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ACID SPHINGOMYELINASE DEFICIENCY: A COMPLEX AND RARE DISORDER THAT NEEDS CLINICIANS' AWARENESS

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ABSTRACT – Acid sphingomyelinase deficiency (ASMD), historically known as Niemann-Pick disease types A and B, is an autosomal recessive lysosomal storage disease caused by mutations in the *SMPD1* gene. These mutations lead to reduced activity of the lysosomal enzyme acid sphingomyelinase (ASM), resulting in the progressive accumulation of sphingomyelin and other glycosphingolipids in multiple tissues and organs.

Storage of undegraded substrates triggers a complex and only partially understood cascade of secondary events, culminating in a progressive multisystem disease with a broad clinical spectrum characterized by neurological and visceral manifestations. Three main phenotypes have been traditionally identified: a severe infantile neurovisceral form (or Niemann-Pick type A), an intermediate chronic neurovisceral form (intermediate Niemann-Pick A/B; Niemann-Pick B variant), and a chronic visceral form (Niemann-Pick type B).

The rarity of ASMD and the resulting lack of clinician awareness contribute to frequent misdiagnoses and delays in diagnosis despite advancements in diagnostic tools. Given the recent introduction of alpha-olipudase enzyme replacement therapy, which may provide substantial clinical benefits when initiated early, timely diagnosis has become crucial.

This review provides a comprehensive overview of ASMD, focusing on the recent advancements in the understanding of the disease pathophysiology, the variability of clinical manifestations, the need to increase clinician awareness to promote early diagnosis, the evolution of the diagnostic approaches, and current and experimental treatment options.

Keywords: ASMD, SPMD1, Niemann-Pick disease, Lysosomal storage disease, Inborn errors of metabolism.

List of abbreviations: AAV: adeno-associated virus; ADA: anti-drug antibody; AE: adverse event; ASMD: acid sphingomyelinase deficiency; ASM-KO: ASM knock out animal models; BBB: blood-brain barrier; BMP: bis (monoacylglycerol) phosphate; BMT: bone marrow transplantation; CNS: central nervous system; CTL: cytotoxic T lymphocytes; C-triol: cholestane-3b, 5a, 6b-triol; DBS: dried blood spot; DLCO: diffusing capacity of the lung for carbon monoxide; GD: Gaucher disease; HCC: hepatocellular carcinoma; HLH: hemophagocytic lymphohistiocytosis; HRCT: high-resolution computed tomography; HSCT: hematopoietic stem cell transplantation; ILD: interstitial lung disease; IMD: inherited metabolism disorder; IT: intrathecal; LC–MS/MS: liquid chromatography-tandem mass spectrometry; LysoSM or LSM: lyso-sphingomyelin; LysoSM 509: lyso-sphingomyelin 509; LSD: Lysosomal storage disease; MLPA: multiplex ligation dependent probe amplification; MS/MS: mass spectrometry; MS/MS: tandem mass spectrometry; NBS: newborn screening; NGS: next generation sequencing; NKT: Natural Killer T; NPA: Niemann-Pick stype A disease; NPB: Niemann-Pick type B disease; NPA/B: Niemann-Pick type A-B disease; PPCS: N-palmitoyl-O-phosphocholine-serine; rhASM: recombinant human ASM; SPM: Sphingomyelin; SRS: splenomegaly-related scores; TCG: 3β,5α,6β-trihydroxycholanoyl-glycine; TFEB: transcription factor EB; WGS: whole genome sequencing; 7-KC: 7-ketocholesterol.

INTRODUCTION

Acid sphingomyelinase deficiency (ASMD), also referred to as Niemann–Pick disease types A, B, and A/B (OMIM #257200, #607616), is an autosomal recessive lysosomal storage disorder caused by pathogenic variants in the sphingomyelin phosphodiesterase 1 (*SMPD1*) gene[1].

These variants lead to a deficiency of acid sphingomyelinase (ASM), an enzyme responsible for the hydrolysis of sphingomyelin (SPM) into ceramide and phosphocholine in lysosomes. ASM deficiency results in aberrant and progressive accumulation of undegraded SPM and other lipids in tissues rich in reticuloendothelial cells, such as the spleen, liver, lungs, bone marrow, and lymph nodes, and into a cascade of secondary events, still partially understood, that contribute to the disease pathophysiology[2].

A phenotypic continuum with variable disease severity and a broad range of clinical manifestations characterizes the ASMD phenotype. However, three distinct phenotypes have traditionally been identified. They are commonly used in the clinical assessment of patients[1,3,4]: an infantile neurovisceral ASMD (Niemann–Pick Disease type A), characterized by rapid neurodegeneration and early death within the first few years of life; a chronic visceral ASMD (Niemann- Pick type B), with slower and attenuated disease progression, significant visceral involvement, minimal or absent neurodegeneration, and survival into adulthood[5-8]; an intermediate phenotype (Niemann–Pick type A/B) that combines neurologic and visceral manifestations, but with a milder course compared to ASMD type A[1,9].

In general, ASMD impacts heavily on patient health and quality of life and is associated with significant neurological and/or physical handicaps.

Until a few years ago, the care of ASMD patients was only based on palliative or supportive treatments. Following the recent regulatory approval of enzyme replacement therapy (ERT) with alpha-olipudase in 2023, for the first time, a disease-modifying therapy has become available. As it is reasonable to expect that timely intervention is associated with a better outcome, enhancing early diagnosis and raising awareness of ASMD have become critical issues.

For several reasons, current awareness of ASMD is poor, and patients often experience diagnostic odysseys before a correct diagnosis is established. One of the reasons for ASMD under-recognition is the rarity of this condition and the insufficient level of information about ultrarare diseases among most general physicians. ASMD has an estimated global prevalence ranging between 1:100,000 and 1:1,000,000 live births. However, certain populations, such as Ashkenazi Jews, have a higher incidence due to specific pathogenic *SMPD1* variants, with a carrier frequency of 1:100 to 1:200[3,10].

ASMD is often under-recognized also because of substantial phenotypic overlap with more common conditions or with other lysosomal disorders[3]. The variability of clinical presentations does not help in this respect, making the diagnosis of ASMD more complex and elusive. The lack of first-line biochemical tests and the limited access to second/third-level confirmatory tests for the diagnosis of ASMD exacerbate this issue and add further barriers to timely diagnosis[10].

The objective of this review is to provide an overview of ASMD, including emerging aspects of its pathophysiology, clinical presentation, diagnostic strategies and advancements in the treatment, with the goal of raising awareness of this condition among clinicians.

THE EVOLVING VIEW OF ASMD PATHOPHYSIOLOGY

In general, an accurate characterization of the mechanisms involved in the pathophysiology of inborn errors of metabolism, including ASMD, is critical for the understanding of processes that cause disease pathology and manifestations and has the potential to translate into the identification of novel therapeutic targets.

