Moeenaldeen AlSayed et al. JBC Genetics. 2023;6(1):041-056
https://doi.org/10.24911/JBCGenetics/183-1664963756

REVIEW ARTICLE

The landscape of acid sphingomyelinase deficiency in a new therapeutic era: insights from experts in the Gulf region

Moeenaldeen AlSayed[1], Fatma Al-Jasmi[2,3], Tawfeg Ben Omran[4], Fathiya Al-Murshedi[5], Rawda Sunbul[6], Nadia Al-Hashmi[7], Talal Al-Enazi[8]

ABSTRACT

Acid sphingomyelinase deficiency (ASMD) is an autosomal-recessive progressive multiorgan metabolic disorder due to pathogenic variants in the sphingomyelin phosphodiesterase 1 gene. It can lead to death in early childhood in its most severe form. According to previous registries, the birth prevalence of ASMD is nearly 0.4-0.6 per 100,000 live births. The diagnosis of ASMD is usually delayed or missed due to the wide variability of clinical manifestations of the disease. Until recently, the management of ASMD patients was based on symptomatic treatments and supportive care; however, the introduction of enzyme replacement therapy (ERT) has revolutionized the management landscape of ASMD. ERT with a recombinant human Acid Sphingomyelinase Enzyme administered intravenously demonstrated a significant improvement in the non-neuronopathic type of ASMD in phase 2/3 trials. In June 2022, the European Medical Agency granted the ERT, olipudase alfa, marketing authorization. The prevalence of inherited metabolic disorders, including lysosomal storage diseases, is relatively higher in the Arab world than in the rest of the world due to the high consanguinity rate. In this study, we aim to review the current landscape of ASMD in the Gulf Cooperation Council countries and gather insights from experts regarding the roadmap to diagnosis, prevalence, and management approaches of ASMD in the region.

Keywords: Acid sphingomyelinase deficiency, lysosomal storage diseases, enzyme replacement therapy, Niemann-Pick disease, acid sphingomyelinase enzyme.

Introduction

Acid sphingomyelinase deficiency (ASMD), also known as Niemann-Pick disease (NPD), is historically divided into two main phenotypes: Niemann-Pick disease type A (NPD-A, OMIM 257200) – a rapidly progressing and fatal neuronopathic disorder, and Niemann-Pick disease type B (NPD-B, OMIM 607616) – a chronic non-neuronopathic, slowly progressive, visceral disorder (1). An intermediate neurovisceral phenotype, called NPD A/B, with intermediate symptoms between NPD-A and NPD-B, is also reported in the literature. The condition is characterized by a progressive, debilitating course that affects multiple organs and can lead to death in early childhood in its most severe form (2). According to the previous registries, the birth prevalence of ASMD is nearly 0.4-0.6 per 100,000 live births (3). ASMD is caused by pathogenic variants in the sphingomyelin phosphodiesterase 1 (*SMPD1*) gene, leading to variable degrees of deficiency of lysosomal acid sphingomyelinase (ASM) enzyme in all tissues. Subsequently, sphingomyelin and other lipids accumulate in the mononuclear phagocytic system and hepatocytes, with secondary impairment in tissue function, organomegaly, and multiple organ failure (4).

ASMD is broadly classified into three phenotypes that vary in the course and clinical presentation. Infantile neurovisceral is the most severe phenotype of ASMD (NPD-A), characterized by progressive neurodegeneration, hepatosplenomegaly, and lung infiltration in early infancy due to severe ASM deficiency (5). While in chronic neurovisceral ASMD (NPD-A/B), the neurological involvement occurs slower than in infantile neurovisceral, leading to better survival. Lastly,

Correspondence to: Moeenaldeen AlSayed
*King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia.
Email: moeen@kfshrc.edu.sa
Full list of author information is available at the end of the article.
Received: 17 January 2023 | **Accepted:** 07 February 2023

chronic visceral ASMD (NPD-B) is characterized by a variable age of onset and slow progression resulting in multisystem affection in the absence of neurological impairment (6). Therefore, the diagnosis of ASMD is usually delayed or missed (particularly in chronic visceral form) due to the wide variation in the clinical presentation of the disease. The diagnosis is confirmed by reduced or absent ASM enzyme activity measured in peripheral blood leukocytes and cultured skin fibroblasts. Dried blood spots (DBS) can be used to measure ASM enzyme activity as a practical screening tool. However, low activity should be confirmed by measurement in peripheral blood leukocytes or cultured skin fibroblasts or/and the presence of a pathogenic variant in both alleles in the *SMPD1* gene (6,7).

Despite the progressive nature of ASMD, symptomatic treatment and supportive care remained the only available management options for affected patients. However, the introduction of enzyme replacement therapy (ERT) has significantly changed the management landscape of the disease (8). Currently, ERT with a recombinant human ASM Enzyme administered intravenously demonstrated a significant improvement in the non-neurological manifestations of ASMD in phase 2/3 trials (8). In addition, ERT showed its safety in adults with chronic ASMD (9). A recent phase 1/2 study demonstrated ERT's tolerability and disease-modifying effects on children with chronic ASMD (10). Based on such results, ERT has been granted breakthrough therapy designation submission by the Food and Drug Administration. In June 2022, the European Medical Agency granted the ERT, olipudase alfa, marketing authorization. Thus, experts from the present report stated that the results of ERT are promising, and its anticipated introduction to clinical practice is likely to advance the management of ASMD. The observed improvements in the ASMD outcomes in clinical trials are expected to be translated into clinical benefits in the real-world setting and advance the treatment landscape of ASMD management. However, multinational collaboration with a larger pool of patients and longer follow-ups are necessary to confirm ERT's long-term clinical benefits. The prevalence of rare metabolic disorders, such as lysosomal storage diseases (LSDs), is presumed to be comparatively higher in the Arab world than in the rest of the world due to the high rate of consanguineous marriages (11). In this report, we aim to review the current landscape of ASMD in the Gulf Cooperation Council (GCC) countries and gather insights from experts regarding the roadmap to diagnosis, prevalence, and management approaches of ASMD in the region.

Methodology

On Friday, Nov 12, 2021, an experts' meeting was held to gather the insights and recommendations of the GCC's experts concerning the current prevalence of ASMD in the region and the unmet medical needs in terms of disease diagnosis and management. The panel consisted of seven experts with comprehensive experience managing rare metabolic diseases. It was affiliated with academic or healthcare institutions within the GCC countries: Kingdom of Saudi Arabia (KSA), Qatar, Oman, and the United Arab Emirates (UAE). The panel represented current practices in different healthcare sectors across the GCC countries. During the preparation of this manuscript, we conducted a comprehensive literature search to retrieve the current evidence for ASMD epidemiology, diagnosis, and management from the following databases: Medline via PubMed, Scopus, Embase, ScienceDirect, ClinicalKey, Cochrane library, and the known guideline organizations and societies guidelines websites, such as the International Niemann-Pick Disease Registry project (www.inpdr.org). The online search covered these databases from their inception till June 2022.

Epidemiology of ASMD

Although ASMD is a pan-ethnic disorder and affects both sexes similarly, the accurate prevalence is unknown. Globally, the estimated birth prevalence is 4-6 per 1,000,000 live births, while the global prevalence is estimated to be 1 in every 250,000 individuals (12). Nonetheless, it is suggested that these figures underestimate the actual burden of ASMD since there are many undiagnosed cases, in addition to the lack of awareness about the disease in the medical community, especially in primary healthcare settings (3,7). Furthermore, the current body of evidence shows differences in the incidence of ASMD according to ethnicity; the highest birth prevalence is found in the Ashkenazi Jewish community, estimated to be 2:3 per 100,000 births for NPD-A (1). Besides, geographical disparities were also noted concerning the epidemiology of ASMD. In South America, the incidence of ASMD was approximately 1 per 500,000 live births (13), compared to 1 per 250,000 live births in Europe (14). In addition, the age of presentation of ASMD varies according to its subtypes, while the incidence of the disease shows slight female predominance (15).

Rare genetic disorders are presumably more prevalent amongst the Arab population than in other parts of the world. Previous reports hypothesized that the high rate of consanguinity (up to 60%) is a significant contributing factor to the comparatively high prevalence of genetic disorders in the Arab world (16).

Only a few reports investigated the incidence and prevalence of ASMD in the Arab world; nonetheless, they showed a comparatively higher prevalence of ASMD than in other parts of the world. Moammar et al. (17) retrospectively retrieved the data of 165,130 live births in the Eastern region of KSA over 25 years. A total of eight cases with NPD type A were identified, given an incidence rate of 5 per 100,000 live births. The overall incidence of LSDs was 44 per 100,000 live births. In another report from the Eastern region of KSA that covered the period from 1983 to 2016, the prevalence of NPD type A/B was 3.31 per 100,000 live births (18). According to Alfadhel et al. (19) the incidence of LSDs was 37 per 100,000 live births at a tertiary center in KSA over 13 years, while one case with NPD type B was identified out of 110,601 live births. In the UAE, Al-Jasmi et al. (20) reviewed LSD cases at the metabolic referral centers to determine the birth prevalence of LSDs and associated genetic variants. The birth prevalence of NPD type B was 0.25

per 100,000, while there were no reported cases of NPD type A. The incidence of LSDs in Oman was reported to be 1 per 2,318 live births (21). In a 2021 systematic review of genetic disorders in Tunisia, the prevalence of ASMD type B was reported to be 1 per 200,000 live births (22). From the above studies, we can conclude that the incidence of ASMD in Arab countries appears to be higher than in western countries.

