Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Infantile Acid Sphingomyelinase Deficiency Presenting With Severe Gastrointestinal and Recurrent Respiratory Symptoms: A Diagnostic Challenge Case Report in Palestine

Abedallah Jabareen
Hebron University
Mo'ath Milhem
Hebron University
Isaac AbuSaleh
Hebron University
Islam Jadallah
Hebron University
Mohammad Milhem
ben_milhem@outlook.com

Palestine Polytechnic University
Shareef Hassan
Hebron University
Muawia Hassan
Palestine Red Crescent Hospital - Hebron Branch

Case Report

Keywords: Acid sphingomyelinase deficiency, Niemann–Pick disease type A, Lysosomal storage disorder Infantile hepatosplenomegaly, Feeding intolerance, Recurrent pneumonia, Diagnostic delay

Posted Date: March 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8751839/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background:
Acid sphingomyelinase deficiency (ASMD), encompassing Niemann–Pick disease types A and B, is a rare autosomal recessive lysosomal storage disorder. Infantile ASMD (type A) typically presents with progressive neurovisceral involvement. However, early manifestations may be nonspecific, leading to delayed diagnosis. We report an unusual presentation of infantile ASMD characterized by prominent gastrointestinal and respiratory symptoms, highlighting diagnostic challenges in pediatric practice.

Case presentation:
An 8-month-old male infant presented with progressive abdominal distension, persistent projectile vomiting, feeding intolerance, failure to thrive, recurrent respiratory infections, and hypotonia since early infancy. He was repeatedly treated for common pediatric conditions without sustained improvement. Imaging demonstrated marked hepatosplenomegaly and recurrent right upper-lobe pneumonia. Laboratory evaluation revealed markedly elevated liver enzymes with preserved synthetic function. Due to the combination of hepatosplenomegaly, hypotonia, and chronic feeding difficulties, a lysosomal storage disorder was suspected. Molecular genetic testing identified a homozygous pathogenic splice-site variant in the SMPD1 gene (c.1340+2T>C), confirming the diagnosis of infantile acid sphingomyelinase deficiency (Niemann–Pick disease type A). Supportive multidisciplinary management was initiated, including nutritional and respiratory care.

Conclusions:
This case illustrates an atypical early presentation of infantile ASMD with predominant gastrointestinal and respiratory manifestations preceding classical features. Awareness of such presentations is essential to avoid diagnostic delay, particularly in resource-limited settings. Early recognition facilitates appropriate supportive care, genetic counseling, and timely referral to specialized centers.

Introduction

A collection of uncommon, hereditary lysosomal storage disorders known as Niemann-Pick Disease (NPD) are typified by impaired intracellular lipid metabolism, which causes sphingomyelin and other lipids to accumulate pathologically in different organs. The liver, spleen, bone marrow, and central nervous system are the main organs affected by this multisystemic disease, which causes severe morbidity and progressive organ dysfunction (1, 2).

The disease is genetically diverse, with a number of subtypes that are primarily categorized as types A, B, and C. These subtypes are each brought on by mutations in distinct genes that impact lysosomal lipid processing. Type C is caused by mutations in either the NPC1 or NPC2 genes, which are involved in intracellular cholesterol trafficking, whereas types A and B are caused by mutations in the SMPD1 gene, which codes for acid sphingomyelinase (3, 4).

Depending on the subtype and age of development, NPD can exhibit a broad range of clinical symptoms. Rapid neurodegeneration and early mortality are the hallmarks of type A, the infantile neurovisceral variety. Type C contains a wide range of neurological and mental symptoms that frequently complicate diagnosis, whereas type B mostly presents with visceral involvement and a longer course (5, 6).

Niemann-Pick disease is difficult to diagnose and necessitates a multidisciplinary approach. It includes advanced imaging tests, genetic testing for harmful mutations, and biochemical assays like sphingomyelinase activity assessment. Due to phenotypic heterogeneity and comorbidity with other lysosomal storage disorders, early and correct identification continues to be a clinical problem (7, 8).

There are currently few and mostly supportive therapeutic alternatives. For types A and B, enzyme replacement therapy and substrate reduction therapies have showed promise; nevertheless, type C management concentrates on treating symptoms and enhancing quality of life. In order to treat the underlying genetic abnormalities, new molecular and gene therapies are being researched (9–11).

Individual case reports are crucial to comprehending the clinical variability, diagnostic difficulties, and therapeutic outcomes of Niemann-Pick Disease due to its rarity and severity. Reporting comprehensive clinical results and discoveries encourages ongoing research efforts in this complex condition, aids in the improvement of diagnostic criteria, and informs clinical management (12).

