Molecular Genetics and Metabolism Reports 38 (2024) 101052

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Diagnostic odyssey for patients with acid sphingomyelinase deficiency (ASMD): Exploring the potential indicators of diagnosis using quantitative and qualitative data

Andrew Doerr [a], Maliha Farooq [b], Chad Faulkner [b], Rebecca Gould [a], Krista Perry [b], Ruth Pulikottil-Jacob [c,*], Pamela Rajasekhar [d]

[a] Fulcrum Research Group, Waltham, MA, United States
[b] Trinity Life Sciences, Waltham, MA, United States
[c] Sanofi, Thames Valley Park, Reading, United Kingdom
[d] Sanofi, Cambridge, MA, United States

ARTICLE INFO

Keywords:
Acid sphingomyelinase deficiency
ASMD
Niemann–Pick
Diagnosis
Clinical presentation
Diagnostic delay

ABSTRACT

Acid sphingomyelinase deficiency (ASMD) is a rare, progressive, and potentially fatal lysosomal storage disease. This two-part international study aimed to understand physician, patient, and caregivers' experiences during the ASMD diagnostic journey. Qualitative interviews were conducted with patients with ASMD type B or A/B, caregivers (for patients <18 years), and physicians (January 2018–May 2019). A quantitative patient chart review was then performed by physicians (1–3 charts per physician) (April to May 2020). Overall, 12 physicians and 27 patients (self-reported, $n = 11$; caregiver-reported, $n = 16$) completed qualitative interviews. Symptoms first presented at approximately 2 years, with physician visits 2 months–1 year later. On average, diagnosis took 3 years and average age at diagnosis was 5 years. During childhood, all patients reported abdominal enlargement and 67% had respiratory issues. Adult patients frequently reported fatigue (64%) and heart problems (36%). In the quantitative study, 86 physicians reviewed 193 ASMD patient charts. At initial presentation, most patients reported abdominal enlargement (pediatric, 55%; adolescents/adults, 39%). Time to diagnosis ranged 0–10 years for patients with ASMD type A/B or type B, and most patients (85%) received an incorrect initial diagnosis. Diagnosis of ASMD can be challenging, and is often delayed due to disease heterogeneity and misdiagnoses.

1. Introduction

Acid sphingomyelinase deficiency (ASMD), historically known as Niemann–Pick disease, is a rare, progressive, debilitating, and potentially fatal lysosomal storage disease [1,2]. ASMD is caused by mutations in the *sphingomyelin phosphodiesterase 1* gene, which results in progressive cellular or tissue damage and impaired function of multiple major organs [3–5]. Approximately 0.4 to 0.6 in 100,000 infants per year are born with ASMD [3,6,7]; however, this may be underestimated because of the rarity of the disease and subsequent lack of awareness.

ASMD represents a wide clinical spectrum of disease severity, with variable clinical features divided over three subtypes: infantile neurovisceral (ASMD or Niemann–Pick type A), chronic neurovisceral (ASMD or Niemann–Pick type A/B), and chronic visceral (ASMD or Niemann–Pick type B) [1,3,8]. ASMD type A is characterized by severe, progressive neurologic deterioration in the first year of life, which typically results in death before 3 years of age [9–13]. ASMD type B has a variable age of onset, ranging from childhood to adulthood [14], with most children surviving into adulthood [3]. Patients with ASMD type B experience a wide range of disease severity with little or no neurologic involvement [5,8]. The most common initial manifestation is hepatosplenomegaly, but patients with ASMD type B may also experience pulmonary dysfunction, dyslipidemia, liver dysfunction, growth deficits, delayed puberty, fatigue, and osteopenia [2–5,8,9,12,13,15]. Liver

Abbreviations: ASMD, acid sphingomyelinase deficiency; COE, center of excellence; eLFT, elevated liver function test; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GP, general practitioner; IRB, Institutional Review Board; LFT, liver function test.

* Corresponding author at: Global Head of Rare Disease Health Economics and Value Assessment, Sanofi UK, Thames Valley Park, Reading RG6 1PT, United Kingdom.
E-mail address: Ruth.Jacob@sanofi.com (R. Pulikottil-Jacob).

https://doi.org/10.1016/j.ymgmr.2024.101052
Received 28 November 2023; Accepted 8 January 2024
Available online 17 January 2024

and respiratory failure are the leading causes of mortality in this population [8,16]. Finally, ASMD type A/B falls in the middle of the spectrum, with patients experiencing neurodegeneration that develops from infancy to childhood, but is slower in progression than seen in patients with type A [3,9]. There is no clear diagnostic test to distinguish between the subtypes of ASMD in routine clinical use, with clinical presentation typically determining subtype [3,17].

The clinical manifestations of ASMD can overlap with other lysosomal storage diseases (e.g. Gaucher disease) [2] and other disorders such as malignancy and primary hepatic disease [11]. Consequently, the diagnosis of ASMD cannot be based entirely on clinical presentation, and biochemical and genetic tests are needed to distinguish ASMD from other diseases [1].

Although several studies have assessed the clinical manifestations and burden of ASMD [1,4,18,19], the experiences of patients and their caregivers during the diagnostic journey are not well known [20]. The aim of this study was to better understand physician, patient, and caregivers' experiences during the ASMD diagnostic journey, including unmet needs and the emotional impact of ASMD.

2. Methods

2.1. Study design

Two separate market research studies were conducted to provide further understanding of patients' experiences of living with ASMD, including additional insights from caregivers and physicians. Initially, a qualitative study was conducted to interview patients, caregivers, and physicians between January 2018 and May 2019. Secondly, a quantitative patient chart review study was performed with physicians on the same topics, to strengthen the qualitative data, between April and May 2020.

2.2. Qualitative study

2.2.1. Study design

The qualitative market research was conducted in two parts. Initially, physicians completed in-depth 60-min telephone interviews between January and March 2018. Patients and caregivers then participated in semi-structured 60-min telephone interviews that took place between October 2018 and May 2019. An additional 15-min pre-interview online survey was completed to gather additional details about their experience with diagnosis. Interview discussion topics included: initial symptoms and change over time; delay to diagnosis; diagnostic tests run; sources of information; accessible support; and overall emotional experience. The questions asked were open-ended to permit free-flowing discussion, as prompted by the interview question guide (**Supplementary Appendix 1**). Interviews were conducted in the native language. All interviews were recorded and transcribed.

2.2.2. Participant recruitment and eligibility criteria

2.2.2.1. Physicians. Physicians were recruited from a list (provided by Sanofi) of those who had previously treated patients with Gaucher disease, with the understanding that these physicians may have also diagnosed and managed patients with ASMD. This list was supplemented with market research panels. A target of 12 healthcare practitioners were planned for recruitment, split equally across the United States, Latin America, Europe, and Asia. Physicians were recruited from the United States, Argentina, Mexico, Germany, Italy, the United Kingdom, Japan, and South Korea. Prior to their interview, physicians were asked to complete a 15-min patient case assignment to ensure they met the necessary criteria. Included physicians were interviewed in their native language (fluency in English was required for interviews in the US), had access to a computer and the internet for the interview, had been practicing medicine for 3 to 35 years post-residency and were involved in the care of at least one patient with ASMD. Clinical trial investigators, paid advisors, and consultants for pharmaceutical or biotechnology companies were excluded.