However, the reports mentioned above were limited to one geographical area and lacked generalizability to the GCC countries' entire population. Besides, most of the studies were retrospective and carried the limitations of misclassification and ascertainment bias. Thus, there is a need for a regional study with multi-center collaboration to truly reflect the actual incidence and prevalence of ASMD in the GCC countries. Besides, a national newborn screening program is required to precisely reflect the current burden of ASMD and other LSDs in the GCC countries.

Experts' opinion

The panel emphasized the lack of national registries and reliable newborn screening programs that can accurately estimate the incidence of ASMD in the GCC countries. Experts from Qatar stated that they have 12 patients with confirmed ASMD in their institution's database (four type A, two type A/B, and six type B). All of them are Qatari, and there are three siblings among them. At the same time, experts from Oman reported three patients with ASMD type B. In UAE, there are four patients with ASMD type B and one with ASMD type A. Concerning KSA. The advisors reported nine confirmed ASMD patients in KSA; two cases have ASMD type A, while the remaining seven have ASMD type B. The experts agreed on the scarcity of published literature that assesses the prevalence of ASMD in the GCC region. They confirmed that many ASMD patients might be undiagnosed; hence, the currently limited figures underestimate the true prevalence of ASMD in the region. Several factors account for this underestimated figure, including the lack of national registries for ASMD in the GCC countries, the lack of newborn screening programs for LSDs in many GCC countries, and limited awareness of the presentation of ASMD among healthcare providers.

Pathogenesis of ASMD and Associated Genetic Variants

ASMD is genetically inherited and results primarily from bi-allelic variants in the *SMPD1* gene presented in the chromosome 11 Band (11p15.4), encoding for ASM enzyme (23), responsible for catalytic hydrolysis of sphingomyelin to ceramide and phosphocholine inside the Lysosomes, which in turn leads to deficiency or impairment of ASM enzyme activity (24). As a result, progressive accumulation of sphingomyelin and other lipids occurs in the brain and other organs, such as the spleen, liver, lung, and bone marrow. The abnormal increase in sphingomyelin in different cells results in damage to related tissues and multiple organ involvement (6). In pathological examinations, the presence of foam cells, which are large lipid-laden cells, in the examined tissues of the affected organ is suggestive of ASMD (6).

ASMD is classified into three phenotypes (A, A/B, B) according to the disease's clinical manifestations, neurological degeneration, and severity. *SMPD1* gene variants reflect the severity of the disease, which in turn correlates with ASM residual enzyme activity (4).

Over 720 distinct known pathogenic variants causing ASMD have been described on the *SMPD1* gene, including frameshift, missense, nonsense, and frame deletions. These variants differ according to geographical variations (24), and the genotype-phenotype correlation is known for some variants (25). To illustrate, three known variants in the SMPD1 gene (R496L, L302P, and fsP330) are commonly present in Ashkenazi Jewish ancestry and represent over 90% of the ASMD patients in this population. The three variants are associated with ASMD phenotype A (26). The *SMPD1* variant (A359D) in Chilean patients was associated with ASMD phenotype B (14). ASMD phenotype A/B is associated with p.W393G and p.Q294K genetic variations (27,28)

In North Africa, (R610del) variant is the most prevalent *SMPD1* variant correlated with a mild form of ASMD phenotype B without neurological impairment (29,30). Moreover, the two alleles (677delT and R608) correlate with severe progressive ASMD phenotype A in Israeli Arabs and ASMD phenotype B in northern Africa, respectively (28,30).

Presentation and Subtypes

Type A

The most severe form of ASMD is NPD-A, also known as infantile neurovisceral ASMD (5). ASM Enzyme activity in this type is deficient to non-existent (31). Early infancy symptoms include failure to thrive, hypotonia, neurodegeneration, dysphagia, hepatosplenomegaly, and pulmonary involvement (2). On the other hand, there is no cardiac or musculoskeletal involvement. Based on the severity of the disease, psychomotor development may generally proceed for several months after birth before plateauing between the ages of 6 and 15 months and regressing. Death usually occurs before 3 years and is caused by respiratory failure due to infection (2).

Type A/B

Compared to infantile neurovisceral ASMD, NPD A/B, also known as chronic neurovisceral ASMD, has a slower progression of neurological symptoms and a longer life expectancy (28,32). It is an intermediate form of ASMD with childhood onset and is characterized by learning disabilities, psychiatric symptoms, extrapyramidal signs, peripheral neuropathy, and ataxia (5). In addition, it presents macular halo, diarrhea, abnormal liver function tests, portal hypertension, liver fibrosis, and hepatosplenomegaly (2). Thrombocytopenia and bleeding tendency are the predominant hematologic signs in these patients (5). Reported cardiac and pulmonary manifestations include early-onset coronary artery disease, mixed dyslipidemia, cardiac valve disease,

interstitial lung disease, abnormal pulmonary function tests, and radiological findings (33-35). Previous reports showed that patients with chronic visceral ASMD showed pulmonary nodules, reticular or reticulonodular patterns, and, eventually, honeycombing (35,36). Moreover, growth restriction, delayed bone maturation, reduced bone density, and bone and joint pain are commonly seen (37). Premature death can occur during childhood or adulthood due to respiratory and liver disease (38,39).

Type B

NPD-B, or chronic visceral ASMD, occurs at any time from infancy to adulthood and is marked by a gradual progression of multisystem disease symptoms without neurodegeneration (4,40). NPD-B is associated with an average life span; however, disease complications such as bleeding, liver failure, and respiratory failure can induce premature death (38,39). Hepatosplenomegaly is the most frequent first symptom in early childhood; however, moderate illness may not be detected until maturity (5). Delays in puberty, tiredness, bone pain, osteopenia, thrombocytopenia, and anemia are common clinical findings in children (37). Pulmonary infections and interstitial lung disease are prevalent, and pulmonary function can deteriorate with time (35,4). Mixed dyslipidemia is observed early in the disease course, and some individuals develop coronary artery disease (34,41). Hepatic fibrosis, ranging from mild to severe, is common, and the worsening of liver disease can lead to early death in some patients (42,43). Progressive portal hypertension and sphingomyelin deposition can lead to progressive splenomegaly (5).

There is considerable overlap in the clinical presentation between ASMD and Gaucher disease. Gaucher disease is the most common LSD. It is an autosomal recessive disorder due to a deficiency of the lysosomal enzyme, known as glucocerebrosidase, resulting in the progressive accumulation of glucosylceramide. The birth incidence is estimated at 1 per 40,000 to 1 per 60,000 live births. Pathogenesis of Gaucher disease is related to genetic variations in the *GBA1* gene. Clinical presentations of Gaucher disease include; hepatosplenomegaly with or without hypersplenism, thrombocytopenia, bony lesions, and osteopenia, in addition to neurological manifestations in type 2 and 3. These symptoms are also common with ASMD. Therefore, differentiation between the two disorders should be integrated as an essential component of the diagnostic algorithm of ASMD (44,45). Thus, parallel testing of ASM and acid β-glucosidase (the deficient enzyme in Gaucher disease) may be recommended to distinguish between the two diseases.

Experts' opinionThe panel agreed that the distribution of the ASMD subtypes in the GCC countries is similar to the global figures. The presentation of the patients with ASMD from the experts' institutions is reported in Table 1.

Natural History

The findings of the natural history studies are summarized in Table 2.

Hepatosplenomegaly and liver function

Wasserstein et al. (40) assessed 29 patients with NPD-B and reported that among patients with NPD-B, the mean volume of the spleen was 12.7 multiples of normal (MN), and the mean volume of the liver was 1.91 MN. In addition, two patients were subjected to splenectomy due to hypersplenism. Similar to these findings, McGovern et al. (46) , who included 59 NPD-B patients in their study, found that 73% and 78% of the patients had hepatomegaly and splenomegaly, respectively, and presented with a mean volume of spleen of 11.1 ± 5.7 and a mean liver volume of 1.9 MN ± 0.7. Four patients had a total splenectomy, and one had a partial splenectomy. They highlighted that spleen volume was negatively correlated with white blood cell count (r = -0.47; $p < 0.001$), hemoglobin (r = -0.33; $p = 0.02$), height Z-score (r = -0.51; $p = 0.0001$), high-density lipoprotein (HDL) (r = -0.62; $p < 0.001$), and positively correlated with triglyceride level ($r = 0.55$; $p < 0.001$) and liver volume ($r = 0.76$; $p < 0.001$). The liver volume correlated positively with the serum level of aspartate transaminase (AST) (r = 0.64; $p < 0.001$) and alanine transaminase (ALT) ($r = 0.60$; $p < 0.001$) (46).

Another study by McGovern et al. (38,47) showed that all patients with NPD-B had splenomegaly, 7.7% underwent total splenectomy, 1.9% underwent partial splenectomy, and 8.7% of the patients had liver diseases such as liver failure and cirrhosis. They proposed that splenectomy is an independent risk factor for mortality in patients with NPD-B.

According to Hollak et al. (4) all patients with NPD-A had hepatosplenomegaly. In contrast, in the NPD-B group, all patients had splenomegaly, 90% had hepatomegaly, and one patient underwent splenectomy due to severe cytopenia. Cassiman et al. (39) showed that 82.6% of patients with NPD-B and A/B had liver dysfunction, 91.4% had hepatomegaly, and 96.6% had splenomegaly. Likewise, Cox et al. (48) reported that hepatosplenomegaly was more frequent in patients with NPD-A (92%), followed by NPD-A/B (83%) and NPD-B (80%).

