

Understanding Acid Sphingomyelinase Deficiency from a Clinical, Molecular, and Therapeutic Perspective

Swapnil Das¹, Fatiha Sultana Fiha¹, Irfan Hoque Tanjid¹,
Rohit Datta¹, Dip Mohajon¹ and Pritesh Ranjan Dash^{2*}

¹Department of Pharmacy, University of Science and Technology Chittagong,
(USTC), Chittagong, Bangladesh.

²Department of Pharmacy, ASA University Bangladesh, Shyamoli, Dhaka, Bangladesh.

*Corresponding author E-mail: pritesh.ju@gmail.com

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Acid sphingomyelinase deficiency (ASMD), also referred to as Niemann-Pick disease types A and B, is a rare lysosomal storage disorder. Mutations in the SMPD1 gene result in insufficient activity of the acid sphingomyelinase (ASM) enzyme, which causes acid sphingomyelinase deficiency (ASMD). This enzyme is necessary for the breakdown of sphingomyelin, a type of sphingolipid found in the membranes of animal cells, particularly in the outer leaflet of the plasma membrane. Without this enzyme, sphingomyelin cannot be broken down, leading to its accumulation in organs such as the liver, spleen, lungs and brain. Historically, acid sphingomyelinase deficiency (ASMD) has been classified as Niemann-Pick disease (NPD) types A and B. Type A is caused by severe deficiency in ASM leading to neurodegeneration and organ enlargement. This type typically results in death by the age of three. In contrast, type B results from partial ASM deficiency and patients typically survive but face various complications throughout their lives. Currently, treatment options for this disease are limited, although many therapeutic approaches are gradually developing. Early diagnosis and effective management can minimize the complications of this disease and increase life expectancy. So, this review aims to provide a comprehensive understanding of ASMD, including its epidemiology, pathogenesis, pathophysiology, clinical presentation and diagnostic approaches necessary for early detection.

Keywords: Acid Sphingomyelinase, Hepatosplenomegaly, Lysosomal storage disorder, Lipid accumulation, Neurodegeneration.

Acid sphingomyelinase deficiency (ASMD) is a lysosomal storage disorder (LSD) caused by impaired activity of the acid sphingomyelinase (ASM) enzyme and, as a result, cellular accumulation of sphingomyelin. It was characterized by extensive tissue infiltration caused by foam cells, storage of lipids, and development of similar symptoms of pulmonary dysfunction, hepatosplenomegaly, and neurodegeneration.¹The

first case ever recorded of the ASMD disease was discovered in 1914 by Albert Niemann in an infant. However, the distinction of this disease from that of Gaucher disease was drawn in 1927 by Ludwig Pick after studying cases of infants suffering from rapid neurodegenerative disorders.²Later, it came to be called Niemann-Pick disease, NPD. It results from mutations that occur in the SMPD1 gene, which is responsible for ASM encoding.

Lack of this enzyme causes lipid accumulation in body tissues, especially sphingomyelin, and is responsible for the phenotypes shown. There are some differences between ASMD A and B types. Thus, the outcomes and the fates of patients are different. ASMD type A is the most severe form of ASMD, because in this type, there is minimal to no ASM residual activity. Thus, this type is a fatal one. It shows symptoms at early infancy 2-4 months of age and little to no ASM residual activity, which causes severe central nervous system damage and quickly progressing systemic manifestation symptoms, primarily hepatosplenomegaly. The mortality is unavoidable and most often occurs in the first 3 years of life. ASMD B, by contrast, has an unusual age of onset, gradual progressive systemic expression of symptoms, and, overall, without neurological compromise. Hepatosplenomegaly is generally the presenting clinical feature, but eventually compromised pulmonary and liver function are also important.^{3,4} Because of the wide spectrum of the disease's severity, the lifespan of patients is highly variable, ranging from very early death to long burdened lives. In 1934, the lipid stored in this disorder was described as sphingomyelin, but not until 1966, when human-sphingomyelin-cleaving enzyme deficiency was reported, was a trial performed on an NPD patient. Characteristics of the subtypes showing the clinical spectrum of ASMD are described in Table 1.⁵

Although there are currently no approved medications for ASMD, ERT (Enzymatic Replacement Therapy) combined with a recombinant human ASM called olipudase alfa is being developed clinically to treat ASMD's non-neurologic symptoms.⁶ To improve patient quality of life and decrease morbidity and disease consequences, contemporary ASMD care aims to mitigate the burden of symptoms using therapies, interventions, and lifestyle changes. People with ASMD have often received medical care from metabolic disease experts. Nevertheless, a group approach to patient care would probably include primary care physicians and additional specialists (such as pediatricians, cardiologists, pulmonologists, hepatologists, and hematologists). Due to the liver's severe impairment in the chronic forms of ASMD, hepatologists or gastroenterologists may initially see children with chronic visceral and chronic neurovisceral

ASMD, while patients with the chronic visceral form cannot show symptoms until they arrive in late adulthood because of respiratory conditions. To make sure that doctors are knowledgeable of the regular evaluations needed to manage the multisystem consequences of ASMD, it is crucial that doctors participating in patient management consult and communicate with one another.⁵ In this review, we summarize the current knowledge on acid sphingomyelinase deficiency, including its epidemiology, pathogenesis, and pathophysiology, outlining its various disease types with their distinctive features. We discuss cellular changes in ASMD causing hepatic, pulmonary and cardiovascular diseases and their impact on the immune system. We further discuss the clinical presentation, diagnostic approaches necessary for early detection, and the available care strategies with the purpose of improving outcomes in patients. Finally, we address aspects of disease management, therapeutic developments, and factors affecting morbidity and mortality in ASMD.

Epidemiology of ASMD

ASMD affects both male and female genders, but the precise dominance is not known. Globally, about 4 to 6 babies out of every 1 million are born with ASMD and around 1 in every 250,000 people are affected. These numbers underestimate the actual impact of ASMD since there are many undiagnosed cases worldwide. So many people aren't even aware of this condition, and this lack of knowledge often causes severe issues.⁷ Additionally, the incidence of ASMD varies by ethnicity. The highest birth prevalence is found in the Ashkenazi Jewish population, with an estimated 2 to 3 cases per 100,000 births for NPD-A. Geographical differences have also been seen. In South America, the occurrence is about 1 in every 500,000 live births. Compared to Europe, the incidence is 1 per 250,000 live births.⁸ The age at which ASMD occurs depends on its subtype, and the disease occurs slightly more in females. Rare genetic disorders are known to be more common among the Arab population compared to other regions worldwide. Earlier studies recommended that the high consanguinity rate, reaching up to 60%, is a huge factor contributing to the relatively high occurrence of genetic disorders in the Arab world.⁹ There are only a few studies that have shown the incidence and prevalence of ASMD

in the Arab nations. However, they expressed a relatively higher chance of ASMD compared to other regions. Moammar et al.¹⁰ conducted a retrospective analysis of data from 165,130 live births in the Eastern region of Saudi Arabia for over 25 years. Eight cases of NPD type A were recorded, corresponding to an occurrence rate of 5 per 100,000 live births. The overall phenomenon of LSDs was reported as 44 per 100,000 live births. Another report from the same region time period from 1983 to 2016, reported a prevalence of NPD type A/B at 3.31 per 100,000 live births. In a 2021 systematic report of genetic disorders in Tunisia, the prevalence of ASMD type B was determined to be 1 per 200,000 live births. It is thus seen from the studies that the incidences of ASMD in the Arab countries are higher compared to the Western world. Understanding the demographic distribution or epidemiology of ASMD highlights the need to explore its underlying genetic and molecular mechanisms.¹¹ The need to investigate the underlying genetic and molecular mechanisms of ASMD is highlighted by knowledge of its prevalence and demographic distribution.