2.2.2.2. Patient and caregivers. Participating adult patients were $\geq$ 18 years old, had a diagnosis of ASMD type B or type A/B and gave consent to discuss their experience. Participating caregivers were providing care for a pediatric/adolescent patient (aged <18 years unless otherwise stated) with ASMD. Caregivers were responsible for making treatment decisions on behalf of the patient, with input from the patient and the patient's physicians. A target of 37 patients and caregivers was proposed, split across the United States ($n = 8$), Latin America ($n = 12$), Europe ($n = 12$), and Asia ($n = 5$). Both patients and caregivers were recruited with the assistance of ASMD advocacy and support groups for each country (including the United States, Argentina, Brazil, Chile, France, Italy, and an international support group); a complete list of support groups are listed in **Supplementary Appendix 1**. Additionally, patients and caregivers were recruited from Mexico, although no advocacy/support group was involved. The study researchers partnered with specialist market research patient recruiters to contact local advocacy groups and invite participants. Respondents who wished to participate contacted the recruiters for screening and scheduling.

2.2.3. Data collection and analysis

Data collected were patient-focused and either self-reported by the patient or provided by caregivers/physicians on their behalf. All participant data were de-identified for analysis. Interviews were analyzed qualitatively using a thematic analysis to identify key themes, issues, and concerns associated with ASMD.

2.3. Quantitative study

2.3.1. Study design

An in-depth chart review was conducted between April and May 2020. Physicians were given a 60-min online survey and were asked to reference up to three patient charts (1 to 3 charts per physician). Interview questions were developed based on the key findings from the prior qualitative interviews, which informed outputs of interest including symptomology, timing of specific milestones throughout the patient journey, testing, and final ASMD diagnosis. Question topics included physician specialty, primary practice setting, patient background (symptom onset and diagnosis), presentation to physician, referral patterns, and treatment decisions.

2.3.2. Participant recruitment and eligibility criteria

Participating physicians gave direct patient care, had been practicing medicine for >2 years (but <36 years) since residency, completed specialist training, and had seen more than one patient with ASMD type A/B and/or type B in the 3 years prior to recruitment. Physicians were recruited from the United States, France, Germany, and Brazil. The target pool of participating physicians included a wide representation across all specialties involved in diagnosing and managing patients with ASMD, including geneticists, metabolic disease specialists, pediatricians/primary care specialists, hepatologists, gastroenterologists, neurologists, hematologists, endocrinologists, and pulmonologists, to ensure a breadth of chart data. A recruitment target of 85 physicians was set (40% geneticists, metabolic disease specialists, and hepatologists, and 60% for other qualified specialists) with 150 patient charts for review.

2.3.3. Data collection and analysis

Patient chart reviews were collected using an online, self-administered 60-min survey and participant data were de-identified for analysis. Statistical tests were performed using independent two

sample *t*-tests; a *p*-value of <0.05 indicated a statistically significant difference between groups. Correlations were assessed using Pearson's rank correlation coefficient.

2.4. Ethical approval

As both the quantitative and qualitative studies were market research and all data were de-identified prior to acquisition and analysis, formal ethical approval and Institutional Review Board (IRB) approval were not required according to the European Pharmaceutical Market Research Association code of conduct [21]. Patient identity and confidentiality were protected at all points throughout the studies. Nevertheless, in the quantitative study, the need for ethical approval in the United States was waived by Advarra IRB; for all other countries IRB approval was not sought nor required due to market research methodology. This research was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation guidelines for Good Clinical Practice, and applicable regulatory requirements. In both studies, all patients provided informed consent to participate in the interview discussion and for their interviews to be transcribed. Patients also consented that aggregate findings could be published.

3. Results

3.1. Qualitative findings

3.1.1. Participant demographics

Interviews were conducted with 12 physicians, followed by interviews with 27 patients and caregivers. At the time of interview, 16 caregivers were reporting on behalf of pediatric or adolescent patients (including two patients aged 18 and 19 years), and 11 adult patients were self-reporting. All 11 patients self-reported a diagnosis of ASMD type B. Of the 16 caregivers, 14 were caregivers for patients with ASMD type B, and two for patients with ASMD type A/B. Most patients ($n = 24$) were diagnosed during childhood, and three patients were diagnosed in adulthood (>30 years of age). Overall, 56% of patients were female and 63% of respondents were in employment (Table 1). Patients, caregivers, and physicians were based across a range of countries (full list in **Supplementary Table S1**).

3.1.2. Initial presentation of ASMD (qualitative analysis)

Symptom onset and initial concerns typically presented at around 2 years of age, and patients attended their first physician appointment several months later (range: 2–3 months to up to one year). Although patients with severe presentations (e.g., serious breathing difficulties) would attend a physician appointment after just a few weeks, for patients with milder initial symptoms, caregivers reported waiting up to a year or more before consulting a physician. One caregiver spoke about their initial assumptions: *"We thought that as [my child] did swimming, that was responsible for the ear infections and pneumonia… for the vomiting, we thought it was just a reflux." [Caregiver, Brazil]*.

Initial physician visits were commonly prompted by symptoms including abdominal pain (mentioned by 44% of patients), other symptoms (e.g., fatigue, enlarged organs, excessive bleeding; 22%), short stature (19%), gastrointestinal (GI) issues (e.g., vomiting, diarrhea, gastroenteritis, stomach pain; 15%), and difficulty breathing (15%). However, because symptoms such as GI issues and pneumonia are common in early childhood, caregivers and physicians reported that initially, they were generally unconcerned with these symptoms. Caregivers attended initial visits with limited expectations, hoping to receive a simple explanation and resolution for the presenting symptom: *"[My child] was also less active, with a big belly, and she had respiratory issues like bronchiolitis, but nothing serious, issues that could have affected a normal child…" [Caregiver, Italy]*.

Prior to diagnosis, many caregivers were told by physicians that the patient's symptoms were normal and would resolve over time. For

Table 1
Patient demographics (qualitative analysis).