Regarding the liver function test, patients with NPD-B were noted to have elevated transaminase (ALT and AST) levels with normal bilirubin levels, except for one patient who died due to liver dysfunction. They observed that bilirubin levels tended to be higher in adults compared with children ($p = 0.01$) (40). In around half of the patients in the McGovern study (46), ALT and AST were increased, whereas total bilirubin was raised in a third. Similar findings were reported by Hollak et al. (4) who found that 2/3 and 19/20 patients with NPD-A and NPD-B, respectively, had elevated levels of liver enzymes, which was more apparent in young patients and those with severe illness.

Lipid abnormalities

Wasserstein et al. (40) showed that the majority of NPD-B patients had low levels of HDL cholesterol, borderline to high triglycerides (TG), low-density lipoprotein (LDL) cholesterol, and total cholesterol (TC). The worst lipid profile was observed in males and adults. In the study

Table 1. *Clinical presentation of the patients with ASMD from the GCC countries.*

Country	No.	Category	No.	Age	Clinical presentation of the patients with ASMD	Outcome
Qatar	12	ASMD A	4	Not reported	Not reported	All died
		ASMD A/B	2	6 years 7 years	Both have neurological manifestations (developmental delay and seizures).	Alive
		ASMD B	6	30 years old 23-years old The remaining are children	The 30-year-old female has a mild disease. She usually develops thrombocytopenia and anemia, mainly during pregnancy, and she has hepatosplenomegaly, and high cholesterol, mainly managed by diet. Her brother is 23 years old; he has the same features. Other patients have no reported features.	Alive
Oman	3	ASMD B	3	11 years old 17 years old 7 years old	***First case's manifestations:*** At the age of 4 months, hepatosplenomegaly was incidentally diagnosed with a chest infection during admission. Currently, he has microcephaly, a learning disability, and hyperactivity. No ataxia, no focal neurological signs, and no autoregression. Diagnosed with interstitial lung disease with low Diffusing capacity for carbon monoxide (DL_{CO}). Required Continuous positive airway pressure at night. He has recurrent epistaxis, elevated transaminases, and mild hyperlipidemia He has macular changes with electroretinography evidence of maculopathy Short stature and kyphosis that is slowly worsening with time. Homozygous with *SMPD1* variant: p.Ala481Val ***Second case's manifestations:*** A 17-year-old female Incidental finding of hepatosplenomegaly at the age of 2 years. She has a history of recurrent epistaxis. Otherwise, she has normal growth and development Normal PFTsLaboratory findings include mild thrombocytopenia, elevated transaminases, and a normal lipid profile. Homozygous for *SMPD1* variant p.Ala415Val ***Third case's manifestations:*** The patient is almost 7 years old and was born in 2015 He presented at the age of 5 months with abdominal distention and was found to have massive hepatosplenomegaly with anemia and elevated liver enzymes, mainly AST. He has no other significant clinical symptoms and is currently stable. He is homozygous with *SMPD1* variant: p.Leu382Phe	Alive

Continued

Country	No.	Category	No.	Age	Clinical presentation of the patients with ASMD	Outcome
UAE	4	ASMD B	4	Adults	They have dyslipidemia and hepatosplenomegaly. One of the patients has mild thrombocytopenia. They have very minimal lung disease.	Alive
	1	ASMD A	1	8 months	The patient presented with a recurrent respiratory infection, global developmental delay On examination, the patient failed to thrive, hypotonia, hepatosplenomegaly, hydrocele, and reducible inguinal hernia. Eye examination showed bilateral cherry red spot. A liver biopsy showed foamy cellular changes and microvesicular steatosis. Diagnosis confirmed with low enzyme activity and *SMPD*1 homozygous (c.762delG)	Lost to follow up
KSA	9	ASMD A	2	1.5 years old. Few months age-old	***The first:*** The patient has massive hepatosplenomegaly. He also has a developmental delay, nystagmus, and bilateral cherry-red spots. Additionally, he has seizure attacks that are not controlled with multiple antiepileptic medications. He was in ICU for a long time. ***The second:*** He presented with developmental delay. He had recurrent hyperactive airway disease and CNS manifestations. Later, he needed recurrent admissions and died because of recurrent chest infections.	Alive, and the second died.
		ASMD B	7	2.5 years old Two patients were 7 years old.	One patient has no CNS manifestations; he has massive hepatosplenomegaly, dyslipidemia, low cell count, complex heart disease (truncus arteriosus, large patent ductus arteriosus, significant ventricular septal defect). One patient and his sister have hepatosplenomegaly and ascites with hyperlipidemia. In two patients, one has abdominal distension, gastroenteritis, and hepatosplenomegaly, while the other is asymptomatic. Two patients had slow disease progression. However, one has a more severe disease.	Alive

Table 2. *Main findings of the studies reporting the natural history of ASMD.*

Variables	Cox et al. (48) (*n* = 100)	McGovern et al. (2) (*n* = 10)	McGovern et al. (46) (*n* = 59)	McGovern et al. (38) (*n* = 103)	Wasserstein et al. (40) (*n* = 29)	Hollak et al. (4) (*n* = 25)
Country	Brazil, Canada, USA	USA	Brazil, France, Germany, Italy, USA	USA	USA	The Netherlands and Belgium
Phenotype, No.						
Infantile neurovisceral	13	10	0	0	0	4
Chronic neurovisceral	6	0	0	8	0	6
Chronic visceral	81	0	59	95	29	15
Features	HS, GI disorders, respiratory disorders, infections	HS, GI symptoms, respiratory symptoms	HS, respiratory infections, ILD, bleeding	HS, TCP, bleeding, ILD, liver disease	HS, TCP, atherogenic lipid profile, pulmonary disease	HS, ILD, TCP
Natural history						
Infantile neurovisceral	--	NR	NR	NR	NA	--
Chronic neurovisceral	--				NA	Gradual decrease in platelet count in some patients
Chronic visceral	Reduction in platelet counts, WBC Increase total bilirubin				Progressive hypersplenism worsening atherogenic profile gradual deterioration in pulmonary function decrease in platelet decrease in WBC counts	Gradual decrease in platelet count Decreased bone marrow fat fractions in chronic visceral disease
Mortality						
Infantile neurovisceral	76.9%	100.0%	NA	NA	NA	100.0%
Chronic neurovisceral	0.0%	NA	NA	87.5%	NA	0.0%
Chronic visceral	2.5%	NA	NR	11.6%	10.3%	33.3%

GI: gastrointestinal; HS: hepatosplenomegaly; ILD: interstitial lung disease; NA: not applicable; NR: not reported; TCP: thrombocytopenia; WBC: white blood cell

of McGovern et al. (46) lipid profile abnormalities were common in NPD-B patients; low HDL-C (74%), high TC (41%), high TG (62%), and high LDL-C (46%). On the other hand, Hollak et al. (4) study that included a group of patients with NPD-A, A/B, and B reported that 12/16 patients had low HDL-C values at baseline; however, throughout follow-up, HDL-C levels steadily fell in two patients and remained steady in the others. LDL cholesterol levels were lower in five cases and higher in one. Adults and children, intermediate and attenuated phenotypes, and sex were shown to have no significant differences.

Moreover, Wasserstein et al. (40) mentioned that statins, exercise, and dietary modifications could improve TG, TC, and LDL-C serum levels. However, these interventions should be applied with caution, as patients with severe NPD-B are associated with deterioration in transaminase levels and pulmonary function after administering statins. Moreover, the risk of coronary artery disease is substantially higher in this group of patients, as the serum levels of HDL-C tended to be low in all age groups and did not respond to the previously mentioned interventions.

Pulmonary studies

The lung is a target organ of the disease and contributes to morbidity and mortality in patients with ASMD (38). Accumulation of foamy macrophages, interstitial fibrosis, and endogenous lipid pneumonia are the most common findings in lung biopsies in adults with NPD-B (49). The pulmonary function tests (PFTs) results indicated a restricted pattern of lung involvement with impaired diffusing capacity, which is consistent with interstitial lung disease. Many NPD-B patients are asymptomatic; however, those more seriously affected may have cyanosis, recurring respiratory infections, shortness of breath, cough, clubbing, and rhonchi (40). In the study of McGovern et al. (46,47) interstitial lung disease and pulmonary dysfunction were reported in 66% of the patients with NPD-B. An increase in the number of patients with abnormal PFT over time, and the fact that older patients with NPD-B were associated with lower mean PFT values compared to younger patients, support the progressive nature of the pulmonary disease in this group (40). In the study of Hollak et al. (4) there is no data on pulmonary function for NPD-A patients; however, variable degrees of restrictive lung disease and impaired CO-diffusion were found in the 21 NPD-B patients. Pulmonary involvement was reported to be higher in patients with NPD-B versus. NPD-A/B (79.2% *vs.* 65.0%), according to Cassiman et al. (39). In NPD-B patients, pulmonary dysfunction is linked to a higher risk of respiratory infections, leading to respiratory failure (39). Recurrent respiratory tract infections and persistent lung function deterioration can worsen the quality of life (48,50-41).