Pathogenesis of ASMD and Associated Genetic Variants

More than 720 different pathogenic variants of the SMPD1 gene associated with ASMD have been identified. These include frameshift, missense, nonsense mutations, and frame deletions. All these variations differ in geographical regions¹² and the genotype-phenotype correlation is distinguished for some variants.¹³ To elaborate, three identified variants in the SMPD1 gene (R496L, L302P, and fsP330) are actively present in Ashkenazi Jewish ancestry and express over 90% of the ASMD patients in this population. The three variants are associated with ASMD phenotype A. The SMPD1 variant (A359D) in Chilean patients was connected with ASMD phenotype B and ASMD phenotype A/B is related to p.W393G and p.Q294K genetic variations.¹⁴ These genetic variations in ASMD lead to biochemical abnormalities that drive the pathophysiological changes observed in patients.

Pathophysiology of ASMD

ASMD (Acid Sphingomyelinase Deficiency) is a rare disease where the fat accumulates in the lysosome and causes disruption in the functions of cells in many organs. The

actual process of this disease is not fully known, but it originates in lysosomes, which break down and recycle cellular substances. When lysosomes do not function properly, cellular processes are affected.^{15,16} This condition accelerates the buildup of other lipids, most prominently cholesterol, ceramide, sphingosine, Lys sphingomyelin, glycosphingolipids, and bis(monoacylglycerol) phosphate. The disease primarily starts with the accumulation of a fat called sphingomyelin in lysosomes but as the fats begin to shift to the cell membrane and other regions of the cell, they lead to many secondary issues. Some of them are:

- Broken cellular signaling in the membrane causes inflammation and cell death.
- Problems in the synthesis of energy due to mitochondrial malfunction.
- Restriction in nuclear transport.¹⁷

Lysosomes are present in many cells, except mature red blood cells. Thus, ASMD affects most cells in the body. Lysosome-dependent immune cells, like monocytes and macrophages are mostly affected. This disease affects organs like the liver and spleen, which contain a large number of fat-filled immune cells, and the lungs, where these cells accumulate in air sacs and surrounding tissues. Other affected organs include the heart, bones, lymphatic system, and blood-forming organs. In some cases, the disease affects the central nervous system (CNS) as fat deposits are present in glial cells and nerve cells (neurons).¹⁸ ASMD has been divided into multiple subtypes as a result of these pathophysiological changes showing up clinically in different ways.

Presentations and Subtypes

Type A

Type A is the severe condition of ASMD, also known as infantile neurovisceral ASMD. The activity of the ASM enzyme in NPD-A is so low that it can be considered as non-existent.⁶ Such conditions during the early stages of life include growth failure, dysphagia, muscle weakness, loss of neurons, spleen and liver enlargement and lung problems. However, there is no cardiac or musculoskeletal involvement. Depending on the intensity of the disease, the development of psychomotor may normally go on for a long time after birth, but only until a maximum of between 6 and 15 months, after which there is stagnation and then backward developmental progress.

Generally, drowning takes place within 3 years and is attributed to chest asphyxia induced by exposure.¹⁹

Type A/B

NPD A/B, also famous as chronic neurovisceral ASMD, is a type with slower neurological progression and longer survival.^{20,21} It is the mildest form of ASMD that originates in the childhood, characterized by disturbances in learning and psychiatric problems, disturbances in movements, peripheral nerve damage, and loss of coordination.²² Besides, it causes macular halo, diarrhea, abnormal liver function tests, portal hypertension, liver fibrosis and enlargement of the liver and spleen.¹⁹ Cardiac and pulmonary features reported are early-onset coronary artery disease, mixed dyslipidemia, cardiac valve disease, interstitial lung disease, abnormal pulmonary function tests, and radiological findings. Growth restriction, delayed bone maturation, reduced bone density, and bone and joint pain are common in this type.²³ Deaths may occur from respiratory and liver disease during both childhood and adult life.^{24,25}

Type B

NPD-B, also known as chronic visceral ASMD, can develop at any point from infancy to adulthood and is characterized by the slow progression of multisystem disease symptoms without neurological degeneration.^{26,27} NPD-B is linked to an average life expectancy, but complications such as bleeding, liver failure and respiratory failure can cause premature death.^{24,25} This type shows many symptoms in early childhood. Delayed puberty, fatigue, bone pain, osteopenia, thrombocytopenia and anemia are frequently observed symptoms in children.²³ Early in the course of the disease, mixed dyslipidemia is identified, and some individuals may even develop coronary artery disease. Mild to severe hepatic fibrosis is common in this type and the worsening of hepatic disease can cause premature death in some cases.^{28,29} Examining the cellular alterations that take place in impacted tissues is crucial to comprehending these clinical manifestations.

Cellular Alterations

Typically, this ASM enzyme plays a role in activity that maintains cell equilibrium through cleaving and resuming membranes because it acts upon its substrate, Sphingomyelin which is part of the cellular membrane. During degradation

processes, it further generates the chemical products phosphocholine and the necessary signaling lipids, Ceramides.²⁹ The deficiency of the ASM enzyme in ASMD patients causes the accumulation of sphingomyelin and hence the production of foam cells, which are lipid-laden cells that are often macrophages but can potentially impact other organ-specific cells. Indeed, the lungs, spleen (which in patients with ASMD may occasionally grow up to 10 times its normal size), bone marrow, lymph nodes, and liver all contain these foamy cells.³⁰ Rarely, the mucosal and submucosal layers of the small and large intestines may contain them. These fat-filled cells eventually stop working correctly and die, which leads to a variety of clinical signs.³¹ ASMD is characterized by progressive liver disease, which is caused by sphingomyelin accumulations in hepatocytes. Similarly, splenomegaly seen in many patients is a result of lipid-laden macrophages.