N (%)	Patients			
	US ($N = 8$)	Latin America ($N = 12$)	Europe ($N = 7$)	Total ($N = 27$)
Patient sex				
Male	2 (25)	7 (58)	3 (43)	12 (44)
Female	6 (75)	5 (42)	4 (57)	15 (56)
ASMD diagnosis				
Type B	7 (88)	12 (100)	6 (86)	25 (93)
Type A/B	1 (13)	0 (0)	1 (14)	2 (7)
Current patient age, years				
5–10	0 (0)	5 (42)	2 (29)	7 (26)
11–17	2 (25)	4 (33)	0 (0)	6 (22)
18–30	1 (13)	3 (25)	2 (29)	6 (22)
31–49	3 (38)	0 (0)	1 (14)	4 (15)
>50	2 (25)	0 (0)	2 (29)	4 (15)
Respondent highest level of education				
Less than high school	0 (0)	2 (17)	0 (0)	2 (7)
High school	0 (0)	2 (17)	4 (57)	6 (22)
Some college	2 (25)	2 (17)	1 (14)	5 (19)
College graduate	4 (50)	3 (25)	2 (29)	9 (33)
Post-graduate	2 (25)	1 (8)	0 (0)	3 (11)
Vocational school/Certificate	0 (0)	0 (0)	0 (0)	0 (0)
Prefer not to say	0 (0)	2 (17)	0 (0)	2 (7)
Respondent employment status:				
Employed full-time	5 (63)	3 (25)	3 (43)	11 (41)
Employed part-time	1 (13)	4 (33)	1 (14)	6 (22)
Not employed, and looking for work	0 (0)	0 (0)	1 (14)	1 (4)
Not employed, not looking for work (including homemakers and students)	1 (13)	3 (25)	1 (14)	5 (19)
Retired	0 (0)	0 (0)	1 (14)	1 (4)
Disabled, not able to work	1 (13)	1 (8)	0 (0)	2 (7)
Prefer not to say	0 (0)	0 (0)	0 (0)	0 (0)
Full time caregiver [caregivers only]	0 (0)	1 (8)	0 (0)	1 (4)
Patient current living with				
Parent(s)	1 (13)	5 (42)	3 (43)	9 (33)
Sibling(s)	1 (13)	2 (17)	4 (57)	7 (26)
Spouse/domestic partner	1 (13)	2 (17)	3 (43)	11 (41)
Child/children under 18 years	6 (75)	1 (8)	2 (29)	7 (26)
Child/children 18+ years	4 (50)	2 (17)	2 (29)	4 (15)
Roommate or friend	0 (0)	0 (0)	0 (0)	0 (0)
Professional caregiver or health aid	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	4 (33)	0 (0)	4 (15)
Live alone	1 (13)	0 (0)	0 (0)	1 (4)

'Respondent' refers to the person responding to the interview (patient or caregivers). ASMD, acid sphingomyelinase deficiency.

example, caregivers were told that the patient's GI issues could be because of diet: *"My abdomen was huge when I was 1 or 2 years old. The doctors just passed it off that I was drinking too much milk or eating too many bananas." [Patient, United States]*.

As symptoms persisted and physicians began to suspect enlarged organs, patients were referred to a variety of specialists (often referred by a primary care physician or pediatrician), with enlarged organs and GI issues being the leading symptoms prompting a referral (38%). Patients and caregivers reported remaining under the care of a pediatrician for up to 2 years (range: 1 month–2 years) before receiving referral to a specialist. In addition to standard blood tests, pediatricians often performed ultrasounds and abdominal palpations, while other specialists performed diagnostic tests relevant to the specific suspected condition (e.g., Gaucher disease or cystic fibrosis; Table 2): *"The tests began when [my family member] was one-and-a-half years old and lasted until he was three. There were a lot of tests." [Caregiver, Chile]*. Only two patients reported receiving a specific misdiagnosis (one patient received a diagnosis of bronchitis and lung tuberculosis, the other patient did not know the name of the diagnosed condition).

3.1.3. Delay to diagnosis (qualitative analysis)

On average, diagnosis of ASMD took around 3 years after initial presentation (range: less than a month to 31 years and 3 months), with patients from the United States tending to reach diagnosis in fewer than 2 years, Latin America in 3 years, and Europe in 4 years. The reported reasons for delayed diagnosis were caregiver hesitation, physicians missing early symptoms, and the long time between booking appointments and seeing specialists. One patient explained: *"No one could understand what I had. In the hematology center, where I had the bone marrow aspiration – I stayed there for a week because they did it wrong – the first diagnosis was leukemia. It was completely wrong, thank goodness. But I still remember that day when the doctor told me that I [may have] leukemia. It was like being run over by a truck." [Patient, Italy]*. Physicians reported that specialist referrals occurred relatively quickly following the onset of symptoms.

In most cases, triggers leading to diagnosis fell into two categories: a build-up of symptomatic evidence (experienced by ~75% of patients), or a sudden development in the patient's case (experienced by ~25% of patients). Sudden developments in patient cases were most commonly incidental, such as a medical emergency, a patient finding a knowledgeable specialist, or another family member receiving an ASMD diagnosis: *"She had her tonsils removed, and while she was having that surgery, the anesthesiologist said 'her liver and spleen are grossly enlarged and I think she may have a storage disorder.' A geneticist came in the recovery room and drew blood and shipped it off." [Caregiver, United States]*.

3.1.4. Diagnosis (qualitative analysis)

The average age at diagnosis was 5.3 years old. Three additional patients were diagnosed during adulthood (aged 30, 41, and 51 years) following mild symptoms that had gone unnoticed for many years; therefore, they were excluded from the above calculation. A total of 63% of patients received a diagnosis of ASMD from a geneticist or metabolic disease specialist (Fig. 1). 'Genetic testing' as referred to by patients/caregivers was the most used diagnostic method and may also have been performed after diagnosis to confirm a specific mutation. Other tests included liver or skin biopsies, enzymatic assays, or lung X-rays. Diagnosis of ASMD typically led to screening of the patient's immediate family members. It was noted that physicians struggled to set expectations because of variable disease progression: *"They told us they had had two (one year-old) patients who died, and another patient who survived for 35 years against any expectation. They gave us this gap, but the main thing was unpredictability." [Caregiver, Italy]*.

3.1.5. ASMD symptom experience (qualitative analysis)

Symptoms experienced during the ASMD diagnostic journey are presented in Fig. 2 and described below. Physicians described similar symptoms as patients and caregivers, but also mentioned symptoms such as general clumsiness or unsteady gait, loss of appetite, and paresthesia.

3.1.5.1. Symptoms experienced in childhood and adolescence. Abdominal enlargement (associated with hepatomegaly and/or splenomegaly) was the most frequently experienced symptom during childhood and adolescence (100%), and was often accompanied by abdominal discomfort or pain: *"The first thing that we noticed is that his tummy was very big. It was getting bigger and bigger, but he had always been very skinny..." [Caregiver, Argentina]*.

Childhood respiratory symptoms were reported by 69% ($n = 11/16$) of caregivers, and 67% ($n = 18/27$) of all patients experienced breathing problems during childhood, including shortness of breath, wheezing, and asthma attacks. Additionally, seven patients had pneumonia during childhood. Two patients experienced recurrent pneumonia infections, of which one patient had recurrent pneumonia that required hospitalization. At the time of the interviews, three pediatric patients were receiving supplemental oxygen due to progressive respiratory issues. *"She got much worse over time. She has a low lung volume and high fat deposit levels. She needed surgery in order to eliminate some of the fat from the lungs. She's connected to the oxygen tanks constantly, even to walk around on the street." [Caregiver, Brazil]*.