Cardiac studies

McGovern et al. (46) showed that 28% of patients with NPD-B had ECG abnormalities, including conduction abnormalities, left ventricular hypertrophy, and sinus bradycardia. Moreover, two patients had a history of myocardial infarction (MI). Regarding echocardiography, half of the patients showed abnormalities such as pulmonary hypertension, moderate to severe aortic regurgitation, mild ventricular dysfunction, and mild mitral valve regurgitation. The same group of investigators published another report that showed a much lower prevalence (8.7%) of cardiac diseases in patients with NPD-B, in the form of valvular heart disease and coronary artery disease (38). In contrast to pulmonary, cardiac involvement was more frequent in NPD-A/B patients than in NPD-B (62.5% *vs.* 39.2%) respectively (39).

Hematologic indices

Platelets and leukocyte count decrease as patients age, indicating the natural course of hematologic problems, although hemoglobin concentration remained constant. The diminishing cell numbers are most likely attributed to hypersplenism. Infection, particularly in the respiratory system, and bleeding episodes are two clinical implications of progressive leukopenia and thrombocytopenia (40). In patients with NPD-A, 4/5 patients had anemia; however, thrombocytopenia was less common in this group of patients. While in the NPD-B, 15/18 patients had thrombocytopenia, and 6/18 patients had anemia, mainly reported in intermediate phenotype and young patients (4). Hematologic manifestations were reported to be more prevalent in NPD-B patients than in NPD-A/B (Anemia 69.2% *vs.* 57.1%; thrombocytopenia 74.1% *vs.* 50%), respectively (44).

Genotype/phenotype correlations

Homozygosity for missense variants such as P330R, P323A, and R608 was linked to mild disease. On the other hand, moderate and severe patients were presented with a combination of heterozygotes for R608 and another variant, indicating that the other missense genetic variations, such as H425K, W391G, R600H, R441X, R496L, P475L, and H567L, are more hazardous (40). Similarly, McGovern et al. (46) reported that the most frequent variant in NPD-B patients was R608 (48%), and the most common type of genetic lesion was missense (59%). They also mentioned that the R608 variant is associated with non-neuronopathic and milder disease (38). Another report found that the most common variants were p.R610del, p.R476W, p.R498L, p.R476W, p.M1T, and p.Q294K (47).

The p.Arg610del variant was detected in 61.9% of individuals with NPD-B in the study of Hollak et al. (4) and 62% in Lidove et al. (52). This genetic variation was consistently linked to NPD-B disease in both compound heterozygous variant and homozygous forms; in this study, 12 of the 25 patients were of Dutch or Belgian ancestry, 7 patients were Turkish, 2 from Morocco, 2 from Tunisia, 1 from Iraq, and 1 of Surinamese descent (4). In the Cassiman study (39), which included a literature review of 85 patients, the most common variant in patients with NPD-B was p.R610del and p.A359D, while in NPD-A/B, the most common variant was p.Q274R. The mild p.L163P variant was found in two patients

with NPD-B, confirming the variant's mild nature. Two sisters were homozygous for the p.R230C variant (4), previously found in a group of NPD-B patients (53). Both had a severe illness history with substantial lung disease but no neurological signs. Both died early, the first from respiratory failure and the second post hematopoietic stem cell transplantation (4).

Other variants were also reported to be linked with NPD-B disease, including p.L551P, p.C91H, and p.L103P variants, while in NPD-A, p.Y539H, p.P477L, p.F465S, p.G29DfsX48, and p.S250R variants were reported. Regarding patients with NPD-A/B, the most reported variants were p.R230C, p.L105P, p.C91H, p.R610del, p.L474QfsX20, and p.V557IfsX19 variants (4).

Neurological and ophthalmological findings

According to McGovern et al. (46) all patients with NPD-B had normal mental development, coordination, muscle strength, sensation, deep tendon reflexes, and cranial nerve function. Peripheral neuropathy was reported in 11%, 25% had cherry-red spots, and 8.4% had cognitive impairment. In another report by McGovern et al. (38) neurological diseases in the form of sensory dyspraxia, learning disabilities, petit mal seizures, and ataxia were recorded in 12.6% of NPD-B patients. Cherry red spots were recorded in 1 out of 4 patients with NPD-A and 1 out of 21 patients with NPD-B in the study of Hollak et al. (4). Furthermore, they reported that severe neurological manifestations also led to early death in 4 out of 5 patients with NPD-A. In patients with NPD-B, 4 out of 21 patients had neurological manifestations, including mental retardation, Parkinson's disease, peripheral facial palsy, multiple sclerosis, and delayed psychomotor development (4). It was reported that neurologic and ophthalmic involvement was significantly higher in patients with NPD-A/B than in NPD-B patients (68.8% *vs.* 33.3%; $p = 0.032$ and 55.6% *vs.* 15.7%; $p > 0.0001$, respectively). Also, patients 18 years old or younger at the time of death or liver transplant had more significant neurological symptoms ($p = 0.048$) (39).

Mortality

In the study of Wasserstein et al. (40) three patients died from ages 9 to 18 years due to liver failure, traumatic subdural hematoma, and long-term complications post a failed bone marrow transplant. Four patients with NPD-A died due to severe neurological manifestations, subdural hematoma, malignant edema, and pneumonia, according to Hollak et al. (4) Five NPD-B patients died, three due to progressive pulmonary disease related to ASMD, one of malignancy and one of unknown cause. The McGovern et al. study reported 18 deaths in patients with NPD-B. Respiratory failure/Pneumonia ($n = 5$) were the leading causes of mortality. Three patients died of liver failure, while three others died of complications post-bone marrow transplant. Subdural bleeding, multi-organ failure, low-output heart failure, liver cancer, splenic vein tear, and postoperative bleeding were among the mortality reasons in one patient each (38). In a retrospective analysis of 100 patients, 12 patients were deceased; ten patients with NPD-A/B died at a mean age of 2.4 years from hepatic failure ($n = 1$), pneumonia ($n = 3$), respiratory failure ($n = 2$), lung disorder ($n = 1$), or unknown causes ($n = 3$). Two patients with NPD-B died from hepatic failure at 2 years of age and respiratory failure at 42 years of age (48). In a recent study, eight patients died from reasons linked to ASMD morbidities. Three patients aged 20, 35, and 71 died from pneumonia. While two patients aged 16 and 65 died from liver failure or cancer, respectively. One patient died due to a tear in the splenic vein at 14. The other two individuals died at 17 and 56 years old due to portal hypertension with esophageal varices and multiorgan failure. Pneumonia was by far the most prevalent cause of mortality (47).

Quality of life assessment

Based on parental reports, diminished quality of life in pediatrics with NPD-B was demonstrated in the following domains: parental impact–emotional, general health perceptions, mental health, and physical functioning, assessed by CHQ-PF50. In adults, the 36-Item Short Form Health Survey questionnaire (SF-36) subscale showed no significant impact of the disease on mental health, role-emotional, social functioning, vitality, bodily pain, role-physical, and physical functioning (46). According to Cox et al. (48) who assessed 100 patients with ASMD, 5% worked part-time due to disability, 16% did not work due to disability, and 27% did not work for other reasons. Early diagnosis and appropriate management are essential for reducing the risk of complications and improving quality of life (52).

Experts' opinion

The panel highlighted that lung involvement in ASMD is usually underdiagnosed, and the percentage of lung involvement in ASMD is considerable and should not be passed unnoticed. Pulmonary involvement amongst ASMD patients from the GCC countries usually includes tachypnoea, shortness of breath, recurrent hyperactive airway disease, and recurrent respiratory infection. On the other hand, the experts stated that most ASMD patients present with hepatosplenomegaly and dyslipidemia. On the other hand, ophthalmological findings were mainly cherry red spots in patients with ASMD type A.

Typically, ASMD patients in the GCC seek medical advice from a general pediatrician or gastroenterologist before seeing a healthcare provider specializing in rare disorders. The lack of awareness about ASMD among general pediatricians and gastroenterologists usually leads to a significant delay in diagnosing ASMD. In a considerable proportion of patients from the GCC region, several years elapse between symptom onset and diagnosis, which can be as long as 3-10 years.

The panel highlighted the need to increase awareness about ASMD symptoms to help healthcare providers prompt early diagnosis and improve patients' quality of life. Moreover, the experts recommended establishing more centers of excellence in the GCC region to help with early and proper diagnosis of rare diseases like ASMD. In addition, enhanced access to diagnostic centers and specialized services will help reduce the diagnostic delay and improve the outcomes of ASMD in the region.

A diagnostic care pathway for ASMD aiming to reduce referral time should be developed and implemented to positively impact the diagnostic journey for this disorder. Educational programs targeting general pediatricians, hematologists, pulmonologists, and gastroenterologists should be conducted.

Diagnostic Approaches

Enzyme activity testing in ASMD

When there is a suspicion of ASMD, an enzyme assay for ASM activity should always be done first, followed by gene sequencing once the biochemical diagnosis has been established (5). To differentiate ASMD from Gaucher disease, glucocerebrosidase activity should be measured simultaneously (54). The presence of ASMD should be demonstrated by the lack of considerably reduced enzyme activity below the cut-off values, considering the numerous unique genetic variants of unknown significance (1). Other clinical and laboratory findings, such as lipid-laden foam cells and mixed dyslipidemia, while highly suggestive of ASMD, do not replace the need for confirmation by enzyme test results. In strong clinical suspicion for ASMD, direct molecular testing for known pathogenic mutations or familial mutations can be performed to confirm the diagnosis. However, if molecular analysis reveals variants of uncertain significance, an enzyme assay is essential to fully confirm the diagnosis.

