver or spleen can lead to an enlarged abdomen. Here we are only talking about in the impact of the size of the abdomen on [you/your child], not the pain that might be associated with the enlargement. Enlargement of the abdomen can cause difficulty sleeping, make it hard to bend over, and [you/your child] may also feel full faster when eating. Later in this survey, we will ask you to think about hypothetical treatments that have different effects on how enlarged [your/your child's] abdomen is. There are 3 possibilities.	Not noticeable: ● [You have/Your child has] very mild enlargement of [your/his/her] abdomen. ● The enlargement is not noticeable to others, but [you/your child] may feel and see the enlargement themselves. Noticeable: ● [You/Your child] experiences some enlargement of [your/his/her] abdomen. ● The enlargement might be noticeable to others if [you/your child] wears tight clothing. ● The enlargement may interfere with sleep, it may be harder to bend over all the way, and [you/he/she] may feel full earlier when eating. Very noticeable: ● [You/Your child] experiences significant enlargement of [your/his/her] abdomen. ● The enlargement will be visible even when [you/your child] wears loose clothing. ● The enlargement will interfere with sleep, your child will not be able to bend over very far, and your child will feel full earlier when [you/he/she] eats.
Abdominal Pain	Patients with ASMD may have pain in their abdomen. The pain may be associated with different activities. The pain may be dull or sharp, and it may be constant or only occasional. Later in this survey, we will ask you to think about hypothetical treatments that have different effects on how painful [your/your child's] abdomen is. There are 3 possibilities.	Occasional: ● [You feel/Your child feels] occasional abdominal pain when [you/he/she] moves around, especially when [you/he/she] lies down or moves in certain ways. ● Your child can do all [your/his/her] usual school and social activities. Frequent: ● [You feel/Your child feels] abdominal pain much of the time when he/she moves around. ● [You have/Your child has] pain if he/she is bumped in the side. ● [You/Your child] may have trouble doing some of [your/his/her] usual school and social activities on days when [you/he/she] is experiencing pain. Constant: ● [You/Your child] may feel dull or sharp abdominal pains all or most of the time when [you/he/she] moves around. ● [You/Your child] has abdominal pain if [you/he/she] is bumped lightly in the side. ● [You/Your child] has trouble doing [your/his/her] usual school and social activities.

(Continued)

Table 2 (Continued).

Symptom/Risk	Description in the Survey	Levels Presented in the Survey
Level of fatigue or tiredness	Patients with ASMD may experience tiredness or fatigue that does not go away, even with rest. Later in this survey, we will ask you to think about hypothetical treatments that have different effects on feeling tired. There are 3 possibilities.	None: ● [You/Your child] is not more tired than other children. ● [You/Your child] is able to do his/her usual school and social activities. Mild to moderate: ● [You/Your child] feels tired. Resting can help, but it may not fully relieve the tiredness. ● [You/Your child] may have trouble with moderate physical activities, such as walking and playing. ● [You/Your child] may not have the energy to do all of his/her usual school and social activities. ● [You/Your child] need to plan ahead to make sure he/she has energy for the activities he/she wants to do. Severe: ● [You/Your child] feels tired. Resting does not help. ● [You/Your child] will not have the energy to do his/her usual school and social activities. ● [You/Your child] will need help with moderate physical activities like moving around, playing, or helping with household chores. ● [You/Your child] may need help taking care of himself/herself, including bathing, dressing, and taking medication.

Notes: [a]Respondents were asked to consider which symptoms/risks they would most want to improve with a hypothetical treatment.
Abbreviation: ASMD, acid sphingomyelinase deficiency

The BWS data were analyzed using a conditional multinomial logit (MNL) model that accounted for correlation in the responses from each respondent.[13,18] Log-odds importance weights were estimated using an MNL model that related respondents' choices for the most and least preferred items to the item-specific variables; items were effects coded.[19] The log-odds importance weights represented the relative weights respondents placed on each item when selecting the most bothersome item. Larger coefficients indicated that the symptoms or risks were considered more important to avoid. Relative importance weights from the log-odds importance weights were then calculated, using a probability-based rescaling procedure.[20–22] A Wald χ^2 test was used to calculate the statistical significance of the difference between each pair of items; differences were considered statistically significant if P values were ≤ 0.05. The analyses were independently replicated by two analysts. The size of the sample precluded analysis of differences across subgroups of respondents.