GI issues during childhood were also frequent (reported by 56% of caregivers); however, cardiovascular complications were typically less frequently experienced by children and adolescents. Some patients and caregivers reported experiencing high cholesterol levels during childhood (13%), which was managed with diet during this period. Of all interviewed caregivers, 25% reported neurologic issues (including developmental delays, slow motor skills, poor co-ordination, seizures, and falling behind at school) in patients during childhood: "*After the diagnosis we did notice she had trouble walking when she was 2 years old. Additionally, in the beginning there seemed to be a very small learning difficulty." [Caregiver, Italy]*.

Half of all caregivers also reported orthopedic problems during childhood, including joint pain and easily broken bones. Additionally, short stature (typically <5 ft in adults, or noticeably shorter than other family members) was reported by 31% of caregivers.

3.1.5.2. Symptoms experienced by adults. Although breathing problems were frequently experienced during childhood, these respiratory issues

Table 2
Specialist visits and assessments during diagnosis (qualitative analysis).

Physician	Pediatrician/Primary care physician	Gastroenterologist/ hepatologist	Hematologist	Pulmonologist	Cardiologist
Tests run	• Abdominal palpations/ultrasound	• Ultrasound • Enzyme assay • Liver biopsy*	• Spinal/bone marrow aspiration	• Chest X-ray • Lung biopsy • Sweat test	• Echocardiograms • Angiograms
Suspected conditions	• Enlarged organs	• Gastric reflux • GERD • Gaucher* • ASMD*	• Leukemia • Anemia • Gaucher	• Cystic fibrosis • Bronchitis • Interstitial lung disease	• Heart failure • Atherosclerosis

* Mentioned about hepatologists only. ASMD, acid sphingomyelinase deficiency, GERD, gastroesophageal reflux disease.

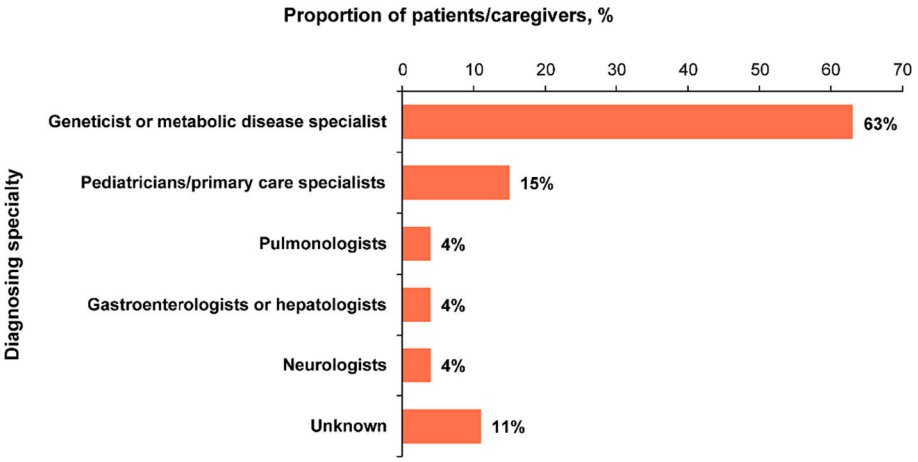

Fig. 1. Diagnosing specialist types ($n = 27$; qualitative analysis).

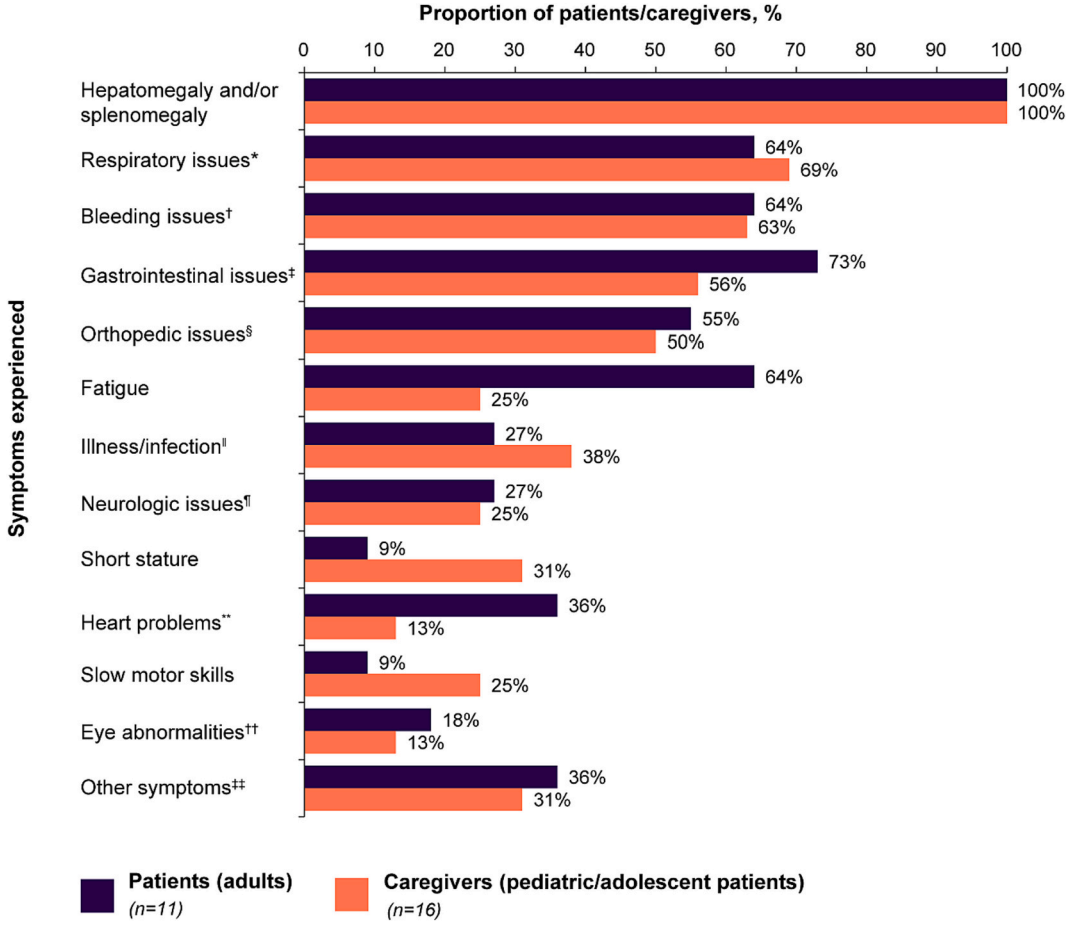

Fig. 2. Frequently reported symptoms during the ASMD diagnostic journey by patients (adults, self-reported) and caregivers (qualitative study).
*Respiratory issues includes shortness of breath, difficulty breathing, and recurrent pneumonia; †Bleeding issues includes bleeding/low platelets, nose bleeds, and bruising; ‡Gastrointestinal issues includes vomiting, diarrhea, gastroenteritis, and stomach pain; §Orthopedic issues includes fragile/broken bones, muscle/joint pain, and joint misalignment; ‖Illness/infection includes recurrent ear infections and being frequently sick/ill; ¶Neurologic issues includes developmental delay and language issues; **Heart problems includes high cholesterol; ††Eye abnormalities includes cherry-red spot, vision loss, and wearing glasses; ‡‡Other symptoms occurred <10% of the time and included: anxiety, jaundice, headaches, high bilirubin, and iron deficiency.
ASMD, acid sphingomyelinase deficiency.

continued to manifest during adulthood (64% of adult patients). One patient who was diagnosed with ASMD during adulthood reported: "*Walking up the stairs I felt like I was going to pass out after three flights. I had to pull off to the side and I could barely breathe…" [Patient, United States]*. Four adult patients were receiving supplemental oxygen at the time of interviews.