Hepatic Disease

ASMD is an attack on major organs, and the liver is one of them. Hepatomegaly represents the enlargement of the liver due to ASMD. Hepatomegaly, one of the most common features of ASMD, results from the buildup of sphingomyelin-filled macrophages (Kupffer cells) within the sinusoidal spaces of the liver. Such as macrophages, often called foam cells, together with the accumulation of sphingomyelin in lysosomes within hepatocytes, are responsible for liver dysfunction. For patients with the chronic visceral form of the disease, liver damage is a leading cause of death.^{24,25,32} According to a study that looked at the causes of mortality for 85 people with chronic ASMD, liver disease was as common among those who passed away as children and adults. This supports the idea that liver illness, at any age, was a major cause of patient mortality.²⁵ The risk of cirrhosis, portal hypertension, and variceal hemorrhage in adults with chronic ASMD is still not well understood. Nearly all adult patients with ASMD (n = 17) showed liver fibrosis of some degree, ranging from severe cirrhosis to early-stage fibrosis, according to a phase I clinical trial screening.³³ Therefore, every safety measure needs to be followed, and one should be aware of them so that the risks can be avoided.

Splenomegaly

The most common early clinical

Table 1. Clinical spectrum of acid sphingomyelinase deficiency (ASMD) subtypes

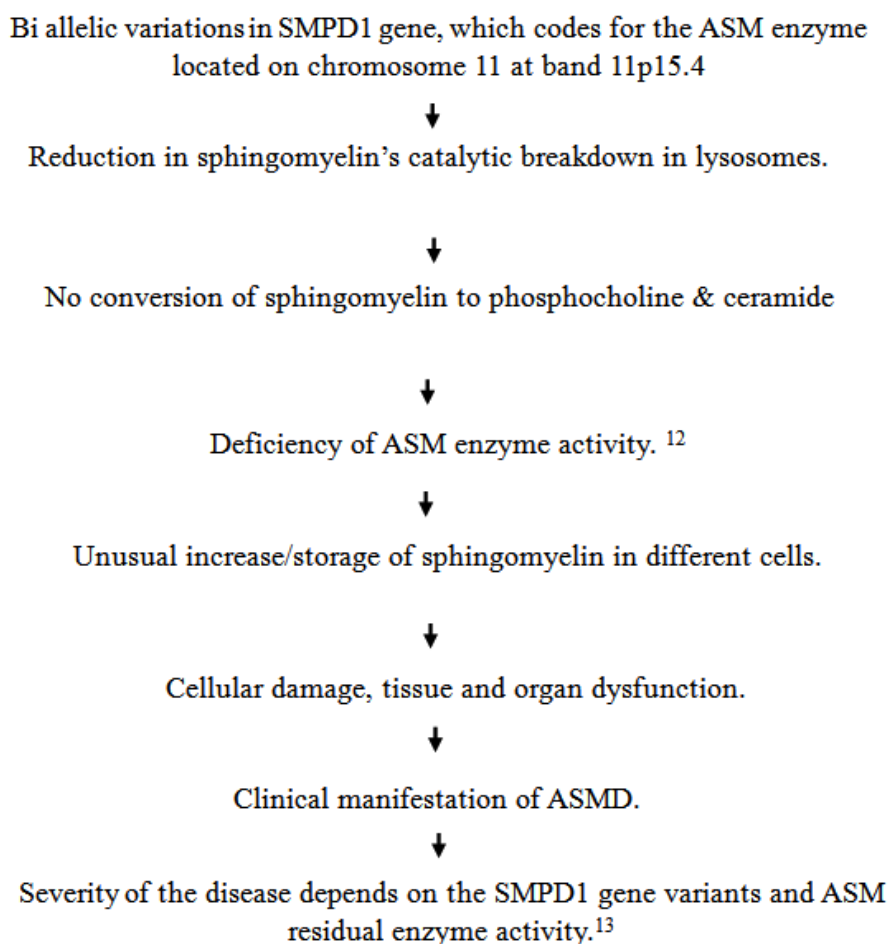
Features	Severe (Neurovisceral infantile, NPD A)	Intermediate (Chronic neurovisceral, NPD A/B or variant B)	Mild (Chronic visceral NPD B)
Typical onset	Symptoms show up early, usually in the first few months of life.	Usually starts in childhood.	Can begin in childhood, but sometimes not until adulthood.
Disease course	The disease moves fast. Kids lose brain function quickly and get sicker over time.	Progresses at a moderate pace. Neurological symptoms develop, but survival is longer than in infants.	The disease creeps along slowly. Most problems are with organs, not the brain.
Key early features	Big liver and spleen often by 2–4 months, weak muscle tone, trouble feeding, delayed development by 6–12 months, eye problems.	Nerve problems come on later, but kids live longer than with the infantile form.	Symptoms vary, but organs get involved—people don't usually lose brain function.
Neurological involvement	Severe, ongoing brain degeneration.	Symptoms vary: some have mild muscle weakness, less reflexes, problems with thinking or movement.	Hardly any or none at all.
Systemic manifestation	Kids don't gain weight well, often get chest infections, and can have trouble with food going down the wrong way.	Many body systems get involved, like in the mild form.	Big liver and spleen, abnormal blood fats, slow growth or puberty, bone problems.
Major complications	Breathing failure, infections, and brain degeneration.	Nerve and organ problems keep getting worse.	Low platelets, lung disease, liver scarring or cirrhosis.
Prognosis/life expectancy	Most children don't live past age 3.	Life span varies—a person can reach their teens or even adulthood.	Life expectancy is often normal, unless organ problems get serious.

sign of chronic ASMD is organ enlargement (organomegaly). It happens in early childhood but in milder cases, splenomegaly (enlargement of the spleen) may not be noticeable.³² Upon study, almost every patient suffering from chronic ASMD experienced splenomegaly.^{25,26,34} Splenomegaly is caused by the lipid-filled macrophages. However, a more rapid increase in spleen size should prompt consideration of portal hypertension as a contributing factor. The enlargement of the spleen can become severe, with its volume exceeding 20 times the normal size. This can lead to hypersplenism, increasing the risks of bleeding and splenic rupture, particularly when accompanied by a decline in platelet counts.³⁵

Pulmonary Disease

The pulmonary involvement is the most important one amongst the multisystem manifestations in sphingomyelin storage disorder.³⁶ Radiographic evidence of spreading lung disease has been recorded in more than 90% of patients suffering from chronic visceral ASMD. According to a pathophysiological process, lipid-laden macrophages penetrate the pleura, bronchial walls, and alveolar septa in pulmonary illness, resulting in increasing lung volume restriction and impaired gas exchange.