In healthy cells, acid ASM exerts its degradative function in lysosomes[11]. The main substrate for ASM is SPM, which is a structural component of most cell membranes and, together with cholesterol, is a major constituent of membrane raft structures[12,13]. Thus, ASM activity is important for membrane degradation and turnover.

The consequence of ASM deficiency is the abnormal accumulation of SPM and other metabolically related lipids in lysosomes, including lysosphingomyelin (sphingosylphosphorylcholine) and bis (monoacylglycerol) phosphate (BMP). Additionally, other lipids, such as glycosphingolipids and cholesterol, accumulate secondarily[2,4].

Storage is most prominent and clinically relevant in cells of the monocyte-macrophage system. Large lipid-laden cells (so-called "foam cells") are usually described in histopathological examination of the liver, spleen, lymph nodes, adrenal cortex, lungs and/or bone marrow[14].

Substrate storage has traditionally been considered the primary player in ASMD pathophysiology. However, recent studies have introduced a significant shift in the vision of the pathophysiology of lysosomal storage diseases, highlighting the critical role of other secondary events in cell and tissue pathology and the development of clinical manifestations. It has been recognized that lysosomes are involved in multiple and crucial functions in cellular homeostasis, and there is growing evidence that damage of these organelles triggers a cascade of pathogenic events, including storage of secondary substrates, abnormal composition of membranes, aberrant vesicle trafficking and consequent defects in endocytosis/exocytosis, and impaired autophagic flux[15-18] (Figure 1).

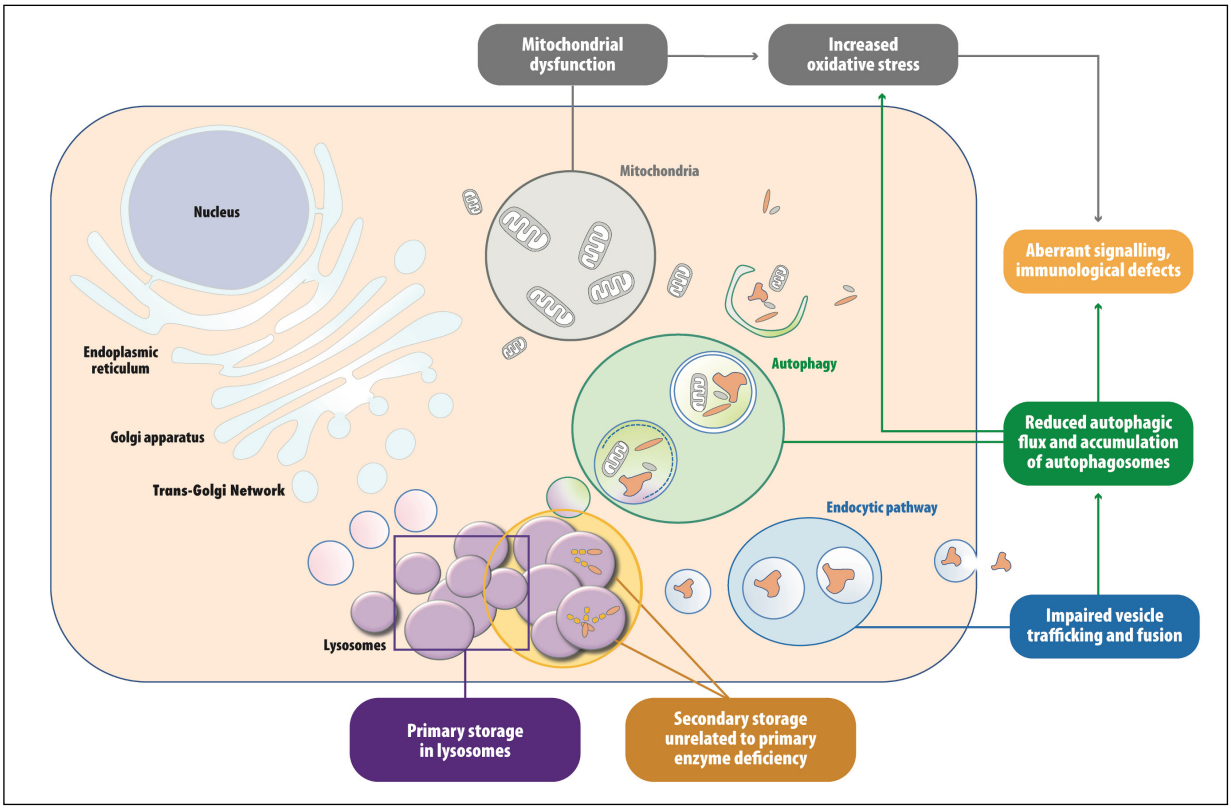

Figure 1. Primary substrate storage in ASM-deficient cells triggers secondary pathogenic events.
Storage of secondary substrates may be implicated in neurodegeneration. Aberrant vesicle trafficking translates into defects in endocytosis-exocytosis, altered distribution of various molecules, and impaired autophagic flux. Impaired autophagy and mitochondrial dysfunction are associated with increased oxidative stress. Aberrant signaling, elicited by these abnormalities, is also part of the pathogenetic cascade of ASMD.

In ASMD, aberrant SPM accumulation is paralleled by secondary accumulation of other lipids, such as GM2 and GM3 gangliosides and cholesterol[2,19], that are known to play a role in neurodegeneration. Furthermore, while it was previously suggested that ASM deficiency leads to ceramide depletion, the complexity of the underlying mechanisms results in more intricate lipid abnormalities both in the plasma membrane and lysosomes.

Interestingly, elevated ceramide levels have been observed in fibroblasts from affected patients[2] and ASM-KO mice (likely due to sphingomyelin breakdown by non-lysosomal sphingomyelinases or by other glyco-hydrolases as β-glucocerebrosidase on the external leaflet of the plasma membrane[2]) along with increased levels of downstream products such as sphingosine and sphingosine-1-phosphate[4].

SPM accumulation in lysosomes is also associated with impaired vesicle trafficking, block of the autophagic flux[20] and nuclear translocation of the transcription factor EB (TFEB), increased oxidative stress, mitochondrial damage and impairment of mitochondrial function, which eventually lead to apoptotic cell death and potentially to neurogeneration[2].

Most of these findings are also supported by analyses of gene expression profiles that showed dysregulation of genes involved in autophagy[21,22], electron transport chain machinery, cholesterol biosynthesis pathway, trafficking and distribution of various molecules[23], synaptic function[24,25], and calcium[26] and lipid hoemostasis[27,28].