Results

Cognitive Pretesting Interviews

In the four cognitive pretesting interviews, participants stated that they generally understood the survey and felt it was appropriate for patients with ASMD or their caregivers. Patients and parents noted that it was sometimes difficult to know whether a symptom was associated with ASMD. Parents also mentioned not knowing their child was experiencing a symptom until the child told them. To more comprehensively identify the range of patients' and parents' experiences, the question that asked respondents to identify the symptoms they had experienced was expanded to contain additional symptoms, including frequent respiratory infections, psychiatric or mental health problems, psoriasis, vision problems, insomnia/difficulty sleeping, asthma, eating disorders, and chance of bleeding from a light hit to the abdomen. Some participants mentioned that it was difficult to know how to respond when the questions included symptoms or risks that they had never experienced. Instructions were clarified to ask respondents to imagine that they (or their child) would eventually experience the symptom or risk, even if they had not yet experienced it, when ranking the items as most or least bothersome.

Sample Characteristics

The survey sample consisted of 20 respondents: 16 respondents in the US (10 patients and 6 parents) and 4 respondents in the UK (1 patient and 3 parents) (Table 3). Of the 11 patients who completed the survey, 8 (72.7%) were female. Of the 9 parents who completed the survey, 4 (44.4%) reported that their child with ASMD was female. Patients in the US had a median age of 5 years (range, 2–51 years) when they were diagnosed with ASMD. The UK patient was 52 years old when diagnosed with ASMD. The median age at diagnosis for children of parents in the UK and the US was 3 years (range, 3–14 years) and 2.3 years (range, 1–6 years), respectively. All patients and parents in our sample reported that they or their child had experienced most of the symptoms of ASMD presented in the survey. Most respondents reported that they or their child had experienced abdominal enlargement (80%), fatigue (75%), abdominal pain (75%), and shortness of breath (60%) (Table 3).

Table 3 Sample Characteristics

Question	**Parents (n = 9)**		**Patients (n = 11)**	
	UK (n = 3)	**US (n = 6)**	**UK (n = 1)**	**US (n = 10)**
How old are you?				
18–30 years old	0	1 (16.7%)	0	2 (20.0%)
31–40 years old	0	1 (16.7%)	0	3 (30.0%)
41–50 years old	2 (66.7%)	1 (16.7%)	0	1 (10.0%)
51–60 years old	1 (33.3%)	3 (50.0%)	1 (100.0%)	4 (40.0%)
How old were you [was your child] when you were [he/she was] diagnosed with ASMD?				
1 year	0	1 (16.7%)		
1.5 years	0	1 (16.7%)	0	0
2 years	0	1 (16.7%)	0	2 (20.0%)
2.5 years	0	2 (33.3%)	0	0
3 years	2 (66.7%)	0	0	1 (10.0%)
4 years	0	0	0	2 (20.0%)
6 years	0	1 (16.7%)	0	1 (10.0%)
14 years	1 (33.3%)	0	0	0
30 years	0	0	0	1 (10.0%)
31 years	0	0	0	1 (10.0%)
39 years	0	0	0	1 (10.0%)
51 years	0	0	0	1 (10.0%)
52 years	0	0	1 (100.0%)	0
Mean (SD)	6.7 (6.4)	3.9 (4.97)	52 (0)	17.2 (18.6)
Median	3	2.3	52	5
Min, max	3, 14	1, 6	52, 52	2, 51
Respondent's gender				
Female	3 (100.0%)	6 (100.0%)	0	8 (80.0%)
Male	0	0	1 (100.0%)	2 (20.0%)
Prefer not to say	0	0	0	0
Child's gender[a]				
Female	2 (66.7%)	2 (33.3%)	N/A	N/A
Male	1 (33.3%)	4 (66.7%)	N/A	N/A
How old is your child?[a]				
0–5 years old	0	0	N/A	N/A
6–10 years old	0	2 (33.3%)	N/A	N/A
11–15 years old	2 (66.7%)	1 (16.7%)	N/A	N/A
16–20 years old	0	0	N/A	N/A
21–30 years old	1 (33.3%)	2 (33.3%)	N/A	N/A
31–40 years old	0	1 (16.7%)	N/A	N/A
41–50 years old	0	0	N/A	N/A
51–60 years old	0	0	N/A	N/A

(*Continued*)

Table 3 (Continued).