Furthermore, as demonstrated by the ASM-deficient mice model, an inflammatory response has been observed that promotes the recruitment



Flowchart 1. Pathogenesis of Acid Sphingomyelinase Deficiency Syndrome

of macrophages to the tissues.³⁵ There have been reports of isolated lung involvement in certain adult ASMD patients without organomegaly.³⁷

Assessments have been conducted and are usually carried out yearly or based on symptoms, considering their severity, through pulmonary function studies, including mainly lung diffusing capacity, oxygen saturation, exercise tolerance as part of pulmonary function tests (using the modified MRC dyspnea scale) and a six-minute walk, chest X-ray even when patients do not frankly present symptoms; classically show a pattern of reticulonodular infiltration.³⁸ Of note, imaging evidence of lung involvement correlates poorly with the severity of pulmonary impairment assessed by pulmonary function tests. Imaging for disease progression, possible with periodic chest X-ray or low-radiation high-resolution CT (HRCT) scanning every 2-4 years, allows for the timely detection of early changes and thus intervention.¹⁷

Cardiovascular Disease

Cardiac impairment is an ordinary sign observed in the patients with severe ASMD. It can also result from pulmonary disease. Overall, this problem is observed at an early age, and children are at high risk. Thus, they should be monitored and treated well. Cardiac valve abnormalities³⁴ are commonly encountered, varying from trivial alterations with little or no clinical impact to major diseases such as mitral regurgitation and aortic stenosis, both of which have been listed in children and adults. Serial electrocardiograms annually and echocardiograms every 2–4 years can

track valvular defects. Cardiac dysfunction, like coronary artery stenosis due to medial and intimal smooth muscle cell hypertrophy—presumably secondary to lysosomes containing sphingomyelin rather than pulmonary disease—has occurred in adults with longstanding ASMD.³⁹ A baseline coronary artery study by HRCT or cardiac CT for coronary mineralization scoring at 18 years of age, and then every 2–4 years. These studies should be synchronized with pulmonary evaluations. Standard management for valve insufficiency is pharmacological treatment and/or surgical correction, which could be in the form of valve repair or valve replacement, depending on the severity of the lesion. In instances of cardiovascular diseases, interventions could include stenting or CABG, where necessary. Any surgery needs to be weighed against all potential risks that may include bleeding complications or other contraindications.⁵

Neurological and Ophthalmological Findings

According to McGovern et al.³⁴ all patients with NPD-B had usual mental growth, synchronization, muscle power, sensation, deep tendon reflexes, and cranial nerve function. Peripheral neuropathy was observed in 11% of cases, cherry-red spots were present in 25%, and cognitive impairment was present in 8.4%. In another statement by McGovern et al.²⁴ neurological diseases, including sensory dyspraxia, learning disabilities, petit mal seizures, and ataxia, were documented in 12.6% of NPD-B patients. Cherry-red spots were found in one out of four NPD-A patients and one out of 21 NPD-B patients

Table 2. Functional effects of acid sphingomyelinase (ASM) on Different Cell Types.⁵⁶

Cell Type	Effects of ASM
Macrophages	ASM ramps up cytokine production and drives inflammatory signals. It helps phagosomes fuse with lysosomes and keeps apoptosis in check.
NK Cells	Affects how these cells work through CD161. causes the signaling pathways of NK cells to become active and include in NK cell apoptosis.
B Cells	B cell activation is facilitated by medications that cluster CD40. involved in the restoration of damaged plasma membranes. Vital to autophagic activity.
CD4 ⁺ T Cells	Engaged in activation controlled by TCRs. Engaged in the polarization of Th1, Th2, and Th17 subtypes. Serves as a Treg negative moderator.
CD8 ⁺ T Cells	ASM keeps the cell membrane flexible, making sure cytotoxic granules get released smoothly so these cells can do their job and kill targets.
iNKT Cells	Engaged in the activation and growth of iNKT cells. Sphingomyelin, an ASM substrate, reduces iNKT activation by blocking CD1d access to antigenic lipids.

in the study done by Hollak *et al.* Additionally, they discovered that extreme neurological problems resulted in early death in 4 out of 5 patients suffering from NPD-A. Among patients affected with NPD-B, 4 out of 21 had neurological complications, such as intellectual disability, Parkinson's disease, facial nerve paralysis, multiple sclerosis, and delayed motor skill development.²⁶ It was reported that individuals with NPD-A/B had significantly more neurologic and ocular involvement than patients with NPD-B (68.8% vs. 33.3%; $p = 0.032$ and 55.6% vs. 15.7%; $p > 0.0001$, correspondingly). Additionally, neurological symptoms were more severe in patients who were 18 years of age or younger at the time of death or liver transplantation ($p = 0.048$).²⁵ ASMD affects different immune cell populations and affects immune function in addition to organ-specific pathology.

Acid Sphingomyelinase's role in the immune system

Receptor binding and signaling are necessary to activate immune cells and then these activated cells identify pathogens. For the activation of the receptor, membrane platforms rich in ceramide are essential. Acid sphingomyelinase enzyme breaks down a substance called sphingomyelin and helps to create these ceramide-rich areas in the membrane. These regions bring

the receptors together by clustering them in the cell membrane. This makes it easier for the receptors to activate properly and enables strong signal transmission inside the cell.⁴⁰

Under a normal physiological state, ASM resides in the lysosomes. Though, under strain, under strain-for example, by the presence of pathogens and cytokines-this enzyme is released and acts on the outer membrane. It hydrolyzes the sphingomyelin present in the outer leaflet of the membrane and, after being converted to ceramide, it leads to the reorganization of standard membrane rafts into larger structures.^{41,42} Then in these larger structures the downstream signaling through the activity of ceramide takes place. Besides forming ceramide-enriched platforms ASM precisely controls the function of Natural Killer T cells.⁴³ The regulation of iNKT cell activity by ASM was shown to be due to the breakdown of sphingomyelin, which has recently been identified as an inhibitor of iNKT cell activation. In this respect, this section summarizes the current concept of ASM expression in several types of immune cells. Major actions of ASM on these cells are outlined in Table 1.⁴⁴ For a conception of the multiple roles of ASM outside the immunological arena, the reader is referred to three recent review articles by Henry *et al.* (2013), Park *et al.* (2020), and Perrotta *et al.* (2015). Macrophages impact different immune cell populations and

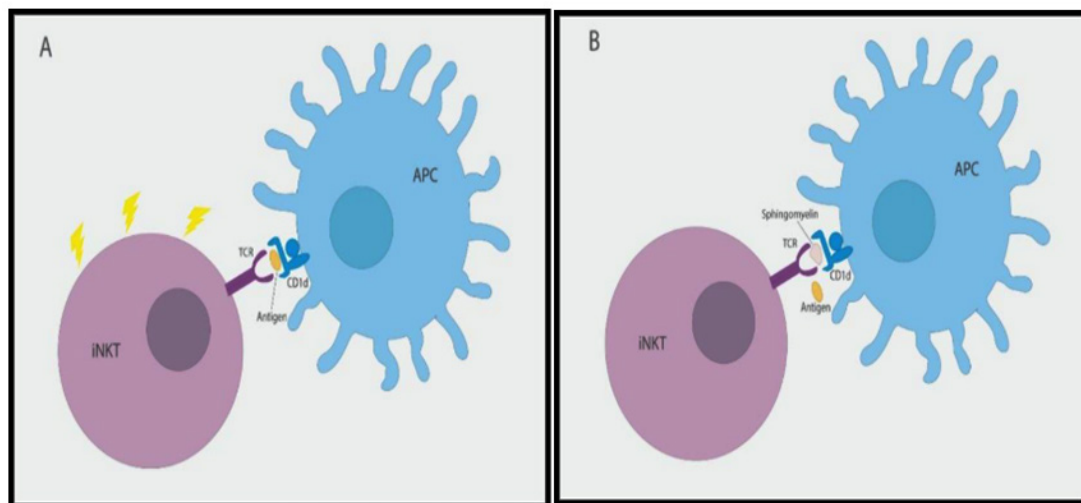


Fig. 1. Effect of sphingomyelin on CD1d-mediated iNKT cell activation.