Aberrant activation of signaling has been recognized as a pathogenetic mechanism of the disease. This event is likely the consequence of ASM's role in the maintenance of membrane composition and integrity. It has been shown that ASM translocates from lysosomes to the outer leaflet of the cell membrane in response to a number of stressor factors (such as radiation, conjugation of cell surface receptors, heat shock, exposure to bacterial pathogens and cytokines)[29-31]. At the plasma cell membrane SPM degradation by ASM leads to membrane raft reorganization into larger platforms enriched in ceramide and consequent activation of downstream signaling proteins through ceramide[29,32]. Pathological alterations in lipid composition, characterized by an imbalanced SPM/ceramide ratio in ASMD, may disrupt the signaling cascade, ultimately resulting in cell stress and apoptosis.

Other studies added further complexity to ASMD pathophysiology. It is of particular interest and relevant for the clinical manifestations of the disease that ASM activity is critical in cells of the immune system[33] and influences macrophage activity, inducing or amplifying inflammatory signals and cytokine production, promoting fusion of late phagosomes with lysosomes, regulating apoptosis and autophagic function.

Improved understanding of ASMD pathophysiology has also derived from the availability since the 1990s of a murine animal model lacking the ASM gene (ASM-KO)[28,34]. ASM-KO animals showed a progressive accumulation of SPM in the brain associated with variable disease severity, indicating the necessity to overcome a threshold in order to evocate neuronal damage[34,35]. The availability of a mouse model of the disease is also important for testing therapeutic approaches for the treatment of ASMD.

THE CLINICAL PRESENTATION OF ASMD - A BROAD AND VARIABLE SPECTRUM OF MANIFESTATIONS

The broad variability of the disease phenotype is a major challenge in the diagnostic approach to patients with ASMD. The clinical presentation, age of onset, and disease progression can vary widely, ranging from neurological decline to multi-organ involvement. It is important to know the main clinical features and suspect the disease in order to start, when appropriate, the diagnostic work-up and allow for timely diagnosis. Based on the presence and rate of progression of neurological manifestations, the disease has been traditionally classified into three forms (Table 1), with variable age at onset and course:

Table 1. ASMD phenotypes and main clinical manifestations.

	ASMD type A	ASMD type A/B	ASMD type B
Age at onset	Infantile	Infantile to childhood	Variable
Neurodegeneration	+++	+ slow	–
Splenomegaly	+++	+++	+++
Hepatic involvement	++	++	+++
Thrombocytopenia	+++	+++	+++
Respiratory	+	+++	+++
Skeletal involvement	+	++	++
Dislypidemia	+	++	++
Cardiovascular	-	++	++
Cherry red spot	++	+/-	+/-
Lifespan	<3 years (19–35 months)	Varies from childhood to adulthood	Variable; survival until the second or seventh decade
Cause of death	Neurodegeneration and respiratory failure	Neurodegeneration and respiratory failure	Pulmonary and hepatic involvement

1. **Infantile Neurovisceral ASMD (Niemann–Pick type A)**
   The most severe form, ASMD Type A, is characterized by little or no residual ASM activity. Symptoms typically appear in infancy with hypotonia and developmental delays that progress towards severe neurodegenerative manifestations in combination with visceral manifestations, such as liver and spleen enlargement, cholestasis, hematological manifestations and bleeding tendency, nutritional difficulties and failure to thrive. Without treatment, most children succumb to the disease by age 3 years due to progressive neurodegeneration[10].

2. **Chronic Neurovisceral ASMD (Niemann–Pick type A/B)**
   This intermediate form of ASMD is characterized by a slower progression of the disease and less pronounced neurological involvement compared to type A. Presentation typically occurs early in life, from infancy to childhood. Non-neurological manifestations can include visceromegaly, atherogenic lipid profile, interstitial lung disease, and hematological, immune and bone involvement. Neurological symptoms may vary, ranging from developmental delay, peripheral neuropathy and ataxia to progressive neurological deterioration or learning and behavioral abnormalities without clear progression[10,36]. Neurological issues such as developmental delays and ataxia typically emerge later in life[37].

3. **Chronic Visceral ASMD (Niemann–Pick type B)**
   The milder form, type B, has a variable age of onset ranging from childhood to adulthood[38-40] and typically lacks neurological involvement. Patients may exhibit splenomegaly, hepatomegaly, atherogenic lipid profile and progressive pulmonary disease, which can lead to liver and lung failure. While many patients have a normal life expectancy, morbidity[3] and mortality arise from complications of pulmonary and liver failure[37,41].

The phenotypic variability of the disease can be attributed to the progressive build-up of sphingomyelin reaching a threshold that causes cellular damage in different tissues[42]. This threshold effect is explained by varying levels of residual ASM activity, which correlate with the severity of the disease, neurological involvement, and the rate of progression. However, *in vitro*, ASM activity analysis alone is not sufficient to predict phenotype. It is reasonable to expect that modifier genes, secondary lipid accumulation, and environmental factors also play a role in disease severity[3,43].

ASMD IS A COMPLEX DISORDER WITH MULTISYSTEM INVOLVEMENT AND PROGRESSIVE COURSE

Like most lysosomal storage diseases, ASMD is a multisystem disease. This is relevant for both diagnosis and care of patients, and different specialists should participate in their management as part of a multidisciplinary team. Each of the clinical manifestations may represent a clue to the diagnosis and be associated with significant morbidity.

VISCERAL MANIFESTATIONS

Splenomegaly is a prominent, frequent and early manifestation. It is commonly observed at diagnosis and should raise the suspicion of a lysosomal disease, such as ASMD[38,39,44,45]. In a study of 59 patients with ASMD type B, splenic volumes ranged from 3.1- to 27.3-times normal, with 85% of patients showing volumes greater than five-times normal[45]. Splenomegaly may also serve as an indicator of disease severity, correlating with other disease parameters[46]. Elevated spleen volume is associated with secondary hypersplenism and an increased risk of bleeding and bruising, although a definitive correlation with platelet count remains unestablished[45].

Hepatomegaly is also a common visceral manifestation in ASMD, typically milder than splenomegaly. Liver involvement may begin early in life, with neonatal cholestasis sometimes being the first symptom[47]. Liver function tests generally show mild abnormalities, such as slight increases in transaminases and bilirubin[45]. However, liver fibrosis is a relevant issue, and it can progress to cirrhosis, even in the absence of significant biochemical alterations. The *SMPD1* mutation p.A359D is strongly associated with significant liver disease and progressive cirrhosis in ASMD type B patients[3]. Focal liver lesions have been observed, although no clear link with hepatocellular carcinoma (HCC) has been established.