Question	**Parents (n = 9)**		**Patients (n = 11)**	
	UK (n = 3)	**US (n = 6)**	**UK (n = 1)**	**US (n = 10)**
61–70 years old	0	0	N/A	N/A
More than 70 years old	0	0	N/A	N/A
Which of the following best describes your employment status?				
Employed full time	2 (66.7%)	3 (50.0%)	0	3 (30.0%)
Employed part time	0	0	0	1 (10.0%)
Self-employed	1 (33.3%)	0	0	0
Homemaker	0	1 (16.7%)	0	1 (10.0%)
Student	0	0	0	1 (10.0%)
Retired	0	1 (16.7%)	0	0
Disabled/unable to work	0	1 (16.7%)	1 (100.0%)	3 (30.0%)
Unemployed but looking for work	0	0	0	0
Unemployed and not looking for work	0	0	0	1 (10.0%)
What is the highest level of education you have completed?[b]				
Primary school education or less	0	N/A	0	N/A
Secondary school education	1 (33.3%)	N/A	1 (100.0%)	N/A
Professional or work-related college qualifications	0	N/A	0	N/A
Undergraduate university degree (eg, BS/BA)	1 (33.3%)	N/A	0	N/A
Postgraduate university degree (eg, MS/MA, MPhil, PhD)	1 (33.3%)	N/A	0	N/A
What is the highest level of education you have completed?[c]				
Less than high school	N/A	0	N/A	0
Some high school	N/A	1 (16.7%)	N/A	0
High school or equivalent	N/A	0	N/A	2 (20.0%)
Some college but no degree	N/A	2 (33.3%)	N/A	2 (20.0%)
Technical school	N/A	1 (16.7%)	N/A	1 (10.0%)
Associate' degree (2-year college degree)	N/A	0	N/A	2 (20.0%)
4-year college degree (eg, BA, BS)	N/A	1 (16.7%)	N/A	2 (20.0%)
Some graduate school but no degree	N/A	0	N/A	0
Graduate or professional degree (eg, MBA, MS, MD, PhD)	N/A	1 (16.7%)	N/A	1 (10.0%)
Which type of Niemann-Pick disease has your child been diagnosed with? If you are unsure, here are links describing the types of Niemann-Pick.				

(*Continued*)

Table 3 (Continued).

Question	Parents (n = 9)		Patients (n = 11)	
	UK (n = 3)	US (n = 6)	UK (n = 1)	US (n = 10)
Niemann-Pick type B (also called ASMD Niemann-Pick disease type B, Chronic Visceral ASMD, or ASMD NPB)	3 (100.0%)	5 (100.0%)	1 (100.0%)	9 (90.0%)
Niemann-Pick type A/B or intermediate Niemann-Pick disease (also called Intermediate Niemann-Pick disease, Chronic Neurovisceral ASMD, or ASMD type A/B)	0	1 (16.67%)	0	1 (10.0%)
What symptoms of ASMD have you [has your child] ever experienced? (Please check all that apply)[d]				
Difficulty breathing/ shortness of breath	2 (66.7%)	2 (33.3%)	1 (100.0%)	7 (70.0%)
Frequent respiratory infections	1 (33.3%)	2 (33.3%)	0	3 (30.0%)
Abdominal pain or discomfort	3 (100.0%)	5 (83.3%)	1 (100.0%)	6 (60.0%)
Abdominal enlargement (from enlarged organs, such as spleen or liver)	3 (100.0%)	5 (83.3%)	1 (100.0%)	7 (70.0%)
Easy bruising	2 (66.7%)	5 (83.3%)	0	9 (90.0%)
Prolonged bleeding (eg, nosebleeds)	2 (66.7%)	1 (16.67%)	0	7 (70.0%)
Fatigue	3 (100.0%)	4 (66.67%)	1 (100.0%)	7 (70.0%)
Difficulty sleeping	1 (33.3%)	3 (50.0%)	0	5 (50.0%)
Migraines or headaches	2 (66.7%)	3 (50.0%)	1 (100.0%)	6 (60.0%)
Diarrhea	2 (66.7%)	3 (50.0%)	0	4 (40.0%)
Pain in bones and joints	3 (100.0%)	3 (50.0%)	1 (100.0%)	7 (70.0%)
Vomiting	1 (33.3%)	2 (33.3%)	0	1 (10.0%)
Acid reflux	1 (33.3%)	2 (33.3%)	1 (100.0%)	4 (40.0%)
Balance and coordination issues	2 (66.7%)	3 (50.0%)	1 (100.0%)	5 (50.0%)
Mental health problems	1 (33.3%)	1 (16.7%)	1 (100.0%)	1 (10.0%)
Other (please specify)[e]	1 (33.3%)	1 (16.7%)	0	7 (70.0%)
Other (please specify)[e]	1 (33.3%)	1 (16.7%)	0	5 (50.0%)
Other (please specify)[e]	1 (33.3%)	1 (16.7%)	0	2 (20.0%)
I [My child] have/has not had any of these symptoms	0	0	0	0