(A) In the absence of sphingomyelin, lipid antigens access CD1d on antigen-presenting cells, bind to the iNKT cell TCR, and trigger activation. (B) In ASM deficiency, excess sphingomyelin occupies CD1d, blocking lipid antigen binding and preventing iNKT cell activation, contributing to ASMD-related immune and clinical features.

are essential for lipid accumulation and immune function.

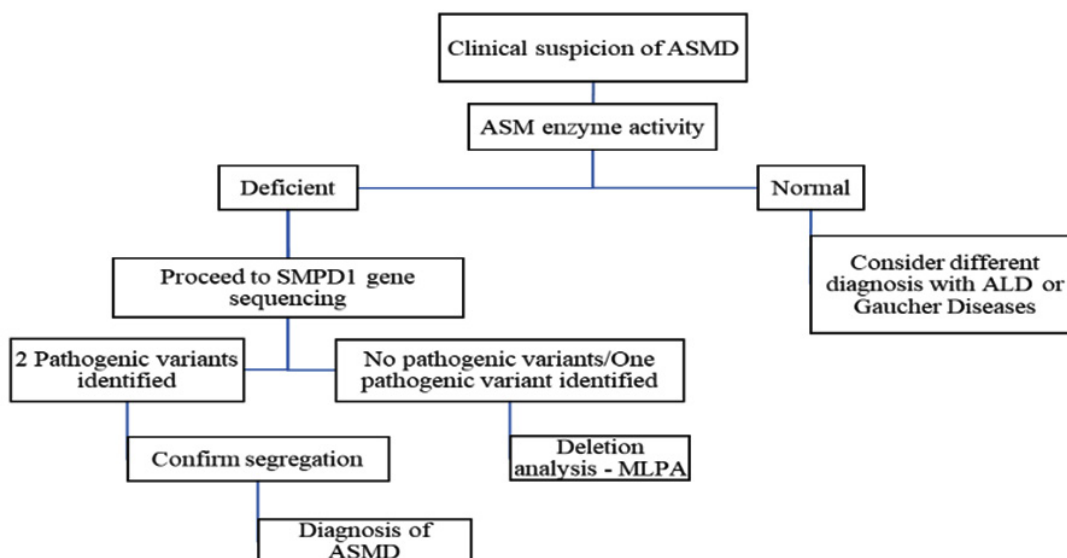
Macrophages

ASMD is directly linked with the dysfunction of macrophages because these cells are one of the main targets for this disorder.^{45,46} Macrophages of ASM KO mice show improper endocytosis of the ASM enzyme by M-6-P receptors.⁴⁵ ASM is also involved in the induction or enhancement of inflammatory responses. One of the most important examples among them is the role of ASM to increase the pro-inflammatory cytokine IL-6 upon treatment with LPS and palmitic acid.⁴⁷ All these findings were verified by the administration of SMA-7, an ASM inhibitor, and this resulted in a remarkable reduction in ceramide formation and the release of pro-inflammatory mediators. ASMD is also crucial in the fusion of late phagosomes with lysosomes, with the facilitation of efficient delivery of lysosomal antibacterial agents and of effective cellular defense mechanisms.⁴⁸ Indeed, this explains why ASM KO mice are more susceptible to infection by intracellular pathogens such as *Leishmania donovani*⁴⁹ and *Listeria monocytogenes*⁴⁹. By the generation of ceramide, ASM has also been associated with macrophage apoptosis induction. This was evidenced, for example, where oxidized low-density lipoproteins

(LDL) induced macrophage apoptosis^{50,51} and in macrophage apoptosis induced by *Pseudomonas aeruginosa*.⁵² Like most pathogens, *Pseudomonas aeruginosa* induces macrophage killing. *P. aeruginosa*-induced alveolar macrophage cell death was controlled by a redox-dependent signaling cascade in which ASM was a pivotal player by generating ceramide-rich membrane platforms. These platforms are required for *P. aeruginosa* to induce NADPH oxidase activation to produce ROS. The ROS in turn activates ASM and ceramide-enriched platform formation that causes cell death via the JNK-dependent pathway.⁵² Activated macrophages secrete proteins in ASMD plasma, like chitotriosidase, that may also serve as critical clinical biomarkers.⁵³ Chitotriosidase levels are high in ASMD but decrease sharply with treatment.⁵⁴

NK Cells

NK cells are an integral part of immunity. Thus, ASM interferes with NK cell functions through CD161. ASM may work by interacting with the intracellular tail of the CD161 molecule when NK cells are activated. In fact, research showing that cross-linking CD161 with anti-CD161 antibodies caused the recruitment and activation of ASM, resulting in ceramide, validated this connection. PKB/Akt and Rsk1/MAPKAP kinase 1 are two NK cell signaling pathways that



Flowchart 2. Clinical Overview and Diagnosis of Acid Sphingomyelinase Deficiency Syndrome

are activated by ceramide, a second messenger. Inhibition of ASM by imipramine blocks these pathways and disrupts the co-stimulatory function of CD161, impairing cell proliferation and co-stimulation of IFN- α .⁵⁵

ASM appears to be involved in NK-organized cell death in addition to its function

in macrophage apoptosis. Ceramide production in a human NK cell line is increased by IL-2 deprivation, which is ASM-dependent and causes apoptosis.⁵⁷ It is one that is distinguished by the breakdown of the X-linked inhibitor of apoptosis protein through ceramide-mediated activation of cytosolic cathepsin B (CTSB), which triggers

Table 3. Laboratory diagnostic workflow for acid sphingomyelinase deficiency (ASMD)

Step	Key Purpose	Main Action
Clinical Suspicion	Identify patients requiring evaluation.	Assess symptoms and clinical features suggestive of ASMD
Biomarkers Assessment	Support preliminary diagnosis	Measure disease-related biomarkers (e.g., NPS and other relevant markers)
Enzyme Activity Testing	Confirm biochemical deficiency	Measure acid sphingomyelinase (ASM) activity
Molecular Testing	Identify genetic cause	Perform gene analysis to detect pathogenic variants or variants of uncertain significance (VUS)
Variant Interpretation	Establish diagnostic validity	Confirm biallelic pathogenic variants consistent with disease
Diagnostic Confirmation	Finalize diagnosis	Integrate clinical, biochemical, and genetic findings
Genetic Counseling	Guide patient management	Provide counseling and family risk assessment

This table organizes the steps and actions related to diagnosing and confirming ASMD based on the provided content.