Liver disease is a leading cause of morbidity and mortality in ASMD, second only to respiratory complications. This is especially true in splenectomised patients, where rapid liver deterioration can occur post-splenectomy. In some cases, liver failure may develop, potentially requiring liver transplantation or leading to significant clinical complications[37].

Regular imaging evaluations (ultrasound or MRI) and liver stiffness assessments are recommended to monitor patient status[44].

NEUROLOGICAL SYMPTOMS

As previously mentioned, neurological symptoms are typically found in patients with the most severe forms of the disease, ASMD type A. Infants with ASMD type A have profound structural changes in the brain, associated with infiltration of foam cells, neuronal cell loss in cerebral and cerebellar cortices, gliosis and demyelination[14]. Neurological symptoms emerge between 7 and 10 months of age, in most cases with developmental arrest, and quickly advance to severe neurodegeneration. This progression affects behavioral, language, and motor skills, leading to pronounced hypotonia and loss of deep tendon reflexes while cranial nerve function remains intact[38,48]. By 12 months, macular cherry-red spots may be observed.

Conversely, in intermediate ASMD phenotypes, neurological manifestations are generally less severe. Around 30% of these patients exhibit symptoms such as hypotonia or hyporeflexia, and some may experience progressive abnormalities, such as motor function loss and cognitive impairment. Neurological symptoms in these cases appear later and progress more slowly than in type A[37,49-53] and cherry-red spots may be present[51,54].

Neurological manifestations generally are not seen in type B patients or are limited to peripheral neuropathy, depression, anxiety, psychosis, as well as chronic pain and fatigue, which affect many patients over their lifetime[4,41,55].

Additionally, recent studies indicate that specific *SMPD1* gene mutations might be linked to an increased risk of Parkinson's disease, with some ASMD type B patients developing Parkinson's disease[38,56].

RESPIRATORY DISEASE

Respiratory involvement is present in all three subtypes of ASMD and significantly contributes to both mortality and morbidity in affected patients[3,36,39,45,57]. This is particularly pronounced in ASMD type B, where patients show varying degrees of interstitial lung disease. The underlying mechanism involves the accumulation of lipid-laden cells in the alveolar septa, bronchial walls, and pleura, leading to a restrictive lung pattern and pulmonary fibrosis, detectable via pulmonary function tests[58]. Pulmonary complications are rare in ASMD type A but typically manifest as recurrent respiratory infections, interstitial lung disease, and aspiration pneumonia, often leading to respiratory failure by age 3 years[58-61]. In ASMD type B, respiratory symptoms generally appear later in life, including recurrent cough, moderate exertional dyspnoea, and frequent respiratory infections. As the disease progresses, these patients develop worsening exertional dyspnoea, respiratory failure, and a need for high-flow oxygen[58].

Pulmonary involvement can be assessed through chest radiography and high-resolution computed tomography (HRCT)[62,63], though there is little correlation between radiological findings and respiratory symptoms. Thus, imaging must be interpreted in conjunction with functional tests and the patient's clinical condition. HRCT often reveals basal interstitial lung disease (ILD) with thickened interlobular septa, interlobular lines in the lower lung zones, and ground-glass opacities in the upper lung zones. Centrilobular nodular opacities or a "crazy paving" pattern, characterized by ground-glass opacities and thickened interlobular septa, may also appear[58,64,65]. Atelectasis and bronchiectasis have been reported. Bronchoscopy may reveal the presence of multivacuolated histiocytes with fine and coarse granules, known as "sea-blue histiocytes," as well as inflammatory cells in bronchoalveolar lavage fluid[58]. In some patients, lung transplantation has been attempted with inconsistent results.

HEMATOLOGICAL DISEASE

Hematological involvement in ASMD is characterized by various abnormalities, including thrombocytopenia, cytopenia, bleeding tendencies and bruising, along with potential complications such as hemophagocytic lymphohistiocytosis (HLH).

Thrombocytopenia is the common hematological abnormality in ASMD, mainly characterized by a reduced platelet count. Despite its prevalence, the platelet counts in these patients are generally not low enough to directly cause severe bleeding. This suggests that other factors beyond platelet levels contribute to the bleeding tendency observed. Thrombocytopenia in ASMD is often linked to the accumulation of lipid-laden cells in the spleen and bone marrow, which can sequester platelets and disrupt normal hematopoiesis[10].

ASMD patients may also exhibit cytopenia, which includes reductions in other blood cell lines, leading to anemia and leukopenia. Leukopenia compromises the immune system, increasing susceptibility to infections[3,10].

Bone marrow aspirates typically reveal numerous foamy cells with small vacuoles and sea-blue histiocytes[66,67]. HLH has been reported as both a complication and, in some cases, the presenting phenotype in patients with ASMD, particularly in infants with ASMD type B. The precise link between sphingomyelinase deficiency and HLH remains unclear. In this respect, it has been proposed that a deficiency in sphingomyelinase could lead to an excessive build-up of sphingolipids, potentially triggering overactivation of immune cells and cytokine storms, which are characteristic of HLH[68].

IMMUNOLOGICAL DISEASE

The correlations between ASMD and immunological defects are an emerging and intriguing aspect of the pathophysiology of this disorder. While it is well known that ASMD patients usually show recurrent respiratory infectious episodes and leukopenia[3,10], only recent studies have examined the direct role of ASM in the regulation of innate and adaptive immune system[33]. Lung macrophages are important players in innate immune responses, inflammation control and tissue remodeling. The reduction of ASM activity in bronchial epithelial cells has been associated with chronic inflammatory state both in unstimulated and infected conditions, with high neutrophil recruitment and elevated levels of cytokine expression[69,70].

ASM seems to have a critical role in different cells of the immune system, mainly due to its role in the promotion of ceramide-enriched platforms. ASM influences macrophage function, promoting inflammatory response, regulating fusion of late phagosomes with lysosomes and modulating apoptosis[70]. ASM-KO mice show phagosome dysfunction with consequent increased susceptibility to intracellular pathogen infection (such as Listeria Monocytogenes and Leishmania Donovani)[71,72]. Moreover, ASM plays a specific role in controlling the activity of Natural Killer T (NKT), regulating antigen-presenting cells and modulating T-cell response[73-75] and in the function of cytotoxic T lymphocytes (CTL) by inducing granule secretion[76]. The release of the cytotoxic granules from CTL is defective in ASM-deficient mice, while B lymphocytes displayed autophagic dysfunction, accumulation of peroxidized lipid droplets and increased levels of reactive oxygen species[77].