DBS, fibroblasts, and isolated peripheral blood can all be used to evaluate ASM enzyme activity (55). Whole blood is typically required by laboratories that take samples from worldwide, allowing the same sample to be used for second-tier testing (5). DBS that are particularly stable may be utilized; however, DBS testing has limits, including the impact of anemia and recent transfusions on findings (56,57). Because of its increased analytical range and more accurate assessment of enzyme activity in the lower detection ranges, tandem mass spectrometry (MS/MS) is preferred for assaying ASM activity over fluorometric assays, as well as radio-labeled native sphingomyelin substrate due to the need for radiochemical licenses (58). With MS/MS tests, there is improved discrimination between unaffected and affected patients, according to fluorometry comparisons (59).

Pathogenic variant

Gene sequencing is indicated following confirmation of the diagnosis by demonstrating diminished ASM activity (5). More than 720 genetic variations have been identified in the (*SMPD1*) gene. Splicing genetic variations, small and large insertions, deletions, and splicing abnormalities often cause little or no residual ASM activity and are more likely to cause severe ASMD phenotype (5). Chronic ASMD is more likely to come from missense and other lesions (such as in-frame codon deletions) that maintain high residual activity (e.g., >5% of wild-type ASM activity, depending on the cell and test method) (60). In the Ashkenazi Jewish community, three genetic variations, p.P333Sfs, p.L304P, and p.R498L, account for more than 90% of NPD-A/B (61).

The most frequent variant in individuals with NPD-B is p.R610, which is seen in 20% of all North African, Western European, and North American patients (62). When homoallelic or heteroallelic, p.R610 is linked with a larger quantity of residual enzyme activity and is considered neuroprotective (5). A 10-year study of 29 individuals with NPD-B found that homozygosity variants of p.P332R, p.P325A, and p.R610del are linked to attenuated illness (40). L549P, fsP189, and L137P account for approximately 75% of the alleles in Turkish patients, and K576N and H421Y variants account for approximately 85% of the alleles in Saudi Arabian patients (70). In Portuguese/Brazilian patients, F480L, R474W, R441X, and S379P variants are common, while in Scottish/English patients, the most common variant is A196P (70). Further studies are required to identify new *SMPD1* variants and their phenotypic correlations.

Biomarkers and follow-up

Once an ASMD diagnosis has been obtained, biomarker testing may benefit disease monitoring. The presence of elevated levels of one or more markers is never enough to diagnose ASMD, even though they might help determine disease severity. As ERT becomes accessible, ASMD biomarkers may become more critical for monitoring therapy responses (5). For example, in NPD-B, plasma chitotriosidase, a biomarker of macrophage activation, is significantly elevated (63). Even though chitotriosidase plasma levels in ASMD are lower than those seen in individuals with Gaucher disease, chitotriosidase might be a viable diagnostic for chronic ASMD (53,64). However, up to 6% of people have a recessively inherited chitotriosidase deficiency, and genetic variations in the chitotriosidase gene that affect test results can lead to inaccurate interpretations of chitotriosidase plasma levels (65,66).

CCL18 levels in the blood are also elevated in individuals with ASMD and Gaucher disease, which can be used as a surrogate measure for disease activity (63,67). When patients with chitotriosidase deficiency, this biomarker becomes particularly useful. In various LSDs, plasma glycosphingolipids are indicators of sphingolipidosis. Glucosyl sphingosine, for example, is a specific and sensitive biomarker for Gaucher's illness that is not elevated in other LSDs (68).

Lysosphingomyelin levels are higher in the DBS and plasma of individuals with chronic ASMD, indicating that it might be used as a biomarker; nevertheless, more research is needed (69).

Diagnostic algorithm

An algorithm for diagnosing ASMD presenting in childhood has been developed based on the common clinical manifestations of ASMD, differential diagnoses, and diagnostic testing approaches. If the patient presents with splenomegaly with or without hepatomegaly, in addition to one or more features suggestive of ASMD such as low HDL-C, hypotonia, developmental delay, and cherry red spots, in that case, he/she should be subjected to ASM enzyme activity. If the activity is low, *SMPD1* gene sequencing should be performed; if not, repeat the

enzyme assay using MS/MS. Gene sequencing results can be used for genotype-phenotype correlation. In case of an unknown phenotype, a clinical assessment should be performed. To detect NDP-B in adults, the same approach should be followed; however, the suggestive features of ASMD are mainly pathologic fracture, interstitial lung disease, and low HDL-C.

Gaucher disease differential diagnosis

Gaucher disease is an autosomal recessive inherited disorder of metabolism that results from a low activity or absence of the glucocerebrosidase enzyme (70). Because individuals with Gaucher disease and NPD have comparable and overlapping clinical symptoms, a thorough laboratory workup examining both diseases simultaneously is critical (5). Type 1 GD is a non-neuronopathic form, and type 2 and 3 are neuronopathic. Type 1 GD and NPD-B symptoms are similar, including failure to thrive, bone marrow involvement, irritability, cytopenia, and hepatosplenomegaly (71). Enzyme assays are used to get a definitive diagnosis for both disorders. Molecular testing can help to verify diagnoses, screen family members, and predict the disease's prognosis (70). It was reported that one patient, out of a total of five patients, with suspected Gaucher had an ASMD and was diagnosed with ASMD type A/B; therefore, it is recommended to test suspected patients for both Gaucher and ASMD simultaneously (72).

Experts' opinion

The experts highlighted the comparatively high incidence of rare metabolic disorders in the GCC region, including ASMD. Thus, patients suspected of ASMD should be immediately referred for ASM enzyme activity assay and genetic counseling. However, they stated that the limited access to genetic testing and enzyme assays in the GCC countries are significant challenges that can delay the diagnosis of ASMD patients; however, the landscape is improving with the introduction of faster and more reliable diagnostic methods such as next-generation sequencing. Additional challenges in diagnosing ASMD include the non-specific and highly variable disease features, prohibitive cost of genomic testing, and lack of awareness amongst healthcare practitioners regarding the overlapping features between ASMD and Gaucher disease.

Therefore, the panel also advocated the development of a unified and comprehensive diagnostic algorithm that can aid in the timely identification and diagnosis of patients with suspected ASMD. This algorithm should advocate ASM enzyme activity in children with splenomegaly, with or without hepatomegaly, and ≥ one suggestive feature of ASMD, such as low HDL-C, high cholesterol, high triglyceride, thrombocytopenia, and anemia. If the activity is low, *SMPD1* gene sequencing should be performed; if not, repeat the enzyme assay using MS/MS.

Management of ASMD

In the current literature, there is no known curative therapy for managing ASMD. Only symptomatic treatments and supportive care are available to improve the quality of life for ASMD patients (6). First, evaluations of the ASMD-diagnosed individuals should be performed to define the severity and extent of the disease so that the management plan can be designed accordingly (73). Management of ASMD manifestations requires an interdisciplinary approach, as it needs coordination between different healthcare physicians (74). Splenectomy may be performed for patients suffering from severe splenomegaly with hypersplenism (75,76). However, some studies proposed that splenectomy is an independent risk factor for mortality in patients with NPD-B (38,47) and should be avoided as much as possible. In addition, liver transplantation is considered for patients with liver failure (1). In extensive lung disease, oxygen supplements and the administration of vaccines against respiratory pathogens to decrease the risk of pulmonary infections are advised (6). Other symptomatic treatments may be prescribed, such as lipid-lowering drugs, multivitamins, mineral supplements, and growth hormone therapy. Besides, psychotherapy has an essential role in management (73). In contrast, the safety concern regarding bone marrow transplantation (BMT) and total lung lavage largely outweighs their benefits for ASMD patients (1).

BMT was proposed in ASMD patients with equivocal results. Previous results showed that BMT might improve neurological involvement; nonetheless, with a high incidence of severe complications of the transplant procedure (77). To date, BMT has been extensively studied in animal models, with limited data on humans and a lack of clinically-relevant outcomes (78). Besides, BMT did not prevent disease progression in a patient with ASMD type A, despite early transplantation (79)

ERT is an intravenously administrated recombinant human ASM to treat non-neurological manifestations of ASMD that is still under clinical development (9). ERT eliminates the progressively accumulated lipid substances resulting from the building-up of sphingomyelin, which improves the symptoms and outcome of the disease (9,80). McGovern et al. (80) performed a phase I, open-label, and non-randomized clinical trial. Only 11 adult ASMD type B patients from one center were enrolled. The safety of the intravenous administration of ERT, with a dose ranging from 0.03 to 1.0 mg/kg, was assessed. The involved patients were followed up after 2 and 4 weeks. The authors found that a dose of more than 0.6 mg/kg is more likely to induce drug side effects and adverse drug reactions (ADRs) the first time of drug administration. Therefore, a gradual increase in the dose is recommended to reduce ERT adverse reactions.

A phase 1b, open-label trial enrolled five adult ASMD type B patients from the US and UK to examine the safety and efficacy of ERT. The patients received an escalated drug dose (0.1 to 3.0 mg/kg) every 2 weeks for 26 weeks. The study proved that a gradual increase in within-patient ERT dose is effective and tolerable in managing ASMD patients without neurological impairment (9).

Recently, the results of the ASCEND trial, an international, phase 2/3, placebo-controlled trial, were released. The trial recruited 36 patients with ASMD type B and

followed for 52 weeks. The results showed a significant improvement in lung functions by 22%, compared to 3% in the placebo arm. Besides, the spleen size decreased by 39.5% at the end of the study, compared with a 0.5% increase in the placebo arm. ERT showed an acceptable safety profile, with only five patients experiencing severe adverse events that were not treatment-related, and none of the patients discontinued treatment (81).