Table 4. Guideline-recommended teamwork for patients with acid sphingomyelinase deficiency (ASMD)¹⁷

Discipline	Primary Role in ASMD Management	Recommended Involvement
Primary healthcare provider	Coordinates overall care, monitors general health and facilitates specialist referral.	All Patients.
Metabolic Specialist	Confirms diagnosis, oversees disease monitoring and guides treatment strategy.	All Patients.
Neurologist	Evaluates and manages neurological involvement.	All Patients.
Hepatologist	Monitors liver function and manages hepatic complications.	As clinically indicated.
Hematologist	Assesses hematologic abnormalities and bleeding risk.	As clinically indicated.
Pulmonologist	Evaluates respiratory function and manages pulmonary disease.	As clinically indicated.
Genetic counsellor	Provides family risk assessment, inheritance counseling and reproductive guidance.	All patients.
Lipidologist/Cardiologist	Manages dyslipidemia and cardiovascular risk.	As clinically indicated.
Psychology or psychiatry specialist	Addresses emotional, behavioral and mental health needs.	As clinically indicated.
Speech and Communicationspecialist	Evaluates swallowing and communication difficulties; provides supportive therapy.	As clinically indicated.

Table 5. Recommended Clinical Monitoring and Assessments for patients with ASMD

Assessment Domain	Clinical Purpose	Frequency	Applicability
Clinical history Physical check-up	Determine the disease's natural history. At least once a year, record growth parameters.	At diagnosis and routine follow up Upon diagnosis, and then at 6–12-month intervals or during each visit.	All patients As clinically indicated.
Nutritional assessment	Assessment of nutritional status.	Initially upon diagnosis, followed by assessment at each clinical visit.	All Patients.
Respiratory assessment	Evaluate recurring chest infections.	Following diagnosis, you should conduct assessments at each follow-up appointment.	All Patients.
Musculoskeletal assessment	Check for discomfort in the extremities and/or fractures.	Every appointment after the diagnosis.	All Patients.
Neurological assessment	Assess neurological function carefully.	At diagnosis and as clinically indicated.	As clinically indicated.
Laboratory testing	Serum tests including albumin, coagulation matrices, and liver enzyme plus transaminases (ALT and AST) help analyze the liver.	Initially at diagnosis, with subsequent assessments conducted at least yearly.	As clinically indicated.
Diagnostic imaging	Lipid profile measurements. When necessary, radiologic measurements of the size of the liver and spleen.	Initially at diagnosis, then repeated as needed.	As clinically indicated.
Swallowing and feeding assessment	Identify dysphagia and aspiration risk.	Baseline and periodic reassessment based on symptoms.	As clinically indicated.
Developmental or cognitive assessment	Monitoring educational requirements and developmental progress through developmental assessment.	Performed after the diagnosis and then at each clinical visit.	As clinically indicated.
Neuropsychiatric evaluation	Record psychiatric symptoms and track treatment outcomes.	Initially at diagnosis, then repeated every 6 to 12 months as needed.	As clinically indicated.
Family support and assistance	At every visit, determine the resources and support needs of the family.	Every appointment after the diagnosis.	As clinically indicated.

caspase-mediated apoptosis.⁵⁸ IL-2, however, triggers NK cell survival through the inhibition of ASM, increasing glucosyl ceramide synthase activity and hence sphingomyelin and ceramide concentrations.⁵⁷

B Cells

One of the two major branches of adaptive immunity is made up of B cells. They oversee immunity mediated by antibodies. The cells can process antigens and present them to other immune cells since they can also deliver antigens. ASM, a crucial component needed for CD40 clustering, has an impact on antigen-presenting cells.⁵⁹ Upon ligation of CD40, ASM moves to the exofacial leaflet of the plasma membrane and secretes ceramide that in turn induces clustering of CD40. In addition, ASM has also been shown to participate in Ca²⁺-dependent repair of plasma membrane damage in B cells. Indeed, studies have shown that inhibition or downregulation of ASM leads to defective membrane repair, whereas administration of extracellular sphingomyelinase restores and even stimulates this healing.⁶⁰ B cells in a cellular model of ASMD B have defects in autophagy, mitochondrial clearance, and lipophagy. In a B lymphocyte cell line derived from a patient with ASMD B, the authors saw the occurrence of mitochondrial fragments in partially degraded structures and an atypical autophagic pattern with an extremely enhanced level of autophagic vacuoles, which was interpreted to be an autophagic stress marker.⁶¹ The outcome of such cell defects is also increased peroxidized lipid droplet content and higher cellular ROS levels through the initial and terminal stages of compromised autophagy. Canonico *et al* therefore went on to explore the effect that rapamycin, an inducible agent causing autophagy, would exert on such cells.⁶⁰ Indeed, they succeeded in showing within this paper that rapamycin suppressed mitochondrial and intracellular ROS, mitophagy vesicle formation, hence reducing lipid droplet accumulation and improving the viability of these cells. These findings prompted the authors to propose a therapeutic use of rapamycin in LSDs, including ASMD B, by at least partial restoration of the autophagic imbalance.⁶¹

CD4⁺ T cells

CD4⁺ T cells are a subpopulation of lymphocytes that secrete particular cytokines to

regulate the immune response. They have the capacity to differentiate into several different effector subtypes, each with distinct functions. These include Th1, Th2, Th17, and Treg cells, among others influenced by ASM activity.⁶² CD4⁺ T cells participate in various regulatory functions in the course of immune response regulation: these include the activation of various cells, such as B lymphocytes, cytotoxic T cells, and non-immune cells; inhibition of immune responses mainly by a subpopulation of T-regulatory (Treg) cells. Their maintenance and function depend on CD28 signaling, which has also been found to activate the ASM system.⁶³ Specifically, how ASM directly impacts CD4⁺ T-cell function remains undetermined. Very recently, new research has investigated such interactions *in vivo* and looked into their consequences.

It binds to intracellular domains of CD3 and CD28, and this binding regulates the signaling of the receptors. The impacts are seen in naïve and memory CD4⁺ T cells. Further, ASM inhibition was also found to impair polarization of CD4⁺ T cells to Th1, Th2, and Th17 subsets, respectively, as evidenced by defective production of IFN- γ , IL-4, and IL-17.⁶⁴ This was also supported by the same observation on ASM's function in augmenting T-cell activation using a mouse model overproducing ASM exclusively in T cells. In these mice, forced expression of ASM in T cells facilitated naïve T-cell differentiation into IFN- γ -producing Th1 cells, further supporting the role of ASM in T-cell activation and polarization.⁶⁵ Recent research has investigated the involvement of ASM in the development of asthma in ASM knockout mice. These mice had a higher number of CD4⁺ T cells in the bronchoalveolar fluid, but lower production of the Th2 cytokine IL-4. This was expected, as in an ovalbumin-induced asthma model, ASM knockout mice were resistant to airway hyperresponsiveness because of a decreased Th2 response.⁶⁶ This protective effect in asthma may be a result of impaired secretory pathway function in ASM-deficient mice. Lack of asm activity in enteric pathogen *Citrobacter rodentium*-infected mice leads to augmented infection. pathology of colitis with high Th1 and Th17 cell levels in the intestinal lamina propria.⁶⁷

ASM KO mice have a significantly higher

regularity of splenic Tregs.⁶⁸ ASM acts as a negative regulator of both the natural and induced Tregs. Similarly, *in vivo* ASM inhibition has been linked to a lower absolute number of conventional CD4⁺ T cells in the study, suggesting that ASM has further effects on CD4⁺ T-cell populations.⁶³ In ASM-deficient mice, effector memory CD4⁺ T cells show a loss of partial resistance to glucocorticoid-induced cell death. This is due to decreased IL-2 production by CD4⁺ T cells. However, this effect is reversed by restoring IL-2 levels, which reiterates the importance of IL-2 in the survival of CD4⁺ T cells during glucocorticoid treatment.⁶⁹

CD8⁺ T Cells

Naive antigen-specific CD8⁺ T cells become cytotoxic T lymphocytes upon antigen recognition. CTLs contain lytic granules whose contents are released upon TCR engagement of the appropriate antigen on APCs. The granules contain granzyme A and B and perforin that form pores in the target cell membrane so that granzymes may penetrate the cytoplasm and induce programmed cell death by activating caspases.