ATHEROGENIC LIPID PROFILE AND CARDIAC DISEASE

An increased cardiac risk has been observed in ASMD patients due to an atherogenic lipid profile from the early stages of the disease. Most ASMD patients exhibit low HDL cholesterol, elevated total cholesterol, high triglycerides, and increased LDL and very low-density lipoprotein cholesterol, with no significant differences between subtypes[78]. Abnormal fasting lipid profiles have also been documented in a study of pediatric patients with ASMD[78]. Electron beam tomography of the coronary arteries in ASMD type B patients revealed positive calcium scores in some of them, suggesting early atherosclerosis, with worsening scores in adulthood[3,78].

Electrocardiogram abnormalities, including sinus bradycardia, left ventricular hypertrophy, and conduction issues, have also been reported[3]. Mild valvular heart diseases, particularly mitral valve regurgitation, are common[3], while left ventricular hypertrophy, moderate to severe aortic regurgitation, and pulmonary hypertension have been identified in a few cases[45].

GROWTH AND SKELETAL DISEASE

Skeletal involvement is a common aspect of ASMD, with most patients experiencing one or more bone fractures throughout their lives[45]. Back and lower extremity pain has been reported in 60% of pediatric patients and 58% of adults[3]. Dual X-ray Absorptiometry scans revealed significant reductions in bone mineral content and bone mineral density at the lumbar spine, hip, and femoral neck[55].

During childhood, growth restriction is common, with affected children often exhibiting below-average height and weight, particularly during adolescence, alongside delayed bone age. However, most adults reach normal height, suggesting a period of catch-up growth during late adolescence or early adulthood[79].

MORTALITY RATE AND CAUSES

ASMD impacts substantially on patient health and may cause premature death. A recent study indicated a mortality rate 21.6 times higher than the general population due to high morbidity from liver and respiratory issues[80]. Survival rates and causes of death vary significantly among ASMD subtypes and patients with similar phenotypes[41].

In ASMD type A, death often results from progressive neurodegeneration and respiratory failure by age 3[3]. In contrast, chronic neurovisceral and visceral forms have more variable survival, with some patients reaching their fifth or sixth decade[37]. The most common causes of death include respiratory failure and liver disease[37,41], and splenectomy is associated with higher mortality due to disease exacerbation affecting the lungs and liver[37]. Patients who die from respiratory issues often experience multi-organ failure. Less frequent causes of death include bleeding, linked to splenomegaly, thrombocytopenia, and severe liver disease, which disrupt coagulation[81], as well as cardiac complications, particularly when combined with pre-existing cardiac comorbidities[41,78,82]. Cancer was noted as a cause of death in five adults, including liver cancer and multiple myeloma, though its association with ASMD remains uncertain, and cirrhosis may be considered an independent well-known risk factor for liver cancer[83]. The high mortality risk from experimental treatments like bone marrow or stem cell transplantation highlights the need for a thorough risk-benefit assessment[41].

FOLLOW-UP AND MONITORING OF PATIENTS

All chronic clinical neurologic and visceral manifestations should be closely monitored in ASMD patients. Clinical guidelines and consensus statements are available in the literature, providing precise information on the type and frequency of evaluations[10].

THE DIAGNOSIS OF ASMD - ASSETS AND CHALLENGES

As previously mentioned, diagnostic delays are a cause of major concern in the care of ASMD patients[3,45,84]. Diagnosis can be delayed by up to a decade, severely impacting patients and their families with prolonged uncertainty and deferred care. In 2024, Doerr et al[84] reported that the average time to ASMD diagnosis was 3 years, ranging from less than a month to 31 years and 3 months, with the overall diagnostic journey spanning 0–10 years from the onset of symptoms. Misdiagnoses were noted in rates ranging from 85% to 7% in quantitative and qualitative studies, respectively.

Disparities between different countries or areas emerged, possibly due to variable awareness of physicians in different countries, different organizations of healthcare, and variable accessibility to diagnostic tests, with patients from the United States receiving a correct diagnosis in fewer than 2 years, Latin America in 3 years and Europe in 4 years.

In most cases, clues to diagnosis fell into two categories: a build-up of symptomatic evidence (in about 75% of patients) or a sudden change or development in patient conditions (in 25% of patients).

For these reasons, efforts are urgently required to raise awareness among a broad range of specialists, including hepatologists, pulmonologists, hematologists, immunologists, neurologists, pediatricians, geneticists, and metabolic physicians, as they often are the first to identify organ-specific symptoms of ASMD[84]. Implementation of networks should be encouraged to facilitate the exchange of information between specialists and referral to expert centers (such as the MetabERN healthcare providers in the EU) (https://metab.ern-net.eu/). Furthermore, it would be advisable to integrate clinical signs and confirmatory analyses (biomarker testing, enzyme testing, genetic analysis) into diagnostic algorithms to optimize the diagnostic process and reduce the diagnostic journey.

CLINICAL SUSPICION AND DIAGNOSTIC ALGORITHMS

Diagnostic algorithms are of great assistance in the approach to ASMD patients. In general, the process begins with clinical suspicion based on the presence of key clinical features. However, given the considerable overlap of ASMD symptoms with those of other conditions, including other lysosomal storage disorders like Gaucher disease, Niemann-Pick type C, or LAL-deficiency, clinical evaluations in most cases are not sufficient to establish a precise diagnosis.

Routine biochemistry (blood cell count, liver function tests) may provide helpful information, but to confirm the diagnosis, it is necessary to perform enzymatic and genetic testing[84] (Figure 2).