Moreover, an international phase 2, open-label trial (ASCEND-Peds/NCT02292654) recruited 20 pediatric patients (aged from 1.5 to 17.5 years) with ASMD type B or A/B from six regions "Brazil, France, Germany, Italy, United Kingdom, and the United States." ERT was administered intravenously, and the dose was gradually elevated within-patient. The drug significantly improved the disease symptoms and tolerability during the 64 weeks of the trial; the average improvement in splenomegaly and hepatomegaly was more than 40%, and the average lung diffusing capacity improved by nearly 33%. Significant improvements were also noted in liver enzymes and growth parameters. ERT showed an acceptable safety profile, with only three patients experiencing severe ADRs (10).

Based on such results, ERT has been granted breakthrough therapy designation submission by the Food and Drug Administration. In June 2022, the European Medical Agency granted the ERT, olipudase alfa, marketing authorization.

Experts' opinion

The experts stated that the results of ERT are promising, and its anticipated introduction to the clinical practice is likely to positively impact the treatment landscape of ASMD. Patients with non-neurological manifestations are more likely to benefit from ERT. Early initiation of therapy in the presymptomatic or early symptomatic stages will also be a key factor in the long-term success of treatment. Thus, future studies should focus on identifying the criteria of the patients with a high probability of achieving response to ERT, the types of required monitoring during treatment, and real-world experience from the GCC region.

In terms of the GCC region's needs, the experts confirmed that establishing a national registry for ASMD would support the substantial role of ERT for ASMD in the region. There is a need for national and institutional guidelines for patient referral to ensure optimal patient management. Also, there is a need for standardized multidisciplinary ASMD management and unified treatment protocol in the GCC region.

Conclusion and Future Directions

The suspected comparatively high incidence of ASMD in the GCC countries demonstrated that developing a comprehensive diagnostic and management approach for such a debilitating condition is a significant unmet need in the region. The current literature shows controversy, and further studies are still required and should be tailored to meet local and regional needs. Therefore, an urgent need to create a practical diagnostic and management algorithm that can significantly reduce the diagnostic delay of the ASMD, improve the prognosis of the patients, and limit the impairment in the quality of life. The current experts' view highlighted several unmet needs in the ASMD landscape in the region. There is a scarcity of published literature that assesses the burden of ASMD in the GCC region. The experts emphasized the lack of a multidisciplinary approach to managing ASMD in the region. Besides, the lack of awareness about ASMD among general pediatricians or gastroenterologists usually leads to a significant delay in diagnosing ASMD. Thus, there is an urgent need to increase awareness about ASMD symptoms and more centers of excellence in the GCC region to help with early and proper diagnosis of ASMD cases.

Acknowledgments

Dr. Gehad El Ashal and Dr. Ahmed Salah Hussein from RAY-CRO provided medical writing assistance and editorial support for this manuscript. Also, we would like to thank Dr. Omar M. Hussein and Dr. Reham Elgarhy from RAY-CRO for their valuable efforts exerted on this project. Medical writing assistance and publication were funded with logistical support from Sanofi.

Funding
None.

Declaration of conflicting interests
The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Consent to participate
Not applicable.

Ethical approval
Not applicable.

Author details
Moeenaldeen AlSayed[1], Fatma Al-Jasmi[2,3], Tawfeg Ben Omran[4], Fathiya Al-Murshedi[5], Rawda Sunbul[6], Nadia Al-Hashmi[7], Talal Al-Enazi[8]

1. King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia
2. Department of Genetics & Genomics, United Arab Emirates University, Al Ain, United Arab Emirates
3. Tawam Hospital, Al Ain, United Arab Emirates
4. Division of Genetic and Genomic Medicine, Sidra Medicine and Hamad Medical Corporation, Ar-Rayyan, Qatar
5. Genetic and Developmental Medicine Clinic, Department of Genetics, Sultan Qaboos University Hospital, Seeb, Oman
6. Qatif Central Hospital, Qatif, Saudi Arabia
7. Royal Hospital, Muscat, Oman
8. Prince Sultan Military Medical City, Riyadh, Saudi Arabia

References

1. Schuchman EH, Wasserstein MP. Types A and B Niemann-Pick disease. Best Pract Res Clin Endocrinol Metab. 2015;29(2):237–47. https://doi.org/10.1016/j.beem.2014.10.002

2. McGovern MM, Aron A, Brodie SE, Desnick RJ, Wasserstein MP. Natural history of type A Niemann-Pick disease: possible endpoints for therapeutic trials. Neurology. 2006;66(2):228–32. https://doi.org/10.1212/01.wnl.0000194208.08904.0c

3. Kingma SD, Bodamer OA, Wijburg FA. Epidemiology and diagnosis of lysosomal storage disorders; challenges of screening. Best Pract Res Clin Endocrinol Metab. 2015;29(2):145–7. https://doi.org/10.1016/j.beem.2014.08.004

4. Hollak CE, de Sonnaville ES, Cassiman D, Linthorst GE, Groener JE, Morava E, et al. Acid sphingomyelinase (Asm) deficiency patients in the Netherlands and Belgium: disease spectrum and natural course in attenuated patients. Mol Genet Metab. 2012;107(3):526–33. https://doi.org/10.1016/j.ymgme.2012.06.015

5. McGovern MM, Dionisi-Vici C, Giugliani R, Hwu P, Lidove O, Lukacs Z, et al. Consensus recommendation for a diagnostic guideline for acid sphingomyelinase deficiency. Genet Med. 2017;19(9):967. https://doi.org/10.1038/gim.2017.7

6. McGovern MM, Avetisyan R, Sanson BJ, Lidove O. Disease manifestations and burden of illness in patients with acid sphingomyelinase deficiency (ASMD). Orphanet J Rare Dis. 2017;12(1):41. https://doi.org/10.1186/s13023-017-0572-x

7. He X, Chen F, Dagan A, Gatt S, Schuchman EH. A fluorescence-based, high-performance liquid chromatographic assay to determine acid sphingomyelinase activity and diagnose types A and B Niemann-Pick disease [Internet]. Anal Biochem. 2003;314(1):116–20. https://doi.org/10.1016/S0003-2697(02)00629-2

8. Thurberg BL, Diaz GA, Lachmann RH, Schiano T, Wasserstein MP, Ji AJ, et al. Long-term efficacy of olipudase alfa in adults with acid sphingomyelinase deficiency (ASMD): further clearance of hepatic sphingomyelin is associated with additional improvements in pro- and anti-atherogenic lipid profiles after 42 months of treatment. Mol Genet Metab. 2020;131(1–2):245–52. https://doi.org/10.1016/j.ymgme.2020.06.010

9. Wasserstein MP, Jones SA, Soran H, Diaz GA, Lippa N, Thurberg BL, et al. Successful within-patient dose escalation of olipudase alfa in acid sphingomyelinase deficiency. Mol Genet Metab. 2015;116(1–2):88–97. https://doi.org/10.1016/j.ymgme.2015.05.013

10. Diaz GA, Jones SA, Scarpa M, Mengel KE, Giugliani R, Guffon N, et al. One-year results of a clinical trial of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency. Genet Med. 2021;23(8):1543. https://doi.org/10.1038/s41436-021-01156-3

11. Ozand PT, Gascon G, al Aqeel A, Roberts G, Dhalla M, Subramanyam SB. Prevalence of different types of lysosomal storage diseases in Saudi Arabia. J Inherit Metab Dis. 1990;13(6):849–61. https://doi.org/10.1007/BF01800209

12. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA. 1999;281(3):249–54. https://doi.org/10.1001/jama.281.3.249

13. Acuña M, Martínez P, Moraga C, He X, Moraga M, Hunter B, et al. Epidemiological, clinical and biochemical characterization of the p.(Ala359Asp) SMPD1 variant causing Niemann-Pick disease type B. Eur J Hum Genet. 2016;24(2):208. https://doi.org/10.1038/ejhg.2015.89

14. Orphanet: Niemann Pick disease type A [Internet]. [cited 2022 Jan 9]. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=77292

15. Pokrzywinski R, Hareendran A, Nalysnyk L, Cowie S, Crowe J, Hopkin J, et al. Impact and burden of acid sphingomyelinase deficiency from a patient and caregiver perspective. Sci Rep. 2021;11(1):1–13. https://doi.org/10.1038/s41598-021-99921-6

16. Al-Gazali L, Hamamy H, Al-Arrayad S. Genetic disorders in the Arab world. BMJ Br Med J. 2006;333(7573):831. https://doi.org/10.1136/bmj.38982.704931.AE

17. Moammar H, Cheriyan G, Mathew R, Al-Sannaa N. Incidence and patterns of inborn errors of metabolism in the Eastern Province of Saudi Arabia, 1983-2008. Ann Saudi Med. 2010;30(4):271–7. https://doi.org/10.4103/0256-4947.65254

18. Al-Sannaa NA, Al-Abdulwahed HY, Al-Ghamdi MS, Abbas Al-Sannaa N, Geneticist C, Hopkins Aramco J. Lysosomal storage disorders (LSDs): the prevalence in the Eastern Province of Saudi Arabia. Int J Neurol Dis. 2017;1(2):38–043.