ASM plays a role in CTL activation by facilitating granule release. In ASM-deficient mice, cytotoxic granule release is delayed, leading to delayed lymphocytic choriomeningitis virus clearance.^{70,71} However, as compared to wild-type mice, the mRNA, protein, and enzymatic processes of granzyme A, granzyme B, and perforin remain unchanged. Both mouse types exhibit normal CD8⁺ T cell growth and antigen-specific activation. Indeed, in ASM-deficient mice, larger granzyme-positive granule clusters accumulate closer to the immunological synapse. In the absence of ASM, vesicle size shrinks only 44% following fusion with the plasma membrane, resulting in poorly released cytotoxic molecules. These findings were further supported by the pharmacological inhibition of ASM activity in CTLs.⁷¹ These findings emphasize the role of ASM in the release of cytolytic granules from CTLs and suggest the possible application of ASM inhibitors in the therapy of immunopathological conditions mediated by excessive cytolytic activities. Indeed, ASM inhibition was clinically explored for the therapeutic benefits in patients suffering from cystic fibrosis against infections of the lung by bacteria.⁷²

iNKT Cells

iNKT cells are T cells responding to lipids by a limited repertoire of TCR, which is specific to the MHC class-I-like molecule CD1d. iNKT cell activity is controlled by non-self and self-lipid ligands denoted by CD1d. iNKT cells are also in charge of tumor growth regulation and infection.⁷³ Although there is a balance between antigenic lipids and non-antigenic lipids that are involved in CD1d in the regulation of iNKT cell activation, little is known about the functional applicability of such non-antigenic lipids that can potentially suppress the activation of the CD1d-restricted NKT cells.^{74,75} ASM KO mice and cells from patients without ASM were used in the study. Mouse deficiency of ASM decreased CD1d-restricted presentation of both endogenous and exogenous lipid antigens to the iNKT. This dysfunction hampered the development of iNKT in the thymus further leading to low levels both in the thymus and systemically. A schematic outline for such a suggested mechanism is given in Figure 1. Indeed, such alterations were improved in young ASM KO mice by the ASM replacement therapy.⁴³ The effectiveness of ASM in ASM KO mice certainly instills faith in the therapeutic potential of ASM therapy for ASMD patients, particularly in the case of pulmonary infections. Lung infections are the most common secondary symptoms of the disease, and iNKT cells play an important role in antimicrobial immunity against the common respiratory pathogens such as *Pneumococcus* and *Pseudomonas*.⁷⁶

Clinical Overview and Diagnosis

Clinical signs are the main clues that point towards the presence of ASMD. Niemann-Pick C, Gaucher disease, acid lipase insufficiency, and other LSDs associated with distinctive hepatosplenomegaly can also exhibit these signs. In this regard, the diagnosis of ASMD requires insufficient ASM enzymatic activity which can be determined by using detached leukocytes, dried blood spots, or cultured skin fibroblasts.⁷⁷ A genetic test for the SMPD1 gene confirms the ASMD diagnosis and enables the patient to get genetic counseling after the diagnosis has been confirmed.⁷⁸

Diagnostic Approaches

Enzyme activity testing in ASMD

If there is any doubt of ASMD, the first thing that should be done is an enzyme assay

for ASM function and then the gene sequencing after confirming the biochemical diagnosis.⁷⁷ To distinguish ASMD from Gaucher disease, glucocerebrosidase activity should be measured at the same time.⁷⁹ The diagnosis of this disease should be confirmed by explaining reduced enzyme activity below the standard cut-off range, while accounting for the many distinct genetic variants of uncertain significance.⁸⁰ Other supportive clinical and laboratory features include lipid-laden foam cells and mixed dyslipidemia, which are highly suggestive of ASMD but do not replace the confirmation by enzyme testing. A molecular test for known pathogenic or familial mutations can confirm the diagnosis in case there is a strong suspicion of ASMD based on clinical findings. However, in cases where molecular studies reveal variants of uncertain significance, confirmation needs to be made through an enzyme assay.

Whole blood is usually required for laboratories that sample from all over the world, so that the same sample can be used for second-tier testing as well. DBS testing has limits, including the impact of anemia and recent transfusions on the results, although it can be utilized for particularly stable DBS.⁸¹ Due to requirements for radiochemical licenses, MS/MS is the preferred procedure for analyzing ASM activity over fluorescence-based assays and radio-labeled native sphingomyelin substrate because of its higher extended measurement range with better accuracy measurement of enzyme activity at the lowest detectable levels.⁸² Treatment plans targeted at lowering morbidity and mortality in ASMD patients are informed by an accurate diagnosis.

General Laboratory Tests

Blood Counts: The ASMD patients more often than not show mild thrombocytopenia which is already suggested by routine blood tests and anemia along with leucopenia or neutropenia may be present.

Lipid profile: People with ASMD have highly aberrant lipid profiles. The majority of the anomalies involve decreased HDL cholesterol and increased triglyceride and total cholesterol levels.⁸³

Imaging: The painting of the liver and enlargement of the spleen are usually detected on simple radiography or during physical examination. However, to assess the size accurately an echogenicity ultrasound is better. CT scans and

MRI are able to provide more confidence for these assessments. Interstitial lung disease may also be suggested by the images taken by chest X-rays or CT images.⁸⁴

Treatment and Management of ASMD

There is still no proper treatment available for ASMD. But currently, enzyme replacement therapy (ERT) using human recombinant acid sphingomyelinase olipudase alfa is in clinical development for the treatment of non-neurological ASMD manifestations. There are two clinical trials are being conducted and they are in phase 2 (NCT02004704) and 2/3 (NCT02004691).⁸⁵ In addition, three studies have been completed, one in phase 1/2 (NCT02292654).⁸⁶ and the other two in phase 1 (NCT00410566; NCT01722526).^{87,88} However, there are still some important limitations. The current ERT cannot pass the blood-brain barrier. Therefore, it is not useful for patients with central nervous system involvement. Consequently, in severe cases, the neurological symptoms are still progressive.⁸⁹ Moreover, long-term information on safety, immunogenicity, and durability of treatment effects is still limited, and the high cost of treatment is a major barrier, especially in developing countries.⁹⁰ Another significant challenge in the management of ASMD is the genetic and clinical variability of patients. Various mutations in the SMPD1 gene cause different severities of the disease, making it difficult to predict the prognosis of patients.⁹¹ Moreover, the prevalence of ASMD is low, and this makes it difficult to perform large-scale clinical trials.⁸⁹ Since there is no permanent treatment approach available, the treatment of ASMD can require a combined effort of specialists working together to enhance the life of the patient. Specialists required include pediatricians, neurologists, hepatologists, ophthalmologists, and many others.⁹² Death is still a significant issue despite the treatment approaches available, and this highlights the need for optimization. Mortality is still a major concern despite available treatments, underscoring the necessity of optimizing care.