In this case, an 8-month-old newborn was diagnosed with Acid Sphingomyelinase Deficiency (Niemann–Pick Disease Type A/B) due to worsening hepatosplenomegaly, recurrent respiratory problems, and failure to thrive. Due of the metabolic disorder's rarity as well as overlapping symptoms including vomiting, developmental delay, and recurring infections, the underlying ailment was misdiagnosed several times in the past. Children with rare lysosomal storage diseases are frequently treated for more common ailments in places with limited resources, where modern metabolic and genetic testing is not easily accessible. This results in needless procedures and prolonged morbidity. This example emphasizes the significance of keeping a high index of suspicion for rare metabolic disorders in babies who exhibit unexplained clinical deterioration and prolonged hepatosplenomegaly. It also emphasizes how important it is for low- and middle-income healthcare systems to promptly identify and treat rare conditions due to a lack of diagnostic resources. **“This manuscript was prepared following the SCARE guidelines “**

Clinical Presentation

An 8-month-old male infant presented to our hospital with a history of progressive abdominal distension, recurrent vomiting, feeding difficulties, and failure to thrive noted since early infancy, the symptoms had gradually worsened over the last two months, and the mother also reported recurrent respiratory distress and episodes of vomiting associated with feeding.

The infant presented with a 5-day history of cough, high-grade fever (39.5 °C) partially responsive to antipyretics, projectile vomiting (4–5 times per day) of non-bilious gastric content, and watery diarrhea

up to 4–5 times daily, without mucus or blood.

The infant's feeding history was marked by early-onset vomiting, poor weight gain, and increasing difficulty tolerating feeds. He experienced repeated respiratory episodes, especially during feeding, and his mother noted persistent lethargy and decreased activity compared with his peers. There was no history of jaundice, bleeding tendency, or seizures. The past medical history included recurrent respiratory infections, documented hypotonia at 4 months, and persistent feeding intolerance. Developmentally, the child could sit with support, maintain head control when assisted, and grasp objects, but axial tone remained decreased.

At **6.5 months of age**, reassessment due to ongoing poor growth again confirmed **hepatomegaly (liver size 9.8 cm)** and borderline splenomegaly on abdominal ultrasound. Liver function tests demonstrated markedly elevated enzymes (ALT 511 U/L, AST 60 U/L, ALP 840 U/L) with normal albumin, further supporting a hepatocellular process.

Physical Examination:

On physical examination, the infant appeared dehydrated, with sunken eyes and dry oral mucosa. He was alert but slightly irritable, though not in severe distress. Respiratory assessment revealed decreased air entry bilaterally, more pronounced on the right side, with suprasternal retraction and bilateral wheezing. Abdominal examination showed a soft abdomen with palpable hepatosplenomegaly. Neurologically, he exhibited persistent generalized hypotonia with normal deep tendon reflexes. Laboratory investigations demonstrated microcytic anemia with a hemoglobin level of 10.2 g/dL and an MCV of 80.5 fL, while white blood cell and platelet counts were within normal limits.

An X-ray was taken on 15\8\2025 (figure 1) and shows right upper-lobe consolidation appearing as a dense opacity in the upper zone of the right lung, consistent with pneumonia, lung volumes are mildly reduced.

There is marked hepatosplenomegaly with enlargement of the upper abdominal organs pushing the diaphragm upward and displacing bowel loops inferiorly. The bowel gas pattern is non-obstructive, and the bony thoracic and abdominal structures appear normal.

He was admitted to the pediatric ward and started on intravenous ceftriaxone, hypertonic saline nebulization, and Ventolin inhalations, oxygen supplementation via nasal cannula was required for two days.

Then a follow-up X-ray on 19/08/2025 (Figure 2) demonstrated persistent right upper-lobe opacity compatible with ongoing pneumonia, with mild bilateral perihilar prominence suggesting airway inflammation. Lung expansion is adequate but slightly reduced. The mediastinal and cardiac contours are within normal limits. Significant hepatosplenomegaly is again evident, displacing bowel loops downward without evidence of bowel obstruction.

The child improved clinically and was discharged on Augmentin syrup, with follow-up in the metabolic clinic.

Discussion

Acid sphingomyelinase deficiency (ASMD), historically first described by Albert Niemann in 1914 (13) which classified as Niemann Pick disease (NPD) types A and B, account a group of autosomal recessive lysosomal storage disorders caused by variant mutations in the SMPD1 gene, which lead to deficient activity of acid sphingomyelinase and accumulation of sphingomyelin inside lysosomes (14). This defect of storage primarily affects cells of the reticuloendothelial system, resulting in progressive hepatosplenomegaly, pulmonary involvement, cytopenias, and early, severe neurological deterioration specifically in the infantile neurovisceral form (15).