19. Alfadhel M, Benmeakel M, Hossain MA, Al Mutairi F, Al Othaim A, Alfares AA, et al. Thirteen year retrospective review of the spectrum of inborn errors of metabolism presenting in a tertiary center in Saudi Arabia. Orphanet J Rare Dis. 2016;11(1):126. https://doi.org/10.1186/s13023-016-0510-3

20. Al-Jasmi FA, Tawfig N, Berniah A, Ali BR, Taleb M, Hertecant JL, et al. Prevalence and novel mutations of lysosomal storage disorders in United Arab Emirates: LSD in UAE. JIMD Rep [Internet]. 2013 [cited 2022 Jan 10];10:1. Available from: /pmc/articles/PMC3755583/ 21. Joshi SN, Hashim J, Venugopalan P. Pattern of inborn errors of metabolism in an Omani population of the Arabian Peninsula. Ann Trop Paediatr. 2022;22(1):93–6. https://doi.org/10.1179/027249302125000238

22. Mezzi N, Messaoud O, Mkaouar R, Zitouna N, Romdhane S, Abdessalem G, et al. Spectrum of genetic diseases in Tunisia: current situation and main milestones achieved. Genes (Basel) [Internet]. 2021 Nov 1 [cited 2022 Jan 9];12(11). Available from: /pmc/articles/PMC8617973/

23. Zampieri S, Filocamo M, Pianta A, Lualdi S, Gort L, Coll MJ, et al. SMPD1 utation update: database and comprehensive analysis of published and novel variants [Internet]. Hum Mutat. 2016;37(2):139–47. https://doi.org/10.1002/humu.22923

24. Pastores GM, Lau HA. Niemann-Pick disease. Encycl Neurol Sci [Internet]. 2021;590–1. https://doi.org/10.1016/B978-0-12-385157-4.00102-0

25. Zhang H, Wang Y, Gong Z, Li X, Qiu W, Han L, et al. Identification of a distinct mutation spectrum in the SMPD1 gene of Chinese patients with acid sphingomyelinase-deficient Niemann-Pick disease. Orphanet J Rare Dis. 2013;8(1):15. https://doi.org/10.1186/1750-1172-8-15

26. Levran O, Desnick RJ, Schuchman EH. Type A Niemann-Pick disease: a frameshift mutation in the acid sphingomyelinase gene (fsP330) occurs in Ashkenazi Jewish patients. Hum Mutat. 1993;2(4):317–9. https://doi.org/10.1002/humu.1380020414

27. Mihaylova V, Hantke J, Sinigerska I, Cherninkova S, Raicheva M, Bouwer S, et al. Highly variable neural involvement in sphingomyelinase-deficient Niemann-Pick disease caused by an ancestral Gypsy mutation. Brain.

2007;130(Pt 4):1050–61. https://doi.org/10.1093/brain/awm026

28. Wasserstein MP, Aron A, Brodie SE, Simonaro C, Desnick RJ, McGovern MM. Acid sphingomyelinase deficiency: prevalence and characterization of an intermediate phenotype of Niemann-Pick disease. J Pediatr. 2006;149(4):554–9. https://doi.org/10.1016/j.jpeds.2006.06.034
29. Vanier MT, Ferlinz K, Rousson R, Duthel S, Louisot P, Sandhoff K, et al. Deletion of arginine (608) in acid sphingomyelinase is the prevalent mutation among Niemann-Pick disease type B patients from northern Africa. Hum Genet. 1993;92(4):325–30. https://doi.org/10.1007/BF01247328
30. Gluck I, Zeigler M, Bargal R, Schiff E, Bach G. Niemann Pick disease type A in Israeli Arabs: 677delT, a common novel single mutation. Hum Mutat. 1998;12(2):136. https://doi.org/10.1002/(SICI)1098-1004(1998)12:2<136::AID-HUMU12>3.3.CO;2-P
31. Thurberg BL. Autopsy pathology of infantile neurovisceral ASMD (Niemann-Pick disease type A): clinicopathologic correlations of a case report. Mol Genet Metab Rep. 2020;24:100626. https://doi.org/10.1016/j.ymgmr.2020.100626
32. Pavlů-Pereira H, Asfaw B, Poupctová H, Ledvinová J, Sikora J, Vanier MT, et al. Acid sphingomyelinase deficiency. Phenotype variability with prevalence of intermediate phenotype in a series of twenty-five Czech and Slovak patients. A multi-approach study. J Inherit Metab Dis. 2005;28(2):203–27. https://doi.org/10.1007/s10545-005-5671-5
33. McGovern MM, Pohl-Worgall T, Deckelbaum RJ, Simpson W, Mendelson D, Desnick RJ, et al. Lipid abnormalities in children with types A and B Niemann Pick disease. J Pediatr. 2004;145(1):77–81. https://doi.org/10.1016/j.jpeds.2004.02.048
34. Ishii H, Takahashi T, Toyono M, Tamura M, Harada K, Yoshida M, et al. Acid sphingomyelinase deficiency: cardiac dysfunction and characteristic findings of the coronary arteries. J Inherit Metab Dis. 2006;29(1):232–4. https://doi.org/10.1007/s10545-006-0226-y
35. Mendelson DS, Wasserstein MP, Desnick RJ, Glass R, Simpson W, Skloot G, et al. Type B Niemann-Pick disease: findings at chest radiography, thin-section CT, and pulmonary function testing. Radiology. 2006;238(1):339–45. https://doi.org/10.1148/radiol.2381041696
36. von Ranke FM, Pereira Freitas HM, Mançano AD, Rodrigues RS, Hochhegger B, Escuissato D, et al. Pulmonary involvement in Niemann-Pick disease: a state-of-the-art review [Internet]. Lung. 2016;194(4):511–8. https://doi.org/10.1007/s00408-016-9893-0
37. Wasserstein M, Godbold J, McGovern MM. Skeletal manifestations in pediatric and adult patients with Niemann Pick disease type B. J Inherit Metab Dis. 2013;36(1):123–7. https://doi.org/10.1007/s10545-012-9503-0
38. McGovern MM, Lippa N, Bagiella E, Schuchman EH, Desnick RJ, Wasserstein MP. Morbidity and mortality in type B Niemann-Pick disease. Genet Med. 2013;15(8):618–23. https://doi.org/10.1038/gim.2013.4
39. Cassiman D, Packman S, Bembi B, Turkia HB, Al-Sayed M, Schiff M, et al. Cause of death in patients with chronic visceral and chronic neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type B and B variant): literature review and report of new cases. Mol Genet Metab. 2016;118(3):206–13. https://doi.org/10.1016/j.ymgme.2016.05.001
40. Wasserstein MP, Desnick RJ, Schuchman EH, Hossain S, Wallenstein S, Lamm C, et al. The natural history of type B Niemann-Pick disease: results from a 10-year longitudinal study. Pediatrics. 2004;114(6):e672–7. https://doi.org/10.1542/peds.2004-0887
41. Orchard EA, Kempson D, Lindsay DC. Niemann-Pick disease type B with severe coronary artery disease and early recurrence after coronary artery bypass grafting. J Clin Lipidol. 2009;3(1):57–8. https://doi.org/10.1016/j.jacl.2008.11.011
42. Labrune P, Bedossa P, Huguet P, Roset F, Vanier MT, Odievre M. Fatal liver failure in two children with Niemann-Pick disease type B. J Pediatr Gastroenterol Nutr. 1991;13(1):104–9. https://doi.org/10.1097/00005176-199107000-00020
43. Thurberg BL, Wasserstein MP, Schiano T, O'Brien F, Richards S, Cox GF, et al. Liver and skin histopathology in adults with acid sphingomyelinase deficiency (Niemann-Pick disease type B). Am J Surg Pathol. 2012;36(8):1234–46. https://doi.org/10.1097/PAS.0b013e31825793ff
44. Stirnemann J, Vigan M, Hamroun D, Heraoui D, Rossi-Semerano L, Berger MG, et al. The French Gaucher's disease registry: clinical characteristics, complications and treatment of 562 patients. Orphanet J Rare Dis. 2012;7(1):77. https://doi.org/10.1186/1750-1172-7-77
45. Stirnemann JÔ, Belmatoug N, Camou F, Serratrice C, Froissart R, Caillaud C, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. Int J Mol Sci [Internet]. 2017 Feb 17 [cited 2022 Jan 19];18(2):441. Available from: /pmc/articles/PMC5343975/
46. McGovern MM, Wasserstein MP, Giugliani R, Bembi B, Vanier MT, Mengel E, et al. A prospective, cross-sectional survey study of the natural history of Niemann-Pick disease type B. Pediatrics. 2008;122(2):e341–9. https://doi.org/10.1542/peds.2007-3016
47. McGovern MM, Wasserstein MP, Bembi B, Giugliani R, Mengel KE, Vanier MT, et al. Prospective study of the natural history of chronic acid sphingomyelinase deficiency in children and adults: eleven years of observation. Orphanet J Rare Dis. 2021;16(1):212. https://doi.org/10.1186/s13023-021-01842-0
48. Cox GF, Clarke LA, Giugliani R, McGovern MM. Burden of illness in acid sphingomyelinase deficiency: a retrospective chart review of 100 patients. JIMD Rep. 2018;41(41):119–29. https://doi.org/10.1007/8904_2018_120
49. Nicholson AG, Florio R, Hansell DM, Bois RM, Wells AU, Hughes P, et al. Pulmonary involvement by Niemann-Pick disease. A report of six cases. Histopathology. 2006;48(5):596–603. https://doi.org/10.1111/j.1365-2559.2006.02355.x
50. Iaselli F, Rea G, Cappabianca S, Fabozzi G, Montemarano M, Vitale C, et al. Adult-onset pulmonary involvement in Niemann-Pick disease type B. Monaldi Arch Chest Dis. 2011;75(4):235–40. https://doi.org/10.4081/monaldi.2011.211
51. Freitas HM, Mançano AD, Rodrigues RS, Hochhegger B, Torres PP, Escuissato D, et al. Niemann-Pick disease type B: HRCT assessment of pulmonary involvement. J Bras

Pneumol. 2017;43(6):451–5. https://doi.org/10.1590/s1806-37562017000000062

52. Lidove O, Belmatoug N, Froissart R, Lavigne C, Durieu I, Mazodier K, et al. Acid sphingomyelinase deficiency (Niemann-Pick disease type B) in adulthood: a retrospective multicentric study of 28 adult cases. Rev Med Interne. 2017;38(5):291–9.