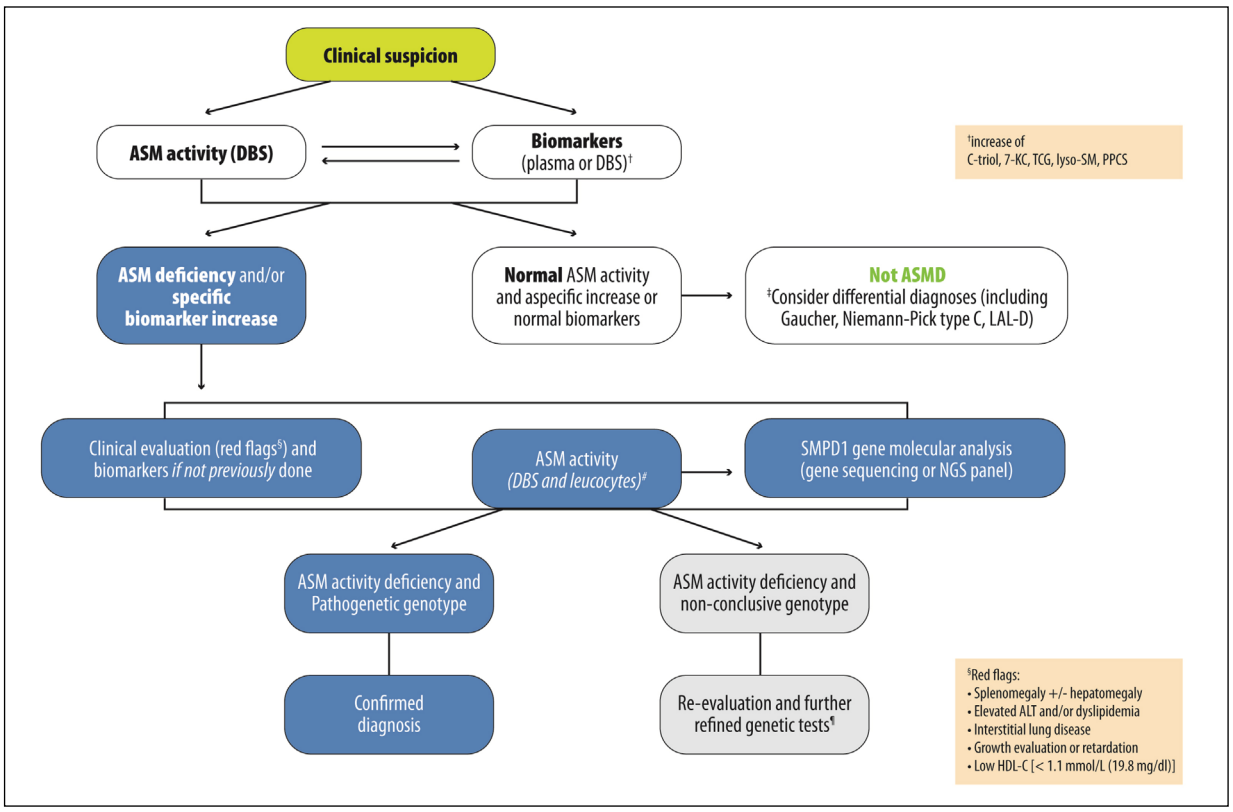

Figure 2. A proposed algorithm for the diagnosis of ASMD.
†Elevated levels of specific biomarkers, including 3β,5α,6β-cholestane-triol (C-triol), 7-ketocholesterol (7-KC), 3β,5α,6β-trihydroxy-cholanoyl-glycine (TCG), lysosphingomyelin (lyso-SM), and N-palmitoyl-O-phosphocholine-serine (PPCS) are indicative for ASMD. Other diseases, such as Niemann-Pick type C, may be considered, but different lyso-SM/PPCS ratios can help to differentiate the two conditions; acid lipase deficiency and cerebrotendinous xanthomatosis also show increased C-triol levels.
‡Due to overlapping manifestations, a differential diagnosis with other LSDs should be considered. Diagnostic work-ups for Gaucher disease, LAL-D and NPC should be regularly (simultaneously) performed.
§Clinical red flags may suggest the specific suspicion and guide the differential diagnosis. Red flags: splenomegaly ± hepatomegaly; elevated ALT and/or dyslipidemia; interstitial lung disease; growth deceleration or retardation; and low HDL-C [<1.1 mmol/L (19.8 mg/dl)].
#ASM activity in dried blood spots (DBS) should be confirmed with leukocyte testing or genetic analysis.
¶The use of MLPA or RNA analysis, with consideration of variants of uncertain significance (VUS) and segregation family studies, is recommended in case of non-conclusive genotype.

A screening algorithm was developed for adult and pediatric patients with splenomegaly and thrombocytopenia to assist clinicians in identifying and differentiating patients for further ASMD or Gaucher disease evaluation if certain red flags are present[85,86]. In the pediatric algorithm, invasive diagnostics, such as bone marrow aspiration or biopsy, are limited to cases where no red flags are identified, and other differential diagnoses need to be explored[86].

ENZYMATIC DIAGNOSIS

ASM activity can be measured in leukocytes, fibroblasts, or dried blood spots (DBS)[3,45]. The assay in DBS is convenient for the stability of dried samples and for the limited invasiveness of sampling. However, DBS has limitations related to pre-analytical conditions, such as sample handling and storage, and possible interference with concomitant conditions or procedures, such as anemia, leukopenia or recent transfusions[10]. Therefore, ASMD in a DBS sample should be further confirmed by enzyme assay in additional samples (leukocytes, fibroblasts) or by genetic analysis. Cultured skin fibroblasts, which have a higher yield in terms of ASM levels compared to leukocytes, are useful in ambiguous cases. The choice of substrate for ASM activity testing is crucial; a short-chain fatty acid sphingomyelin analog is preferred with tandem mass spectrometry (MS/MS) for its accuracy and sensitivity. MS/MS is more reliable than fluorometric assays[10]. Moreover, quality assessment studies have shown that the use of fluorogenic substrates often results in high false-negative rates, particularly in the presence of specific variants (such as the p.Q294K variant), which are associated with misleadingly high *in vitro* enzyme activity. Conversely, MS/MS assays are more accurate, provide better differentiation between unaffected and affected individuals[3], and can be used in multiplex assay conditions that are suitable for neonatal screenings.

BIOCHEMICAL MARKERS

The measurement of biomarkers in biological fluids or in DBS is often performed in association with the enzymatic assay for the diagnosis of several lysosomal storage diseases, including ASMD. Biomarkers are substances that indicate abnormalities in biological processes, often correlating with disease manifestations and outcomes. They are valuable tools not only for the diagnosis but also for monitoring disease course or the effects of therapies, such as ERT.

Biomarkers can either be directly linked to lysosomal dysfunction or reflect secondary effects on cell, tissue, or organ functions[87,88]. Previously used biomarkers in ASMD have proven unsatisfactory due to their low specificity. Although oxysterols, such as cholestane-3β,5α,6β-triol (C-triol) and 7-ketocholesterol (7KC), are elevated in ASMD[89,90], they show modest increases also in other LSD and neonatal cholestasis[91-93]. Similarly, the bile acid derivative N-3β,5α,6β-trihydroxycholanoyl-glycine (TCG) resulted elevated in both NPC and ASMD[94,95].

Chitotriosidase, a chitinase secreted by macrophages, is elevated in conditions involving macrophage activation, including LSDs like Gaucher disease. Serum levels reflect tissue infiltration by foam cells and correlate indirectly with substrate storage. However, its usefulness in ASMD is limited due to a lack of specificity. In addition, partial or complete enzyme deficiency may result from a common *CHIT1* gene mutation, present in 5% of the population[96].