Cardiovascular symptoms progressed during adulthood, with patients developing additional cardiac issues in later life, such as high

cholesterol ($n = 8$), hypertension ($n = 1$), heart failure ($n = 1$), fatty tissue infiltration of the myocardium ($n = 1$), and tachycardia ($n = 1$). In total, 36% of adult patients experienced heart problems: *"I also had my heart race when I walked around the house. My heart wasn't strong enough to circulate my blood and get oxygen into my blood. I've even had situations where I'm sitting and my heart will race because my oxygen level is really low." [Patient, United States]*.

Eye abnormalities also persisted into adulthood, with 18% of patients reporting eye abnormalities (including cherry-red spot, vision loss, and wearing glasses) during their disease course. Adults experienced vision problems, such as requiring glasses or undergoing laser eye surgery. Additionally, one patient underwent surgery to remove fatty tissue in the eye and experienced partial loss of vision which she attributed to ASMD. While only 25% of caregivers reported patients experiencing fatigue in childhood and adolescence, 64% of adult patients experienced fatigue, emphasizing low energy levels and being frequently tired with age.

3.1.6. Patient support and information (qualitative analysis)

Patients and caregivers reported receiving little information or material on their ASMD diagnosis from their physician, and therefore turned to the internet for answers. Patients noted that much of the literature available regarding ASMD was in English only, causing additional complications for non-English speakers: *"I was relieved with the diagnosis…but, I also felt lost because of the lack of information… unfortunately here in Brazil, it is unheard of. If you search Niemann–Pick B, then only international doctors come up. It is in English…" [Patient, Brazil]*.

It was noted that physicians rarely directed patients and caregivers to support groups; instead, patients identified foundations and Facebook support groups themselves (13/27 [48%]), though not all participated. The remainder of patients believed existing support groups to be lacking and sought support elsewhere, often from therapists, friends, and family: *"I did have questions, but the answers were always the same. The number of people with ASMD is so small that specialists can't answer your questions. If I ask 'what will happen to me in the future?' They can't answer." [Patient, Italy]*.

3.1.7. The emotional impact of ASMD (qualitative analysis)

Worry, frustration, and weariness were common emotions experienced by patients and caregivers when undergoing the diagnostic process: *"It felt like a maze, like I was a rat in a maze. You expect a solution for your child and that they are going to get better. I felt terrible, I just wanted to do whatever I had to do for my child." [Caregiver, Brazil]*. The lack of information available on ASMD also contributed to patients' and caregivers' reactions to diagnosis, including feeling helpless/alone (44%), sadness/despair (41%), scared/worried (15%), and lost/confused (7%).

The uncertainty of how ASMD progression may occur carried an emotional burden for patients and their caregivers. Constant hospital visits, worsening of symptoms, and inadequate management strategies were reported as emotionally draining: *"It is like a bomb, we don't know when something could happen…we know that one of her organs could burst, and she would perish without us being able to do anything. So, it is like a bomb." [Caregiver, Brazil]*.

3.2. Quantitative findings

3.2.1. Responding physicians and patient case demographics

Physicians ($n = 86$) provided 193 charts for analysis and practiced across the United States ($n = 41$), France ($n = 15$), Germany ($n = 15$), and Brazil ($n = 15$). The most common specialties included geneticists or metabolic disease experts ($n = 12$), neurologists ($n = 12$), and pediatricians ($n = 11$), with other specialties including primary care physicians, endocrinologists, and internal medicine physicians. A total of 96 patients received care at a center that physicians self-reported to be a center of excellence (COE) and 97 at non-COEs.

Overall, there were a similar number of charts for patients with ASMD type A/B and type B; however, the Brazilian charts skewed more toward type B (Table 3). Of 193 patient charts, 64% of patients were male ($n = 123$). At the time of interviews, 37% of patients were children (aged 1 to 9 years old), 34% adolescents (10–19 years old), and 30% adults (≥20 years old; Table 3).

3.2.2. Symptoms and indicators of ASMD during the diagnostic journey (quantitative analysis)

Patients experienced an average of five symptoms prior to their ASMD diagnosis. Overall, the five most frequent symptoms/indicators experienced during the diagnostic journey were hepatomegaly and/or splenomegaly (72%), fatigue (35%), elevated liver function tests (eLFTs, 32%), growth delay (30%), and thrombocytopenia (23%). Most patients with these symptoms experienced them at initial presentation. Some symptoms were experienced more frequently by patients with type B compared with type A/B, including hepatomegaly (50% versus 35%; $p < 0.05$), thrombocytopenia (30% versus 16%; $p < 0.05$), and fibrosis and/or liver cirrhosis (16% versus 5%, $p < 0.05$). However, the most experienced symptoms did not always result in suspicion of ASMD. For example, of the 83 patients who experienced hepatomegaly, in only 24 patients (29%) did this trigger suspicion of ASMD.

3.2.2.1. Symptoms experienced by age of diagnosis. At initial presentation, the most frequent symptoms/indicators experienced by pediatric patients were hepatomegaly and/or splenomegaly (55%), eLFTs (27%), and growth delays (26%), whereas for adolescent and adult patients, hepatomegaly and/or splenomegaly (39%), thrombocytopenia (20%), and eLFTs (14%) were most experienced (**Supplementary Fig. S1**).

Symptoms experienced over the course of the diagnostic journey varied according to the age the patient was diagnosed (Fig. 3). Hepatomegaly and/or splenomegaly were the most frequently experienced symptoms/indicators by patients diagnosed as children (57%) and adolescents (65%), whereas patients diagnosed as adults experienced thrombocytopenia most frequently (33%). Patients diagnosed as children were more likely to report growth delays (36% of pediatric patients); whereas, 20% of patients diagnosed as adolescents and 7% diagnosed as adults reported growth delays ($p < 0.05$). Additionally, 22% of patients diagnosed as children experienced poor weight gain

Table 3
Patient demographics (quantitative analysis).