53. Brinkman J, Wijburg FA, Hollak CE, Groener JE, Verhoek M, Scheij S, et al. Plasma chitotriosidase and CCL18: early biochemical surrogate markers in type B Niemann-Pick disease. J Inherit Metab Dis. 2005;28(1):13–20. https://doi.org/10.1007/s10545-005-4416-9

54. Oliva P, Mechtler TP, Schwarz M, Balendran S, Cobos PN, Lukacs Z, et al. Differential diagnosis of Niemann-Pick disease types A and B in cases of suspected Gaucher disease. Mol Genet Metab. 2020;129(2):S121. https://doi.org/10.1016/j.ymgme.2019.11.314

55. Gal AE, Brady RO, Hibbert SR, Pentchev PG. A practical chromogenic procedure for the detection of homozygotes and heterozygous carriers of Niemann-Pick disease. N Engl J Med. 1975;293(13):632–6. https://doi.org/10.1056/NEJM197509252931304

56. Kuchar L, Sikora J, Gulinello ME, Poupetova H, Lugowska A, Malinova V, et al. Quantitation of plasmatic lysosphingomyelin and lysosphingomyelin-509 for differential screening of Niemann-Pick A/B and C diseases. Anal Biochem. 2017;525:73–7. https://doi.org/10.1016/j.ab.2017.02.019

57. Gelb MH, Turecek F, Scott CR, Chamoles NA. Direct multiplex assay of enzymes in dried blood spots by tandem mass spectrometry for the newborn screening of lysosomal storage disorders. J Inherit Metab Dis. 2006;29(2–3):397–404. https://doi.org/10.1007/s10545-006-0265-4

58. Legnini E, Orsini JJ, Mühl A, Johnson B, Dajnoki A, Bodamer OA. Analysis of acid sphingomyelinase activity in dried blood spots using tandem mass spectrometry. Ann Lab Med. 2012;32(5):319–23. https://doi.org/10.3343/alm.2012.32.5.319

59. Gelb MH, Ronald Scott C, Turecek F, Liao HC. Comparison of tandem mass spectrometry to fluorimetry for newborn screening of LSDs. Mol Genet Metab Rep. 2017;12:80. https://doi.org/10.1016/j.ymgmr.2017.05.004

60. Lipiński P, Kuchar L, Zakharova EY, Baydakova GV, Ługowska A, Tylki-Szymańska A. Chronic visceral acid sphingomyelinase deficiency (Niemann-Pick disease type B) in 16 polish patients: long-term follow-up. Orphanet J Rare Dis. 2019;14(1):55. https://doi.org/10.1186/s13023-019-1029-1

61. Wasserstein MS. Acid sphingomyelinase deficiency. In: Pagon R, Adamm M, Ardinger H, et al., editors. GeneReviews. Seattle, DC: University of Washington; 2015.

62. Simonaro CM, Desnick RJ, McGovern MM, Wasserstein MP, Schuchman EH. The demographics and distribution of type B Niemann-Pick disease: novel mutations lead to new genotype/phenotype correlations. Am J Hum Genet. 2002;71(6):1413–9. https://doi.org/10.1086/345074

63. Sheth JJ, Sheth FJ, Oza NJ, Gambhir PS, Dave UP, Shah RC. Plasma chitotriosidase activity in children with lysosomal storage disorders. Indian J Pediatr. 2010;77(2):203–5. https://doi.org/10.1007/s12098-009-0249-0

64. Sikora J, Pavlu-Pereira H, Elleder M, Roelofs H, Wevers RA. Seven novel acid sphingomyelinase gene mutations in Niemann-Pick type A and B patients. Ann Hum Genet. 2003;67(Pt 1):63–70. https://doi.org/10.1046/j.1469-1809.2003.00009.x

65. Boot RG, Renkema GH, Verhoek M, Strijland A, Bliek J, de Meulemeester TM, et al. The human chitotriosidase gene. Nature of inherited enzyme deficiency. J Biol Chem. 1998;273(40):25680–5. https://doi.org/10.1074/jbc.273.40.25680

66. Bussink AP, Verhoek M, Vreede J, Ghauharali-van der Vlugt K, Donker-Koopman WE, Sprenger RR, et al. Common G102S polymorphism in chitotriosidase differentially affects activity towards 4-methylumbelliferyl substrates. FEBS J. 2009;276(19):5678–88. https://doi.org/10.1111/j.1742-4658.2009.07259.x

67. Deegan PB, Moran MT, McFarlane I, Schofield JP, Boot RG, Aerts JM, et al. Clinical evaluation of chemokine and enzymatic biomarkers of Gaucher disease. Blood Cells Mol Dis. 2005;35(2):259–67. https://doi.org/10.1016/j.bcmd.2005.05.005

68. Murugesan V, Chuang WL, Liu J, Lischuk A, Kacena K, Lin H, et al. Glucosylsphingosine is a key biomarker of Gaucher disease. Am J Hematol. 2016;91(11):1082–9. https://doi.org/10.1002/ajh.24491

69. Chuang WL, Pacheco J, Cooper S, McGovern MM, Cox GF, Keutzer J, et al. Lyso-sphingomyelin is elevated in dried blood spots of Niemann-Pick B patients. Mol Genet Metab. 2014;111(2):209–11. https://doi.org/10.1016/j.ymgme.2013.11.012

70. Nagral A. Gaucher disease. J Clin Exp Hepatol. 2014;4(1):37–50. https://doi.org/10.1016/j.jceh.2014.02.005

71. Puri RD, Kapoor S, Kishnani PS, Dalal A, Gupta N, Muranjan M, et al. Gaucher disease task force. Diagnosis and management of Gaucher disease in India - consensus guidelines of the Gaucher disease task force of the society for Indian academy of medical genetics and the Indian academy of pediatrics. Indian Pediatr. 2018;55(2):143–53. https://doi.org/10.1007/s13312-018-1249-9

72. Oliva P, Schwarz M, Wiesinger T, Scott J, Sansen S, Mechtler T, et al. The incidence of acid sphingomyelinase deficiency (ASMD) in cases of suspected Gaucher disease, genotype-phenotype correlation together with Lyso-SPM biomarker. Mol Genet Metab. 2021;132(2):S79. https://doi.org/10.1016/j.ymgme.2020.12.186

73. Wasserstein MP, Schuchman EH. Acid sphingomyelinase deficiency. GeneReviews® [Internet]. 2021 Feb 25 [cited 2022 Jan 10]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK1370/

74. Pastores GM, Hughes DA. Non-neuronopathic lysosomal storage disorders: disease spectrum and treatments [Internet]. Best Pract Res Clin Endocrinol Metab. 2015;29(2):173–82. https://doi.org/10.1016/j.beem.2014.08.005

75. Chen Z, Chen Z, Wu S, Wang X. Niemann-Pick disease resulting in spontaneous splenic rupture in an adult: report of a case. Surg Today. 2008;38(5):473–5. https://doi.org/10.1007/s00595-007-3641-2

76. Simões RG, Maia H. Niemann-Pick type B in adulthood. Case Rep. 2015;2015:bcr2014208286. https://doi.org/10.1136/bcr-2014-208286

77. Victor S, Coulter JB, Besley GT, Ellis I, Desnick RJ, Schuchman EH, et al. Niemann-Pick disease: sixteen-year follow-up of allogeneic bone marrow transplantation in a type B variant [Internet]. J Inherit Metab Dis. 2003;26(8):775–85. https://doi.org/10.1023/B:BOLI.0000009950.81514.c8

78. Schuchman EH, Desnick RJ. Types a and B Niemann-pick disease. Mol Genet Metab. 2017;120(1–2):27–33. https://doi.org/10.1016/j.ymgme.2016.12.008

79. Morel CF, Gassas A, Doyle J, Clarke JT. Unsuccessful treatment attempt: cord blood stem cell transplantation in a patient with Niemann-Pick disease type A. J Inherit Metab Dis. 2007;30(6):987. https://doi.org/10.1007/s10545-007-0700-1

80. McGovern MM, Wasserstein MP, Kirmse B, Duvall WL, Schiano T, Thurberg BL, et al. Novel first-dose adverse drug reactions during a phase I trial of olipudase alfa (recombinant human acid sphingomyelinase) in adults with Niemann-Pick disease type B (acid sphingomyelinase deficiency). Genet Med. 2016;18(1):34–40. https://doi.org/10.1038/gim.2015.24

81. Wasserstein M, Arash-Kaps L, Barbato A, Gallagher R, Giugliani R, Guelbert N, et al. One-year results of the placebo-controlled ASCEND trial of olipudase alfa enzyme replacement therapy in adults with chronic acid sphingomyelinase deficiency. Mol Genet Metab. 2021;132:S64–5. https://doi.org/10.1016/S1096-7192(21)00178-5