Key biomarkers for ASMD, reflecting primary storage of SPM, include sphingosylphosphorylcholine (lyso-SM) and N-palmitoyl-O-phosphocholine-serine (lyso-SM509). Lyso-SM is the de-acetylated form of SPM, while lyso-SM509 is its carboxylated analog. Both are linked to sphingomyelin accumulation and can be measured in plasma, tissues, and DBS[92,93,97-102]. Elevated levels of lyso-SM and lyso-SM509, with lyso-SM509 being significantly higher than LysoSM, are reliable indicators of ASMD[102] and correlate with disease severity[102]. Although modestly elevated in NPC, they exhibit only a two-to threefold increase, lacking specificity for this condition[92,93,99,101,103]. MS/MS multiplex methods allow for the simultaneous measurement of these and other sphingolipid biomarkers, which allows the discrimination of ASMD from other lysosomal disorders and is also applicable in NBS [104,105].

A novel biomarker, SM 16:0, identified by Gaudioso et al[106], shows the highest accumulation and toxicity in ASM-KO neurons, where it causes lysosomal permeabilization and exocytosis with consequent oxidative stress and cell death. Thus, this marker correlates with brain damage and holds promise both as a therapeutic target and as a diagnostic tool.

GENETIC DIAGNOSIS

The diagnostic approach to ASMD should be completed by the molecular analysis of the *SMPD1* gene using direct Sanger sequencing (in cases with a high level of suspicion or in familial cases) or by next-generation sequencing (NGS) of lysosomal gene panels when patient phenotypes are less specific[10]. Genetic testing is also important for genetic counseling. If only a single pathogenic variant is found in patients with highly

evocative phenotypes, additional testing with multiplex ligation dependent probe amplification (MLPA) or whole genome sequencing (WGS) may be required to identify gene deletions or deep intronic mutations.

Recent studies indicate that the *SMPD1* gene is located in an imprinted region with preferential maternal expression, which may impact phenotypic expression based on allele inheritance. It has been hypothesized that heterozygous carriers of a maternal *SMPD1* mutation may show mild forms of ASMD[107].

As of 2022, over 346 *SMPD1* variants have been identified, with 295 classified as disease-associated in the HGMD Professional. These include missense, nonsense, frameshift, indels, and intronic variants, with few large alterations[108-110]. Genotype–phenotype correlations are difficult because most mutations are private and may also be influenced by epigenetic factors. In general, nonsense, frameshift, or large deletion mutations typically lead to severe neurovisceral phenotypes, while missense variants are mostly associated with non-neurological forms if some ASM activity remains. Notable exceptions include the p.W32X mutation, which leads to a non-neurological phenotype due to alternative transcription[111], and the p.R3AfsX76 mutation, linked to ASMD B in Chinese patients[112]. The most common variant, p.R610del, causes a non-neuronopathic phenotype and is prevalent in the Maghreb area, Spain and France[113]. The p.L304P, p.R498L and p.F333SfsX52 variants are common in Ashkenazi patients with the infantile neurovisceral phenotype[114-116].

NEWBORN SCREENING

The approach to the diagnosis of ASMD may change significantly in the future with the advent of newborn screening (NBS) programs for this disease. The availability of advanced technologies such as tandem mass spectrometry (MS/MS) and liquid chromatography-tandem mass spectrometry (LC–MS/MS) has dramatically enhanced screening capabilities for different classes of inborn errors of metabolism[117-119]. Some lysosomal storage disorders are emerging as excellent candidates for expanded NBS programs due to their progressive nature, the potential for early diagnosis and the availability of disease-modifying therapies. Using NBS evaluation algorithms to prioritize screening programs for inborn errors of metabolism[117,120], eight lysosomal disorders were identified, including ASMD, that scored above the selected threshold and were thus considered suitable for NBS.

A pilot NBS program for ASMD was implemented in Illinois (USA) in 2015, using MS/MS to measure ASM activity. From 2014 to 2023, 1,203,900 infants were screened, with 10 testing positive for ASMD. All positive cases were confirmed through biochemical and molecular testing, with no false positives or pseudo-deficiencies identified[121]. These results provided support for the inclusion of ASMD in NBS programs.

For an NBS program for ASMD to be implemented, several issues (similar to those faced in screening programs for other lysosomal storage disorders) must be addressed, including the need for accurate cut-off values (as ASM enzyme activity can vary widely among both the general population and affected newborns). In this respect, the use of specific biomarkers as a second-tier test may help improve specificity and accuracy. Additional issues, such as the availability of adequate resources and technologies, specific training for healthcare providers, provision of follow-up care and treatments, assessment of cost-effectiveness, and ethical and psychological concerns, are common to other lysosomal disorders.

CLINICAL AND BIOCHEMICAL MARKERS IN CLINICAL STUDIES

Surrogate biochemical markers may not reliably indicate disease progression or therapeutic efficacy, leading to challenges in identifying the best clinical endpoints for treatment trials. Measuring clinical responses in rare disease trials (typically 6–12 months) is difficult, often requiring longer evaluation periods to detect significant changes[122].

For ASMD, clinical trials have focused on improvements in pulmonary function and hepatosplenomegaly. Splenomegaly, a major feature in ASMD, correlates with disease severity and impacts quality of life, being associated with increased bleeding risk and liver disease[122]. In the olipudase alfa phase 2/3 trials, spleen volume reduction, measured by MRI, and improved splenomegaly-related scores (SRS) were primary endpoints[123]. Progressive lung disease is also significant, with diffusing capacity of the lung for carbon monoxide (DLCO) used as an innovative endpoint in the olipudase alfa trials. A reduction in DLCO correlates with disease severity and long-term outcomes[123]. Both DLCO and spleen volume have proven effective as endpoints for assessing disease progression and treatment response. Secondary endpoints, such as liver volume changes and improvements in fatigue and quality of life, remain unvalidated[122].

Liver fibrosis assessment, using noninvasive ultrasound-based transient elastography, is proposed as an important endpoint for managing ASMD. Current clinical trials are exploring MRI techniques to detect early lipid accumulation and fibrosis in the liver of ASMD patients (NCT05904366) and evaluating breath profiles for potential use as surrogate endpoints, particularly for patients with DLCO measurement difficulties (NCT05914727).

INNOVATIVE THERAPEUTIC STRATEGIES AND FUTURE PERSPECTIVES

For long, prior to the approval of ERT, supportive care was the only option available for ASMD patients. Supportive management of patients must be based on a multi-professional team to monitor and plan, when needed, therapeutic interventions to preserve or improve respiratory and cardiovascular functions, to promote growth and correct dyslipidemia with personalized diets, to prevent or control potential episodes of bleeding, to provide educational support and physical therapy[44].

Hematopoietic stem cell transplantation (HSCT) has been attempted in ASMD patients, with improvements in hepatosplenomegaly and blood counts but severe complications and limited efficacy on neurological symptoms[124-127].

More recently, research in ASM-KO mice suggested that early HSCT can achieve high levels of engraftment, although neurological benefits remain limited[128]. Other strategies, such as the direct intracranial injection of bone marrow-derived cells, have also been explored to provide a localized source of ASM in the central nervous system (CNS)[124]. Pre-symptomatic cord blood transplantation also resulted in limited benefits in neurovisceral ASMD[129].