N (%)	Patients				
	US $n = 97$	Brazil $n = 28$	France $n = 37$	Germany $n = 31$	Total $N = 193$
Patient sex					
Male	65 (67)	15 (54)	26 (70)	17 (55)	124 (64)
Female	32 (33)	13 (46)	11 (30)	14 (45)	69 (36)
ASMD diagnosis					
Type B	43 (44)	20 (71)	17 (46)	14 (45)	95 (49)
Type A/B	54 (56)	8 (29)	20 (54)	17 (55)	98 (51)
Current patient age (years)					
Child (1–9)	35 (36)	14 (50)	15 (41)	7 (23)	71 (37)
Adolescent (10–19)	37 (38)	10 (36)	11 (30)	7 (23)	66 (34)
Adult (20)	25 (26)	4 (14)	11 (30)	17 (55)	58 (30)
Patient status					
Currently managed	43 (44)	11 (39)	22 (59)	12 (39)	85 (44)
Not currently managed	46 (47)	17 (61)	14 (38)	19 (61)	93 (48)
Deceased	8 (8)	0 (0)	1 (3)	0 (0)	15 (8)

ASMD, acid sphingomyelinase deficiency.

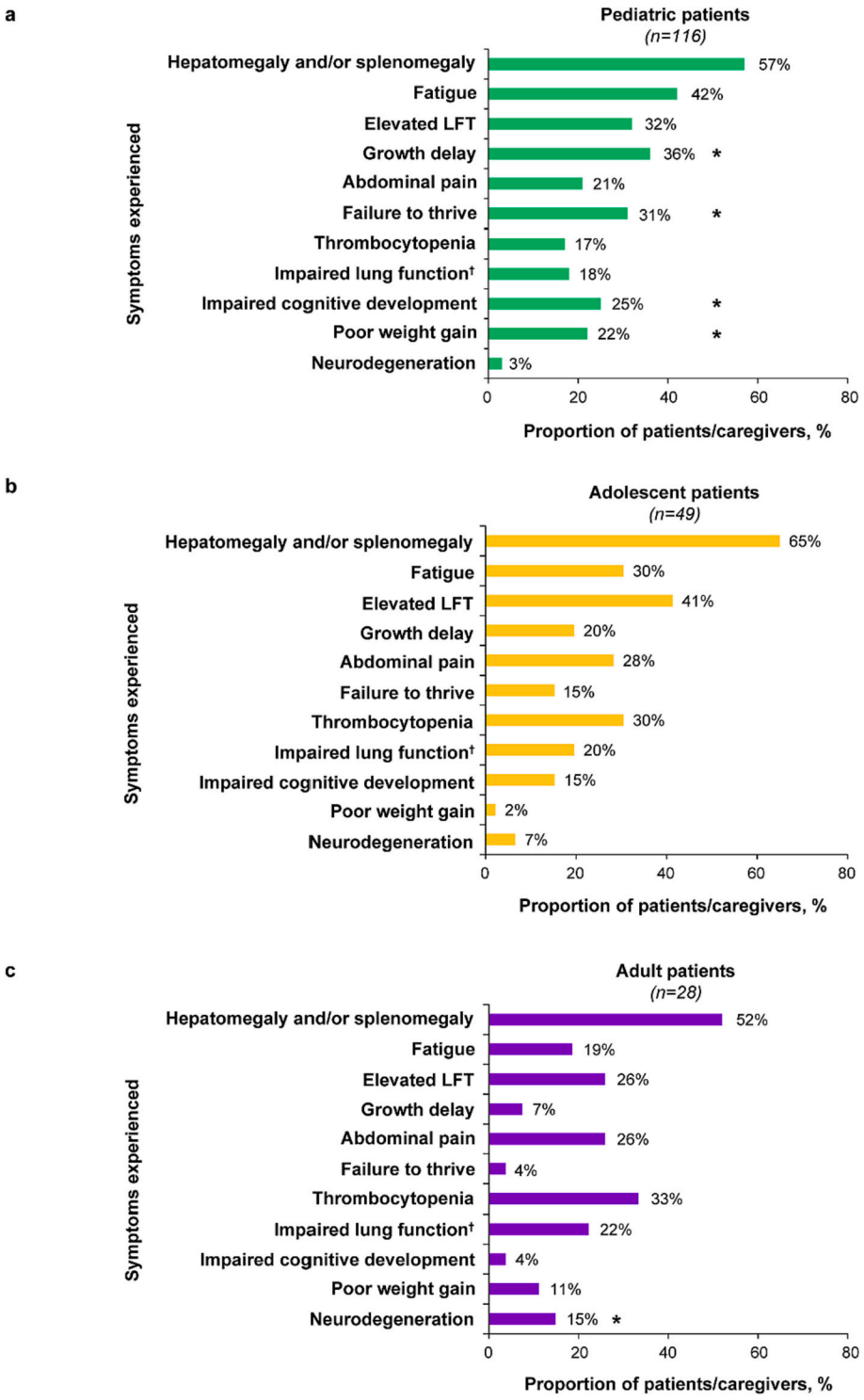

Fig. 3. Symptoms experienced over ASMD diagnosis journey according to age at diagnosis (quantitative study; $n = 193$).
Pediatric patients were aged 1–9 years old; adolescent patients aged 10–19 years old and adult patients aged ≥20 years old. *Denotes statistical significance compared with other age groups; $p < 0.05$. †Impaired lung function includes conditions such as interstitial lung disease and asthma.
ASMD, acid sphingomyelinase deficiency; LFT, liver function test.

over the course of their diagnostic journey, compared with 2% of adolescents and 11% of adult patients ($p < 0.05$). Neurodegeneration was also more frequently experienced in patients diagnosed as adults (15%) compared with those diagnosed as adolescents (7%) and children (3%; $p < 0.05$).

3.2.3. *Time to diagnosis (quantitative analysis)*

The journey from experiencing symptoms that led to a physician visit to ASMD diagnosis ranged from approximately 0 to 10 years for patients with ASMD type B or type A/B, with a median age at experiencing symptoms that led to a physician visit of 6 years and 7 years, respectively. Adult patients had the longest diagnostic journey (range from approximately 0 to 10 years from initial symptoms that led to a

physician visit), compared with pediatric patients (approximately 0 to 4 years) and adolescents (approximately 0 to 3 years), with median age at experiencing symptoms of 38 years, 3 years, and 11 years, respectively. Time to diagnosis was similar between patients who were treated at a COE (approximately 0 to 10 years) and those who were treated at a non-COE (approximately 0 to 9 years); median age at experiencing symptoms that led to a physician visit were 6 years and 7 years, respectively.

Overall, the median age at ASMD diagnosis was 7 years for patients with ASMD type A/B, and 6 years for ASMD type B. In total, 60% of patients were diagnosed in childhood ($n = 116$), 25% in adolescence ($n = 49$), and 15% in adulthood ($n = 28$). Median age at ASMD diagnosis varied by region (**Supplementary Fig. S2**). The time between experiencing symptoms (that led to the initial physician visit) and final ASMD diagnosis was shortest for adolescents, compared with pediatric and adult patients.