Notes: [a] This question was shown only in the parent survey. [b] This question was shown only in the UK version of the survey. [c] This question was shown only in the US version of the survey. Highest level of education for US patients was missing for 1 patient. [d] Respondents were able to select more than one answer to this question. [e] Patient respondents provided the following free-text symptoms: eyesight, enlarged spleen causing issues with the heart (plaque build up), abnormal growth, low white blood cells, ACTH, memory issues, cherry red spot in eyes, lung issues (wall thickening and ground glass and high pulmonary artery pressure), low platelets, bending over, tremors in my hands and twitching in face, and delayed growth. Parent respondents provided the following free-text symptoms: neutropenia, intermittent swelling and burning tingling in hands and feet, working memory difficulties, osteopenia, and developmental delay.

Abbreviation: ASMD, acid sphingomyelinase deficiency; SD, standard deviation; UK, United Kingdom; US, United States

Best-Worst Scaling

The BWS results indicated heterogeneity in respondents' preferences pertaining to items of potential symptoms or risks presented in the survey. Among patients, only constant abdominal pain and severe fatigue were never selected as least bothersome; noticeable abdominal enlargement and easy bruising were the only items never selected as most bothersome. Among parents, every item was selected as least bothersome by at least one parent across all the questions (Table 1). Frequent headaches, mild-to-moderate fatigue, and easy bruising were the only items never selected by parents as most bothersome. Patients' and parents' preferences for ASMD symptoms and risks were generally aligned, with slight differences in the order of ranking.

Figure 2 presents the BWS rescaled relative importance estimates from the MNL model for patients and parents so that the most important item to patients—constant abdominal pain—is set to 10. The scaled relative importance weight for each of the remaining items can be interpreted as the effect of that item on utility relative to the utility of constant abdominal pain for that sample. Tables B1 and B2 in Appendix B present the statistical significance of the difference between each pair of items. For patients, constant abdominal pain was rated as most bothersome of all items included in the BWS exercise, although there were no statistically significant differences (at a threshold of $P \leq 0.05$) between constant abdominal pain and severe pain in bones or joints and severe fatigue. The next most bothersome item was chance of bleeding in the spleen (which was statistically significantly different from constant abdominal pain [$P = 0.046$]). Constant abdominal pain ($P = 0.001$), severe pain in bones and joints ($P = 0.004$), and severe fatigue ($P = 0.014$) were statistically significantly more bothersome to patients than constant shortness of breath. For patients, the relative weights for constant shortness of breath, frequent abdominal pain, chance of bleeding in the spleen (defined herein as caused by a light hit to the abdomen), headaches, and diarrhea were not statistically different from one another. The only items statistically significantly less bothersome than frequent shortness of breath were mild-to-moderate fatigue ($P = 0.017$), both levels of abdominal enlargement (very noticeable enlargement [$P = 0.002$] and noticeable enlargement [$P \leq 0.000$]), and easy bruising ($P \leq 0.000$).