ERT introduced a major advancement in the treatment of ASMD. ERT is based on the administration of recombinant human enzymes that are internalized by cells and delivered to lysosomes through the mannose or the mannose-6-phosphate receptor pathway[130].

Olipudase alfa is a recombinant human ASM (rhASM) that replaces the defective enzyme activity in lysosomes. Olipudase alfa was approved in 2022 for the long-term treatment of non-central nervous system symptoms of ASMD[131]. As of 2024, Olipudase alfa has received regulatory approval in Brazil, Japan, Europe and the USA, with pending approvals in other countries[10].

Four clinical studies were conducted before its approval. These included a single-center, open-label trial to identify the maximum tolerated dose (NCT00410566[132]) and a phase 1B study evaluating safety and tolerability at escalating doses (NCT01722526[133,134]). The efficacy of the therapy was primarily investigated in a phase II/III international, multicenter, randomized, double-blind, placebo-controlled trial (ASCEND, NCT02004691, EudraCT 2015-000371-26) in 36 adults with ASMD type B, randomized to receive olipudase alfa or placebo, with dose escalation up to 3 mg/kg[123].

A phase II international trial (ASCEND-Peds) assessed the safety and efficacy of olipudase alfa in 20 pediatric patients, showing good tolerance and significant improvements in disease markers[135].

Overall, the results of these studies showed an improvement in key disease manifestations that are known to persist or deteriorate over time with reductions in spleen and liver volumes, improved lung function, improved platelet counts and lipid profiles, reductions in disease biomarkers, and improved growth in children. A long-term follow-up showed sustained improvements in clinical outcomes in treated adults[136].

In both trials, the ERT was well tolerated; adverse events were generally moderate and resolved without sequelae. Anaphylaxis and other severe hypersensitivity reactions were rarely reported[137]. Access to appropriate medical support for managing these reactions, along with successful desensitization regimens, enabled the continuation of therapy. Anti-drug antibody (ADA) titers remained low, and no neutralizing antibodies were produced.

ERT with rhASM also impacted biochemical markers. A gradual reduction in LysoSM was observed, accompanied by a transient increase in ceramide release immediately after the infusion during the initial treatment phases.

Real-life studies suggest that olipudase alfa positively impacts the physical, emotional, and mental well-being of patients and their families, despite no improvement in neurological symptoms[138], including some patients with infantile neurovisceral ASMD who have received the therapy under compassionate use for visceral manifestations.

Although the results of the clinical trials and the first real-life experiences appear to be promising and offer new opportunities for patients, similar to other lysosomal diseases that are treatable with ERT, this approach remains associated with some limitations and unmet medical needs.

First, no clinical efficacy of ERT on CNS manifestations can be anticipated[139]. Recombinant enzymes are large molecules (Olipudase alfa has a molecular weight of approximately 75 kDa) that are not expected to cross the blood–brain barrier and reach therapeutic levels in the brain.

Another reason for concern was the transient increase in ceramide levels observed after ERT infusions. Ceramide has pro-inflammatory effects, stimulates cytokine release, and can thus be implicated in infusion-related adverse events, primarily characterized by temporary increases in transaminase levels, fever and acute reactions. These issues can be managed by gradually reaching the therapeutic dose over the first 16 weeks, following a dose-escalation scheme to a final target of 3 mg/kg/day. Also, there is a need to establish clear criteria for the initiation and assessment of therapy, especially for phenotypes at the extremes of the clinical spectrum. The collection and analysis of real-world data will be crucial to define future guidelines for starting, stopping, and monitoring treatment[140].

NOVEL THERAPEUTIC APPROACHES UNDER PRECLINICAL DEVELOPMENT

The development of innovative therapeutic approaches for ASMD is still limited to a few strategies, none of which has reached clinical translation.

To tackle the limitations due to rhASM inability to cross the blood-brain barrier (BBB) and to evaluate the potential of ERT for correcting CNS pathology, repeated intracerebroventricular injections of the recombinant enzyme were performed in the ASM-KO mice. A widespread distribution rhASM throughout the CNS was observed, with a significant reduction of lysosomal accumulation of sphingomyelin throughout the brain, the spinal cord and viscera and improvement of the disease phenotype[141]. These results may indicate that approaches based on brain-penetrant chimeric enzymes (that are under clinical development by systemic administration in other lysosomal storage disorders) may represent a feasible approach also for ASMD.

Synthetic apolipoprotein A-I mimetics, acting as lipid scavengers, have demonstrated efficacy in reducing lipid accumulation and improving liver function in mouse models[142]. Dietary interventions, such as choline-deficient diets, may reduce sphingomyelin production and accumulation; under experimental conditions in ASMD-KO mice, a choline-free diet proved to be safe and effectively reduced macrophage and microglial activation in the liver and brain, respectively. However, it did not significantly affect sphingolipid levels, nor did it prevent neurodegeneration, suggesting that this dietary approach may not be a viable option for managing neurovisceral ASMD patients[143].

Like many other metabolic conditions, gene therapy holds great promise also for the treatment of ASMD. Gene therapy is based on delivering the wild-type copy of the defective gene to patients through the use of various viral vectors[130,144]. The development of gene therapy approaches for the treatment of ASMD is still in an initial stage. *In vivo* approaches based on adeno-associated virus (AAV) serotype 9 encoding human ASM (AAV9-hASM) vectors have been tested preclinically in ASM-KO mice. The vector was administered by cerebello-medullary cistern injection, which resulted in widespread transgene expression in cerebrospinal fluid and different brains. An evaluation at two-months after administration showed that the treatment prevented motor and memory impairment, sphingomyelin accumulation, lysosomal enlargement, and neuronal death[145].

An *ex-vivo* approach in ASM-KO mice based on the use of bone marrow cells transduced with retroviral vectors encoding human ASM[146] demonstrated limited efficacy, comparable to bone marrow transplantation (BMT). Significant improvements were seen in organomegaly, although no improvement in brain pathology was observed.

CONCLUSIONS

In conclusion, ASMD has long been neglected. Increasing the awareness of physicians on ASMD will likely translate into earlier diagnoses and timely interventions.

ERT has introduced a major breakthrough in the treatment of this previously untreatable disease. Although the search for novel and more effective therapies is still in the initial phase, it is reasonable to expect that the coming years will offer new opportunities to patients.

Insights into the pathophysiology of the disease and secondary abnormalities elicited by substrate storage will likely help identify new therapeutic targets. It is possible to think that combinatory use of different therapeutic approaches will allow us to overcome the current limitations of ERT.

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