3.2.4. *Diagnosis (quantitative analysis)*

3.2.4.1. Diagnosing specialty according to age at diagnosis. Of all 116 patients diagnosed as children (≤9 years old) and 49 patients diagnosed as adolescents (aged 10–19 years old), 53% ($n = 61$) and 35% ($n = 17$),

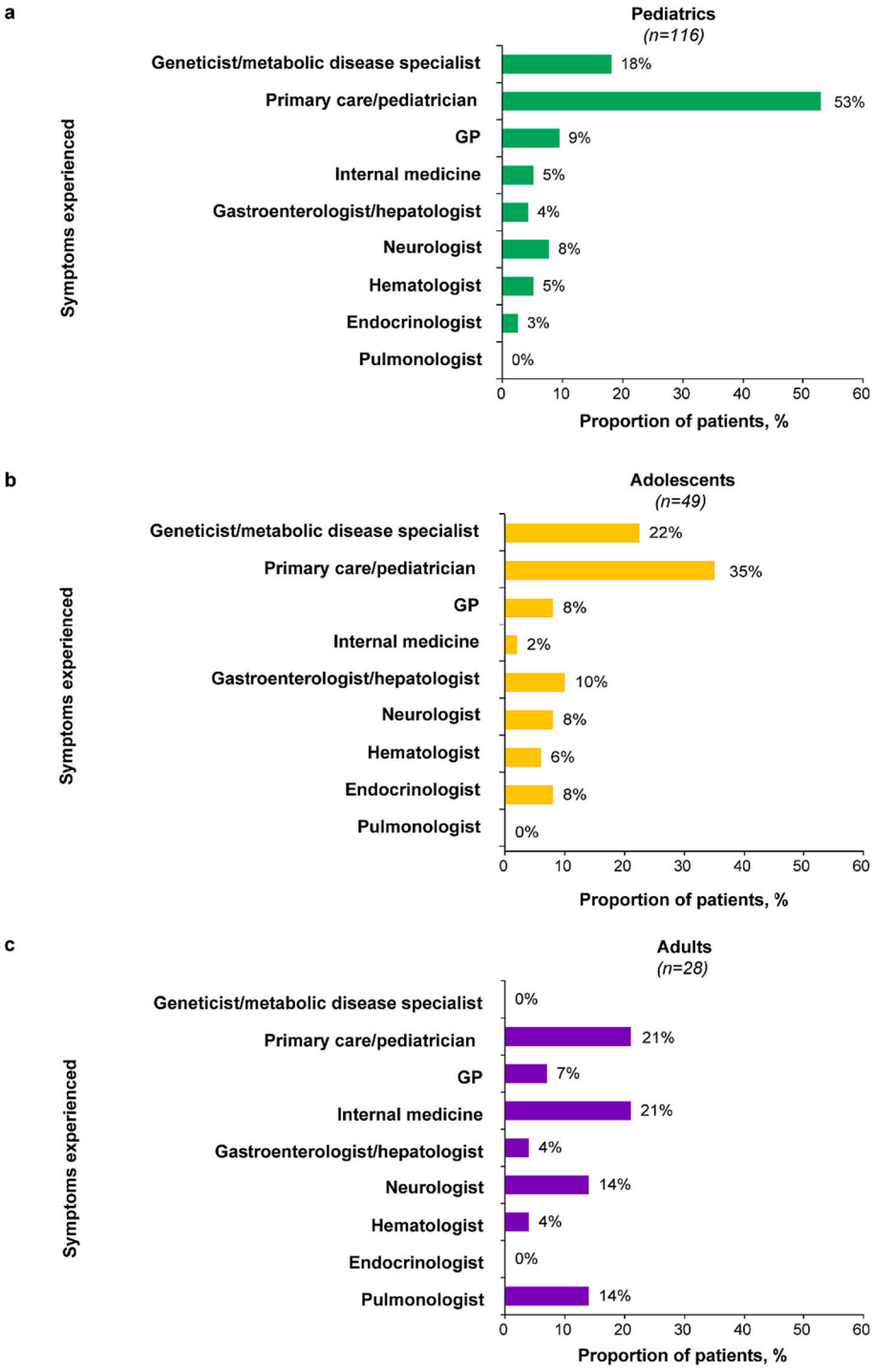

Fig. 4. Diagnosing specialties consulted at first presentation according to age of diagnosis (quantitative analysis).
Emergency Medicine and Critical Care specialists were not included in this research. GP, general practitioner.

respectively, first presented to a pediatrician (Fig. 4). Of the 28 patients diagnosed with ASMD during adulthood, 21% first presented to a primary care specialist or internal medicine physician (Fig. 4). On average, three healthcare professionals were seen per patient.

3.2.4.2. Diagnostic tests. Physicians were aware of the testing status for 82% of all patients ($n = 158$); however, testing history may not have been complete for all charts if the physician was not the diagnosing physician or had referred the patient for confirmation of diagnosis. Over the course of the diagnostic journey, the most utilized clinical assessment was ultrasound (47%), while the most frequently utilized laboratory assessments were eLFTs (mentioned in 50% of the patient charts), comprehensive metabolic panels (48%, not including molecular genetic testing), complete blood counts (46%), and acid sphingomyelinase (ASM) activity tests (38%); molecular genetic tests were also used (received by 7% of patients). Over half of pediatric patients (52%, $n = 48/92$ with known testing status) received comprehensive metabolic panel tests, and clinical and laboratory assessments such as eLFTs (50%) and ultrasounds (48%) were also commonly reported. In patients diagnosed as adult/adolescents ($n = 66$, with known testing status), clinical and laboratory assessments commonly performed included eLFTs (50%), complete blood counts (46%), and ultrasounds (45%).

3.2.4.3. Misdiagnoses. Only 15% ($n = 28$) of patients received ASMD as their first diagnosis, while the remaining 85% ($n = 165$) of patients received an initial incorrect diagnosis (or suspicion of another disorder) before a later diagnosis of ASMD. For patients with available information ($n = 19/28$), reasons that led to ASMD as the initial and only diagnosis were symptoms (66%), a family history of ASMD (31%), and diagnosis during newborn screening (10%). Triggers for diagnosis in pediatric patients were symptom onset (73%, $n = 8$; 50% of which were triggered by a single symptom), family history (27%), and newborn screening (18%). Diagnosing physicians were primarily pediatricians (46%) and geneticists (39%). For patients diagnosed with ASMD type B, 11% received ASMD as their initial diagnosis compared with 18% of patients with type A/B. Patients with a prior misdiagnosis ($n = 165$) were most likely to be suspected of chronic liver dysfunction (59%), pulmonary dysfunction (41%), Niemann–Pick disease type C (30%), hematologic malignancies (29%), or Gaucher disease (26%).

4. Discussion

The purpose of this research was to expand the current understanding of the diagnostic journey experienced by patients with ASMD. Patients and caregivers were interviewed to document their perspectives of receiving diagnoses and living with ASMD; these results were further strengthened by a quantitative physician survey-based review of patient charts. The insights obtained from these studies are essential to provide further awareness into the unmet needs of patients with ASMD, especially qualitative data, which are limited and provide valuable information on the experiences of patients and caregivers.