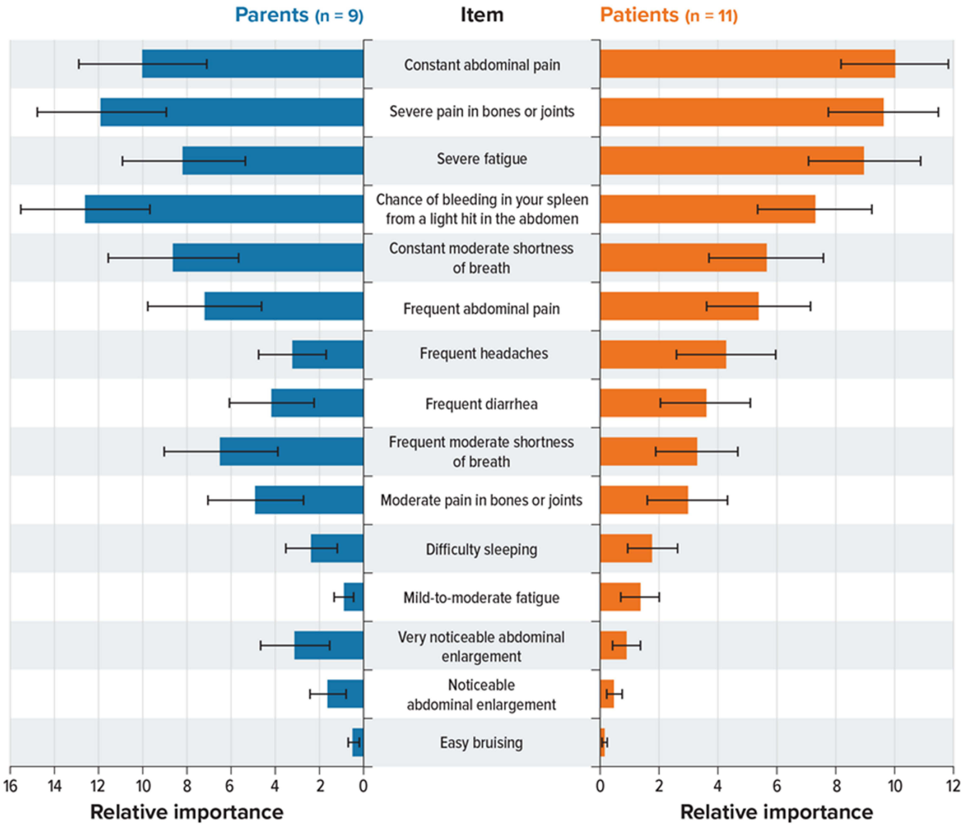


Figure 2 Best-Worst Scaling Main-Effects Item Relative Importance for Patients and Parents.

Notes: The relative importance is scaled so that constant abdominal pain is set to 10. Error bars represent the scaled 95% confidence interval around the point estimate.

Parents viewed chance of bleeding in the spleen as the most bothersome item relative to all other BWS items, although there were no statistically significant differences between the chance of bleeding and severe pain in bones or joints, constant abdominal pain, and constant moderate shortness of breath. Further, there were no statistically significant differences between constant shortness of breath and severe pain in bones or joints, severe fatigue, constant abdominal pain, chance of bleeding in the spleen, frequent abdominal pain, or frequent moderate shortness of breath. However, frequent moderate shortness of breath was statistically significantly more bothersome than difficulty sleeping ($P = 0.006$), mild-to-moderate fatigue ($P \leq 0.000$), either level of abdominal enlargement (very noticeable enlargement [$P = 0.037$] or noticeable enlargement [$P = 0.001$]), and frequent headaches ($P = 0.039$).

For both patients and parents, the largest differences in severity levels were observed for fatigue, joint pain, and abdominal pain. Parents did not statistically significantly differentiate between either level of abdominal enlargement, shortness of breath, and abdominal pain.

Discussion

Patients with ASMD experience a wide range of symptoms and symptom severity, reflecting the heterogeneity of this rare disease. Limited data exist regarding patient and parent perceptions of how bothersome potential ASMD symptoms and risks may be. To fill this gap, we conducted a preference survey in the US and UK to quantify patients' and parents' perceptions of the most and least burdensome ASMD symptoms and risks from a set of 15 potential symptoms and risks. Object-case BWS methodology was used to explore patient and parent preferences for these 15 potential symptoms and risks.