Over time, ASMD has been subdivided into three phenotypic categories: the severe infantile neurovisceral form (historical Type A), the chronic visceral form (Type B), and intermediate A/B phenotypes reflecting partial residual enzymatic activity (16). In classical Type A, residual ASM activity is typically < 1% of normal, leading to rapid disease progression with fatal neurodegeneration in early childhood. In contrast, higher residual activity underlies the more protracted Type B phenotype (17).

The clinical presentation of our patient is highly consistent with the severe infantile neurovisceral phenotype. The early onset of recurrent vomiting and feeding difficulty at approximately two months of age, followed by progressive failure to thrive, recurrent respiratory infections, and marked hepatosplenomegaly by six months reflect rapidly advancing visceral involvement. The significantly elevated liver enzymes (ALT 511 U/L; ALP 840 U/L) in early infancy are notable, as hepatic injury although well characterized in ASMD does not always manifest with such profound biochemical derangement at this age. Persistent hypotonia documented from four months of age further aligns with early neuromuscular involvement described in Type A disease.

The molecular identification of a homozygous splice site variant, SMPD1 c.1340 + 2T > C, provides definitive diagnostic confirmation (18). Although splice-site mutations have long been recognized among pathogenic SMPD1 variants, this specific alteration has not been widely reported in the existing literature or disease registries, suggesting a potentially novel allele contributing to the expanding mutational spectrum of ASMD. Given that pathogenic splice-site variants often abolish or severely impair normal mRNA splicing, this mutation is mechanistically consistent with the severe phenotype observed in this patient (19).

This case contributes important insights to the understanding of early-onset ASMD. The prominent gastrointestinal presentation recurrent projectile vomiting, feeding intolerance, and poor weight gain was clinically significant months before the full expression of hepatosplenomegaly. Although feeding difficulties are described in ASMD, they are not typically emphasized as initial manifestations (19). This case therefore underscores the need to consider lysosomal storage disorders in infants with persistent feeding issues accompanied by subtle neuromuscular abnormalities.

This recurrent respiratory distress which associated with feeding and culminating in pneumonia highlights the interplay between pulmonary disease and visceral involvement. Alveolar macrophage lipid accumulation, coupled with risk of infection and potential aspiration, likely contributed to the respiratory manifestations seen in this case, reflecting a known but often underappreciated component of infantile ASMD (20).

Notably, unusual transaminase elevation observed at six months of age in this patient, as most reported cases demonstrate hepatomegaly well before any substantial biochemical evidence of hepatic injury. Such an early and pronounced rise in liver enzymes suggests either an accelerated pattern of visceral disease or heightened hepatic susceptibility to sphingomyelin accumulation, potentially exacerbated by recurrent infectious episodes. This constellation of findings may therefore reflect a more aggressive disease trajectory within the ASMD infantile spectrum (21).

It is worth mentioning, this case carries regional relevance. Reports of ASMD from the Middle East remain limited, and the identification of a potentially novel pathogenic SMPD1 variant contributes valuable genetic data for populations in this region. Moreover, delays in diagnosis due partly to overlapping symptoms with more common pediatric disorders such as GERD, recurrent viral infections (22), emphasize the need to expand awareness and metabolic evaluation pathways in settings where lysosomal storage diseases are under-recognized.

Treatment options for the infantile neurovisceral form in children remain limited despite increasing therapeutic advances. Enzyme replacement therapy with oxidase alfa has shown substantial benefit for non-CNS manifestations in chronic ASMD but is not indicated for the severe Type A form due to its inability to cross the blood–brain barrier (23). Management remains largely supportive, focusing on nutritional adequate, respiratory care, infection control, and genetic counseling.

Conclusion

In summary, this case exemplifies the classical yet variable early presentation of infantile ASMD, with rapidly progressive visceral disease, early neuromuscular involvement, and marked hepatic dysfunction. The identification of a likely novel SMPD1 splice-site variant further expands the genetic spectrum of the disorder and reinforces the need for early metabolic and molecular evaluation in infants presenting with persistent feeding difficulties, hepatosplenomegaly, and recurrent respiratory illness. Early diagnosis is essential to guide supportive care, provide accurate family counseling, and enable potential inclusion in emerging research and therapeutic studies.

Declarations

The work has been reported in line with the SCARE criteria.

Informed Consent

Written informed consent was obtained from the patient parents for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal if requested.

Ethical approval:

Institutional Review Board (IRB) approval was not required for this single case report. Written informed consent for publication was obtained from the patient's parents."

Methods

"This work has been reported in line with the SCARE criteria."

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Acknowledgements

The authors express their gratitude to the patient and their family for their great contribution.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

We declare that no conflict of interest could be perceived as prejudicing the impartiality of the research reported.

Data Availability:

Data is available on request from the authors.

Clinical trial number

not applicable.