Acknowledging the heterogeneity of the qualitative and quantitative study populations (type of ASMD and age-specific differences), a wide range of symptom manifestations were reported for patients with ASMD. In the qualitative study, abdominal enlargement (100%), respiratory issues (69%), bleeding disorders (63%), and GI issues (56%) were the most frequently reported symptoms in pediatric patients during the diagnostic journey. These results were largely corroborated by the quantitative study, where 57% of pediatric patients had hepatomegaly and/or splenomegaly, 18% had impaired lung function, and 21% had abdominal pain. These symptoms of ASMD are in keeping with those commonly reported in the literature [5,8,9,11,15], with a study by McGovern et al. (2017) reporting frequent symptoms, including bleeding (49%), pulmonary infections (42%), shortness of breath (42%), and diarrhea (20%) in 59 patients with ASMD type B [3]. In the same study, splenomegaly (78%) and hepatomegaly (73%) were also commonly experienced at initial presentation with ASMD compared with 55% of pediatric patients in the present quantitative study [3]. The aforementioned symptoms are consistent with the consensus recommendations of symptoms required for diagnosis [11], highlighting the heterogeneity of disease presentation and thus the challenge of diagnosing ASMD.

In the qualitative study, symptoms experienced during childhood often progressed throughout adulthood, with some additional complications manifesting. For example, as patients reached adulthood, respiratory symptoms worsened and breathing issues became the most prominent symptom, as well as a greater prevalence of fatigue and heart conditions. The results from the quantitative study also show that patients diagnosed as adults most frequently reported thrombocytopenia, as well as fatigue. Short stature and slow motor skills were more predominant in the qualitative interviews with caregivers compared with adult patients, which is supported by the quantitative study that found that impaired cognitive development and growth deficits were more common in pediatric patients compared with adults. This finding is consistent with a previous retrospective chart review of 100 patients with ASMD, which found that growth was less than what was expected (compared with expected growth for the general population) throughout childhood for 50% of patients with ASMD type B and for all patients with type A/B [9]. The monitoring of these manifestations involves the use of clinical and laboratory assessments [22]. In the quantitative study eLFTs (50%), comprehensive metabolic panels (48%), ultrasounds (47%), and complete blood counts (46%) were the most utilized assessments, in line with the recommendations from Wasserstein et al. (2019), which suggest that liver and pulmonary function tests and complete blood counts should be considered to monitor patients with ASMD [2].

The results from both studies indicate that many of the initial symptoms of ASMD are not directly linked or attributed to ASMD. This may delay diagnosis and highlights an educational opportunity to boost disease awareness. In the qualitative study, patients took an average of 3 years (ranging from 2 to 4 years) to reach an ASMD diagnosis, while the quantitative results suggest an average overall diagnostic journey ranging between 0 and 10 years, after experiencing symptoms that led to seeking care. The slow disease onset, heterogenous symptom manifestations, and low incidence of the disease are thought to contribute to making the diagnosis of ASMD challenging [3,23]. These results are supported by McGovern et al. (2008) who reported a delay between initial presentation and diagnosis of 4.9 years [15]. Misdiagnoses were also reported in both studies; however, at vastly different rates, with 85% of patients in the quantitative study and 7% in the qualitative study being misdiagnosed. This disparity in rates of misdiagnoses may be reflective of the differences in methodologies used in each study, with the very low rate of self- and carer-reported misdiagnosis possibly a result of poor communication or recall. On average, patients saw three physicians over the course of their ASMD diagnosis. From the results of both the quantitative and qualitative analyses, patients were typically diagnosed after seeing a geneticist or metabolic disease specialist; therefore, early referral to these specialists could improve the rates of earlier diagnoses.

Patients and caregivers reported receiving little information from their physician regarding their diagnosis; turning to the internet yielded limited results as a result of very little disease specific-information available, particularly for their subtype of ASMD. The inadequate amount of information available contributed to a substantial emotional burden for patients and their caregivers, such as feelings of despair, loneliness, and frustration. The emotional consequences of a lack of available information were also reported in a qualitative case study by Henderson et al. (2009) that explored patients' and families' experiences of ASMD type B. In this study, social isolation and peer rejection were identified as significant stressors, and parents and adult patients expressed their frustration regarding the lack of available information and treatment [20]. In both this study and the results of Henderson et al.,

uncertainty of how their disease progression may occur carried a substantial emotional burden. Patients reported sources of information and support groups to be lacking, highlighting an unmet need in the ASMD patient care pathway.

4.1. Limitations

The results reported here were collected from two separate standalone market research studies at different points in time across different geographical regions; therefore, the two cohorts and their results are not directly comparable. The methodologies also differed between the two studies; in the qualitative study, symptoms were retrospectively reported by the caregiver or patient for the duration of their life, compared with the quantitative analysis, where symptoms were retrospectively extracted by a physician from patients' medical records and therefore, may not represent true symptom onset. As with all qualitative research, these findings represent the experiences and opinions of a select group of respondents and consequently, the results cannot be extrapolated beyond the population studied. Similarly, in the quantitative study, the charts selected by physicians may not be representative of their complete patient population and the self-selected nature of the patient charts may introduce bias. As physicians were recruited from ASMD advocacy and support groups, it is likely that the selected physicians are more familiar with ASMD compared with a more general group of physicians. Additionally, breaks in medical records due to switching physicians or receiving referrals were likely, so the full medical histories of some patients could not be accounted for. Given the rarity of ASMD, this quantitative research may have captured an overlap of patients while visiting different specialties, based on different parts of their journey.

Therefore, direct relationships between the studies cannot be made. Despite these limitations, this analysis provides invaluable insight into physician, caregivers, and patients' experiences of ASMD, the journey to diagnosis, and potential gaps in current care pathways.

5. Conclusions

Through both quantitative data and qualitative market research, key symptomology, reasons for delays to diagnosis, and patient referral patterns were explored to provide further understanding of the diagnostic odyssey for patients with ASMD. Diagnosis of ASMD can be challenging, as a result of the heterogeneity of disease presentation, frequent misdiagnoses, and limited information available to patients and their caregivers. Increased awareness of the disease could result in timelier diagnoses for patients living with ASMD.

Consent for publication

Individual patients are not identified in the publication.

Funding

Sanofi sponsored the research and development of this manuscript.

CRediT authorship contribution statement

Andrew Doerr: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Maliha Farooq**: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Chad Faulkner**: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Rebecca Gould**: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Krista Perry**: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Ruth Pulikottil-Jacob**: Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Pamela Rajasekhar**: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

AD and RG are employees of Fulcrum Research Group, a company which was paid by Sanofi for work related to this study. MF, CF, and KP are employees of Trinity Life Sciences, a company which was paid by Sanofi for work related to this study. RPJ and PR are employees and stockholders of Sanofi.

Data availability

The datasets generated and analyzed during the current study are not publicly available due to patient privacy and confidentiality. Anonymized data can be made available from the corresponding author upon reasonable request.

Acknowledgments

The authors would like to thank the patients, families, caregivers, and physicians who participated in this research, and the International Niemann Pick Disease Association and National Niemann Pick Disease Foundation for their assistance in publicizing the opportunity to participate in the qualitative study among their members. Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Emily Evans, of Ashfield MedComms, an Inizio company, and funded by Sanofi in accordance with Good Publication Practice guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2024.101052.

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