The MNL results, when corrected to account for correlation in the responses within each respondent, indicated that, on average, patients and parents had similar views on what were the most and least bothersome ASMD symptoms or risks presented in the survey. Patients ranked constant abdominal pain, severe pain in bones or joints, and severe fatigue as the most bothersome potential symptoms or risks, followed by a chance of bleeding in the spleen (although it was only statistically significantly different from constant abdominal pain [$P = 0.046$]). It should be noted that severe fatigue was defined as fatigue so severe that the respondent might need help taking care of themselves and doing daily activities. The next most bothersome potential symptom or risk, constant shortness of breath, was statistically significantly less bothersome to patients than severe pain in bones and joints ($P = 0.004$), severe fatigue ($P = 0.014$), and constant abdominal pain ($P = 0.001$). Parents had similar ratings, but in a somewhat different order. Parents viewed the chance of bleeding in the spleen as the most bothersome potential symptom or risk, although there was no statistically significant difference between the chance of bleeding and the next most bothersome items: severe pain in bones or joints, constant abdominal pain, and constant moderate shortness of breath. Irrespective of the findings from the BWS exercise, all 15 items constituted moderate-to-severe potential symptoms and risks that should receive prompt medical attention.

Our findings are broadly consistent with qualitative evidence indicating fatigue, shortness of breath, bleeding, and pain to be among the most bothersome ASMD symptoms for patients and caregivers.[7] By evaluating and quantifying the relative impact of potential ASMD symptoms and risks, our study provides novel insights into the experiences of patients with ASMD and their caregivers that can inform shared decision-making with their physicians. Our results suggested some heterogeneity between patients and parents in the perceived burden of potential symptoms and risks. The chance of bleeding in the spleen was frequently selected as the most bothersome potential symptom or risk, chosen 22 times by patients and 26 times by parents. However, among the items that were selected as most bothersome at least 20 times by either patients or parents, the chance of bleeding in the spleen was the item most often selected as the least bothersome potential symptom or risk, indicating differing views about the impact of this item. Heterogeneity in our findings is not unexpected, given that ASMD affects multiple organ systems and has a heterogeneous presentation,[2] and patients' individual impressions of the bothersomeness of ASMD symptoms and risks reflect their unique experiences and circumstances.

Prior research supports the patient-perceived burden of respiratory symptoms and abdominal symptoms;[23] the burden of other factors, such as ASMD-related fatigue and pain, is less well known. Our results suggested that several ASMD-related symptoms or risks carry a similar degree of bothersomeness. Although reductions in abdominal enlargement were less important overall than severe pain, fatigue, and constant shortness of breath, some respondents in our study prioritized spleen size over frequency of shortness of breath. A possible explanation for the importance of this item is that abdominal enlargement can contribute to fatigue, shortness of breath, and early satiety.

As with many rare diseases, generic measures may not comprehensively capture patients' experiences with the disease, and no ASMD-specific PRO measure exists to capture ASMD-specific disease burdens and symptom severity.[2] There are challenges associated with adapting existing PRO measures to rare diseases, particularly diseases with a heterogeneous presentation such as ASMD.[24–26] For example, although symptoms of Gaucher disease may seem similar to those of ASMD, adapting a Gaucher disease measure for use in ASMD would not be suitable because symptoms of Gaucher disease are not always similar to those observed in patients with ASMD.[27] Another difficulty in adapting a PRO measure is testing and demonstrating the validity of the adapted measure and its items, due to the small size of the patient population.[28] Nevertheless, the results of this survey provided a potential foundation for the future development of a specific ASMD PRO measure. Such a measure could provide data on patient quality of life, help prioritize the symptoms of ASMD, and inform treatment improvements.