References

1. More R. Sphingomyelin / cholesterol lipidosis. 2025;1–12.
2. Disease N pick. Niemann-Pick Disease. 2025;1–2.
3. Schuchman EH, Desnick RJ. Types A and B Niemann-Pick disease. Mol Genet Metab. 2017;120(1–2):27–33.

4. Bremova-ertl T, Patterson M. Niemann-Pick Disease Type C Summary. 2025;1–28.
5. Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis [Internet]. 2010;5(1):16. Available from: https://doi.org/10.1186/1750-1172-5-16
6. Patterson MC, Mengel E, Vanier MT, Schwierin B, Muller A, Cornelisse P, et al. Stable or improved neurological manifestations during miglustat therapy in patients from the international disease registry for Niemann-Pick disease type C: an observational cohort study. Orphanet J Rare Dis [Internet]. 2015;10(1):65. Available from: https://doi.org/10.1186/s13023-015-0284-z
7. Marie T, Maria J, Richard WD, Stefan A. Diagnostic tests for Niemann-pick disease type C (NP-C) : a critical review. 2025;5–6.
8. Encarnação M, Ribeiro I, David H, Coutinho MF, Quelhas D, Alves S. Challenges in the Definitive Diagnosis of Niemann-Pick Type C-Leaky Variants and Alternative Transcripts. Genes (Basel). 2023 Oct;14(11).
9. Schuchman EH. The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann–Pick disease. J Inherit Metab Dis [Internet]. 2007;30(5):654–63. Available from: https://doi.org/10.1007/s10545-007-0632-9
10. Tirelli C, Rondinone O, Italia M, Mira S, Belmonte LA, De Grassi M, et al. The Genetic Basis, Lung Involvement, and Therapeutic Options in Niemann-Pick Disease: A Comprehensive Review. Biomolecules. 2024 Feb;14(2).
11. Bremova-Ertl T, Schneider S. Current advancements in therapy for Niemann-Pick disease: progress and pitfalls. Expert Opin Pharmacother. 2023;24(11):1229–47.
12. Carey JC. The importance of case reports in advancing scientific knowledge of rare diseases. Adv Exp Med Biol. 2010;686:77–86.
13. McGovern MM, Dionisi-Vici C, Giugliani R, Hwu P, Lidove O, Lukacs Z, et al. Consensus recommendation for a diagnostic guideline for acid sphingomyelinase deficiency. Genet Med [Internet]. 2017;19(9):967–74. Available from: https://doi.org/10.1038/gim.2017.7
14. Pacheco CD, Lieberman AP. The pathogenesis of Niemann-Pick type C disease: a role for autophagy? Expert Rev Mol Med. 2008 Sep;10:e26.
15. Pfrieger FW. The Niemann-Pick type diseases - A synopsis of inborn errors in sphingolipid and cholesterol metabolism. Prog Lipid Res. 2023 Apr;90:101225.
16. McGovern MM, Wasserstein MP, Bembi B, Giugliani R, Mengel KE, Vanier MT, et al. Prospective study of the natural history of chronic acid sphingomyelinase deficiency in children and adults: eleven years of observation. Orphanet J Rare Dis. 2021 May;16(1):212.
17. Wasserstein MP, Schuchman EH. Acid Sphingomyelinase Deficiency. In: Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. Seattle (WA); 1993.
18. Corbeira DV, Marie T. Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann-Pick disease types A , B and A / B) Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann – Pick disease types A , B and A / B). Orphanet J Rare Dis [Internet]. 2023; Available from: https://doi.org/10.1186/s13023-023-02686-6

19. Geberhiwot T, Wasserstein M, Wanninayake S, Bolton SC, Dardis A, Lehman A, et al. Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann-Pick disease types A, B and A/B). Orphanet J Rare Dis. 2023 Apr;18(1):85.
20. Wasserstein MP, Aron A, Brodie SE, Simonaro C, Desnick RJ, McGovern MM. Acid sphingomyelinase deficiency: prevalence and characterization of an intermediate phenotype of Niemann-Pick disease. J Pediatr. 2006 Oct;149(4):554–9.
21. Mcgovern MM, Avetisyan R, Sanson B jan, Lidove O. Disease manifestations and burden of illness in patients with acid sphingomyelinase deficiency (ASMD). 2017;1–13.
22. Schuchman EH. The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann-Pick disease. Int J Clin Pharmacol Ther. 2009;47 Suppl 1:S48-57.
23. Diaz GA, Giugliani R, Guffon N, Jones SA, Mengel E, Scarpa M, et al. Long-term safety and clinical outcomes of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency: two-year results. Orphanet J Rare Dis. 2022 Dec;17(1):437.

Figures



Figure 1

x-ray



Figure 2

Follow up x- ray

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SCAREGuidelineChecklist2025.docx