How is Optimal Care Delivered for ASMD

Some ASMD patients are able to cope with only a multi-system disease with mild progress in certain areas of management. Along with the healthcare experts, ASMD patients have reported a better experience only if they had been followed up by a group of multidisciplinary

healthcare professionals who have the proper knowledge about ASMD. Such patients should be referred to the centers that are well recognized for ASMD management if available. Strength of Guidance: 1, Quality of Evidence: A, Specialist Viewpoint: Full agreement 75%, partial agreement 19%, slight agreement 6%, partial disagreement 0%, full disagreement 0%. Most clinical research papers about rare diseases, which are classified as multisystemic, point towards greater patients satisfaction after utilizing specialized services. There are reports of improvement in compliance rates as well as better attendance for appointments in comprehensive care clinics compared to traditional approaches.⁹³

If we consider the outline of the health systems, the competencies offered and the patient's requirements of that particular country, it is possible to establish a multidisciplinary group (MDG) to help coordinate ASMD patients in an effective manner. This approach promotes sharing and coordination of care while also ensuring that barriers to communication across disciplines are removed. In order to monitor the ASMD which is progressive and multisystemic, an international expert guideline has been formulated. Monitoring goals should be set at the time of diagnosis. They should be reviewed regularly to make sure that the complications of the disease are under control, and the patient's quality of life is enhanced.⁹⁴

How Should Burnout of Illness be Assessed

The presentation of ASMD along with the survival rate greatly depends on the subtype of the disease, age at which it was diagnosed, the organs affected and the complications associated with it.⁹⁵ Out of the 3 types, ASMD type A has the worst survival rate as it has a shorter life expectancy with a relatively consistent advancement of the disease.^{94,95} ASMD type B, on the opposite end of the spectrum, has a wide range of symptoms that affect the disease's severity, progression pace, and life expectancy.^{4,96,97} A&B is a type where the patients have combined traits of both type A and B and this mix goes hand in hand with a slower progression of neurodegeneration. There exist clinical guidelines to help monitor ASMD.⁹⁸ and more importantly, there exists a marking triad that can help in the diagnosis detection early stages, and help in changing the course of treatment. The key triad that marks ASMD amalgamates an

abnormal methylation pattern of TP73, increased mRNA levels of CPHM, and diminished levels of CD11b-expressing monocytes (Table 4).

Mortality

In the analysis of Wasserstein et al three patients, aged 9 to 18 years, passed away due to liver failure, traumatic subdural hematoma, and long-term difficulties due to an unsuccessful bone marrow transplant. Four patients suffering from NPD-A lost their lives because of extreme neurological manifestations, subdural hematoma, malignant edema, and pneumonia, according to Hollak et al.⁹⁶ Five patients with NPD-B lost their lives from this illness. Three of these were caused by worsening lung disease. One patient died from cancer, and the cause of death is unknown for another patient. In an investigation by McGovern and colleagues, they discovered 18 deaths in NPD-B patients. The main causes for these were respiratory failure, which caused five deaths. Liver failure was responsible for three deaths. Another three deaths occurred due to complications after a bone marrow transplant. Other causes of death included bleeding in the brain, failure of multiple organs, heart failure, liver cancer, a burst spleen vein, and bleeding after surgery e bleeding was among the causes of mortality in one patient each.⁹⁴ In a retrospective analysis of 100 patients, 12 were deceased. Among these NPD-A/B patients, ten deaths occurred at a mean age of 2.4 years. The causes included lung disorders (n = 1), respiratory failure (n = 2), pneumonia (n = 3), hepatic failure (n = 1), or unknown reasons (n = 3). Two NPD-B patients also died: one at 42 years from respiratory failure and another at 2 years from hepatic failure.⁹⁹ A recent study reported the deaths of eight patients due to ASMD. Three patients, aged 20, 35, and 71, passed away due to pneumonia. Two patients, aged 16 and 65, died from liver failure and cancer. One patient, aged 14, passed away due to a splenic vein tear. The other two individuals, aged 17 and 56, died from portal hypertension with esophageal varices and multiorgan failure. Pneumonia was the primary cause of mortality in these patients.¹⁰⁰

CONCLUSION

ASMD is an ultra-rare lysosomal storage disease distributed worldwide and associated with over 200 variants in the SMPD1

gene. The pathogenesis results from deficient acid sphingomyelinase activity and disrupted sphingomyelin metabolism, leading to widespread pathophysiological consequences: cellular changes that underlie the multisystem involvement include the liver, spleen, lungs, and, in severe forms, the central nervous system. It manifests as a number of fairly well-defined phenotypes, which range from chronic non-neuronopathic forms to rapid neurodegenerative variants. Besides its function in lipid metabolism, acid sphingomyelinase is also an important modulator in immune regulation but especially in controlling Natural Killer T cell activation. Diagnostic methods such as biochemical analysis, genetic analysis, and neuroimaging studies are used for early detection and disease classification. However, the limitations in sensitivity, accessibility, and standardization of these methods emphasize the need for further advances in the diagnostic area. In terms of therapy, enzyme replacement therapy is a promising area, but its failure to target the central nervous system, variable efficacy, and high cost create many problems. Taken together, these results indicate that future studies should aim at genotype-phenotype correlation analysis, CNS-targeted therapies, and standardization of diagnostic and monitoring procedures to improve patient survival and quality of life.

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Author Contributions

Pritesh Ranjan Dash: Supervision (lead), Project Administration(lead), Conceptualization(lead), Formal analysis (supporting).; Swapnil Das: Supervision (equal), Project Administration(equal), Conceptualization(equal), Formal analysis (lead), Methodology(lead), Investigation(lead), Data Curation(lead).; Fatiha Sultana Fiha: Methodology(equal), Investigation(equal), Data Curation(equal), Resources(lead), Writing – Original Draft(lead), Writing – Review & Editing(lead); Rohit Datta: Methodology(supportive), Investigation(supportive), Data Curation(supportive), Resources(equal), Writing – Original Draft(equal), Writing – Review & Editing(equal); Dip Mohajon: Resources(supportive), Visualization(lead), Data Curation(supportive); Irfan Hoque Tanjid: Resources(supportive), Visualization(equal), Data Curation(supportive).

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