Limitations

Some limitations of this study should be considered. The survey presented 15 actual or potential symptoms and risks associated with ASMD types B or A/B identified as important to patients with ASMD in prior qualitative research;[7] not all symptoms and risks associated with ASMD were presented. Not all respondents had experienced all symptoms presented in the surveys, and the symptoms and risks were separated from their pathophysiologic basis. Whether experience with a symptom or risk would have led a respondent to rank it as more or less bothersome would depend on the individual and the symptom or risk. Because of the small sample size and because most respondents had experienced most of the symptoms included in the BWS exercise, we were unable to analyze whether having experienced a given symptom or risk influenced the respondent's perception of its impact. Further, many ASMD symptoms and risks are interrelated. Splenomegaly, for example, may be associated with abdominal enlargement, fatigue, difficulty sleeping, easy bruising, shortness of breath, abdominal pain, or chance of bleeding in the spleen. Because of splenomegaly's association with other clinical manifestations of ASMD, multiple items in the surveys could be related to splenomegaly, potentially confounding the results. Likewise, it is unclear whether patients consistently interpreted fatigue as persistent overwhelming tiredness or whether they confounded the experience of fatigue from other symptoms such as shortness of breath; however, pretest interviews did not observe this issue.

The BWS approach has been widely used in healthcare settings to rank the importance of symptoms and outcomes. Patients and caregivers who participated in the pretesting of our surveys were able to understand the exercise and were able to select the most and least bothersome potential symptoms and risks. Future research should explore the impact of other known features of ASMD, including hepatomegaly, gastrointestinal symptoms, cardiac disease (eg, atherogenic dyslipidemia, coronary artery disease, or heart valve disease),[2] and musculoskeletal manifestations, which will aid in understanding the burden of ASMD's clinical presentation. Future research should also explore whether patients' prior experiences with the symptoms and risks of ASMD have an influence on their perceptions of their impact.

The samples were recruited through patient advocacy organizations, whose preferences may not be representative of the broader population of ASMD patients or their caregivers. All clinical information was self-reported by the respondents, including ASMD type, and was not verified in patient health records, although the survey described the corresponding ASMD and Niemann-Pick classifications and contained links to websites that described the ASMD classifications. The sample size for this study was small, resulting in potential uncertainty in the findings. In addition, there is the potential that some respondents may have been relatives (eg, a sibling or parent of another respondent), possibly influencing the results. Recruiting patients with rare diseases into patient preference studies is a challenge, and studies of rare diseases often lack data on patient preferences, although such data can be important for decision-makers. In future quantitative preference studies of rare diseases with small sample sizes, researchers could consider mixed-methods studies that capture quantitative rankings via qualitative interviews. Alternatively, patient preference methods that produce individual-level data, such as the threshold technique, could be considered.

Conclusions

ASMD is a rare disease with a heterogeneous set of symptoms, which makes it challenging to identify priorities for research on treatments or develop disease-specific PROs. Little quantitative data exist on the preferences of patients and caregivers regarding the burden of potential ASMD symptoms and its impact on quality of life. Recruiting for studies of rare disease populations is challenging; however, despite this study's small sample size, results provide important insights into patient views and concerns. This study, designed based on research and input from patients and caregivers, provides evidence on the relative impact of potential ASMD symptoms and risks that adds to the base of knowledge about the preferences of ASMD patients. Patients and parents had similar relative preferences when ranking potential symptoms and risks, although their responses displayed heterogeneity across the sample. Understanding patients' concerns will help clinicians, researchers, and other stakeholders better support patient communities.

Abbreviations

ASMD, Acid sphingomyelinase deficiency; BWS, Best worst scaling; CNS, Central nervous system; MNL, Multinomial logit; NNPDF, National Niemann-Pick Disease Foundation; NPUK, Niemann-Pick United Kingdom; PRO, Patient reported outcome; SAS, Statistical Analysis System; SD, Standard deviation; UK, United Kingdom; US, United States

Ethics Approval and Informed Consent

The study design was reviewed by RTI International's institutional review board and determined to be exempt from full review. All pretest participants and survey respondents were required to provide informed consent; participation in the survey was voluntary.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

CM is an employee of RTI Health Solutions and receives funding from commercial and federal entities to conduct studies on healthcare, outside the submitted work. JC was an employee of RTI Health Solutions at the time of the study conduct. RPJ is an employee of Sanofi and may hold shares and/or stock options in the company. LN and DJ were full-time employees of Sanofi when this study was conducted. The authors report no other conflicts of interest in this work.

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