Indian Journal of Pharmacy Practice., 2025; 18(2):239-242.
https://www.ijopp.org

Case Report

# A Rare Case of Type A Niemann-Pick Disease and its Treatment Approaches

**Venugopal Vignesh[1], Sivakumar Kalaivani[2], Deivendran Lokeshvaran[2], John Aswin[2], Dyneese Geetha Abinish[2,*]**

[1]Department of Paediatrics, Government Medical College and Hospital, Nagapattinam, Tamil Nadu, INDIA.
[2]Department of Pharmacy Practice, Government Medical College and Hospital, Nagapattinam, Tamil Nadu, INDIA.

**ABSTRACT**

Niemann-Pick disease is a rare genetic lysosomal storage disorder characterised by disrupted lipid metabolism, leading to harmful lipid accumulation in organs such as the liver, spleen and brain. It is classified into several types, with Type A being the most severe and often fatal in early childhood, while Type B presents with milder symptoms. The diagnosis is based on clinical presentation and is confirmed through genetic testing. Current therapeutic approaches, including enzyme replacement therapy, show potential benefits by reducing lipid storage and improving clinical outcomes. This case report presents a 1-year-old male with global developmental delay and hepatosplenomegaly presented with a sudden seizure, along with a history of fever, cold and cough. Examination revealed febrile status, pallor, abnormal facies and a systolic murmur. Laboratory findings showed anaemia and mild hyperbilirubinemia and imaging revealed hypomyelination. Genetic testing confirmed Niemann-Pick disease Type A. The patient was referred to a specialised centre for enzyme replacement therapy and multidisciplinary care. This case underscores the potential of enzyme replacement therapy in improving outcomes for Niemann-Pick Disease, while highlighting the challenges of high costs, limited tissue penetration and the blood-brain barrier. Early diagnosis and specialised care remain critical in managing this condition and future research should focus on adjunctive therapies to enhance treatment efficacy.

**Keywords:** Case report, Enzyme replacement therapy, Lysosomal disorder, Niemann-Pick disease, Niemann-Pick Type A.

**Correspondence**
**Dr. Dyneese Geetha Abinish**
Department of Pharmacy Practice, Government Medical College and Hospital, Nagapattinam, Tamil Nadu, INDIA.
Email: drabinishdgpharmd@gmail.com

**Received:** 02-10-2024;
**Revised:** 20-10-2024;
**Accepted:** 23-10-2024.

## INTRODUCTION

Niemann-Pick Disease (NPD) is a genetic lysosomal disorder that disrupts lipid metabolism, leading to the harmful buildup of lipids in various organs, including the spleen, liver, lungs, bone marrow and brain.[1] It is a severe and life-threatening disorder that carries substantial health risks and often leads to significant illness and mortality, especially among children.[2] It is classified into four subtypes: A, B, C and E. Type A, the infantile neurovisceral form, involves very low Acid Sphingomyelinase (ASM) activity and is usually fatal by age three, leading to neurological deficits and impaired growth. Type B is less severe, with varying visceral symptoms and minimal neurological involvement. Type C (NP-C) presents diverse systemic, neurologic and psychiatric symptoms at any age, often beginning with infantile jaundice and hepatosplenomegaly, while adults may have minimal or no hepatosplenomegaly. Type E is a rare adult-onset variant.[3] Type A and B are rare, affecting about 1 in 250,000 individuals overall, but they are more prevalent in Ashkenazi Jews, where the incidence increases to 1 in 40,000. NP-C is similarly rare, affecting approximately 1 in 150,000 people, with a higher occurrence noted among those of French-Acadian descent in Nova Scotia.[4] Examination findings show a wide range of symptoms affecting various body systems. These include liver and spleen enlargement, lung problems like interstitial disease and recurrent infections and skin discolouration such as jaundice. Cardiovascular issues involve low platelet counts and high cholesterol levels, while bone-related issues may include growth problems and bone mineralisation delays. Eye symptoms often include a distinct red spot in the retina surrounded by a pale area, along with corneal and lens abnormalities. Neurologically, patients may experience difficulties with movement (ataxia, dystonia), swallowing (dysphagia), speech (dysphonia), developmental delays, intellectual disabilities and tremors, as well as eye movement abnormalities (vertical supranuclear gaze palsy) which highlights the complex and widespread impact of NPD on the body.[5-8] Although lysosomal storage diseases that affect the kidneys are uncommon, NPD should be considered as

**DOI:** 10.5530/ijopp.20250162

a possible diagnosis in patients presenting with lipid metabolism disorders and renal insufficiency.[9]

Type A and B result from mutations in the SMPD1 gene, which lead to a marked decrease in ASM activity. This deficiency causes the accumulation of sphingomyelin and other lipids in lysosomes, resulting in cellular damage. The disease severity varies due to over 180 different mutations in SMPD1, showing diverse effects based on genetic differences across regions. NP-C, categorised into C1 and C2 depending on NPC1 or NPC2 gene mutations, involves faulty NPC1 and NPC2 proteins located in late endosomes and lysosomes. This impairment disrupts cholesterol transport, leading to the toxic buildup of cholesterol within lysosomes, which damages cells and organs.[10]

Diagnosing guidelines for NPD were updated, focusing on a thorough clinical assessment for suspected cases and referral to specialised metabolic disorder centers. They stress examining symptoms like neurological, eye-related and psychiatric issues to catch NP-C early. Psychiatric symptoms, including cognitive decline and mood disorders, are common in adults with NP-C and can be prominent. Assessing eye movements, especially detecting vertical gaze problems early with video-oculography, is crucial for accurate diagnosis and timely treatment.[11] However, diagnosing NP-C early is challenging due to delayed suspicion and testing, which prolongs the time without specific treatment or genetic counseling. Recognising symptoms promptly and ensuring appropriate diagnostic tests are crucial. Recent advances in quick and simple laboratory tests offer hope for faster diagnosis, potentially integrated into broader screening efforts. Continuous genotyping updates of the NP-C gene variation database are essential to distinguish disease-causing mutations and improve our understanding of genotype-phenotype correlations, possibly with the aid of biomarkers.[12]

Advancements in treating Lysosomal Storage Diseases (LSDs) include CNS-directed Enzyme Replacement Therapy (ERT) for Niemann-Pick A (NP-A) disease. This approach uses cannula-based infusions of Human Acid Sphingomyelinase (HASM) to reduce sphingomyelin accumulation in the brain, aiming to alleviate both CNS and systemic disease symptoms. While promising, challenges persist in maintaining therapeutic HASM levels and achieving widespread efficacy across all affected brain regions in NP-A disease.[13] Dysfunctional clathrin-mediated endocytosis leads to build-up of lysosomal substrates. Using polymer nanocarriers that target ICAM-1 via a non-clathrin pathway enhances delivery of recombinant ASM, reducing substrate accumulation and potentially enhancing treatment efficacy for these diseases.[14] ERT thus stands as a pivotal treatment for conditions like lysosomal storage diseases. It works by producing artificial enzymes in different cell types, purifying them and administering them through intravenous injections. This approach has proven effective in managing symptoms, marking significant progress in medical treatment.[15]

This case report aims to discuss a unique presentation of NP-A in a 1-year-old male patient, focusing on the genetic aspects of the disease and underscoring the critical role of ERT in its management. It also aspires to enhance understanding of the disease and advocate for the importance of appropriate therapeutic strategies.

## CASE DESCRIPTION

A 1-year-old male child was brought by his parents to the government medical college and hospital, Nagapattinam, with a sudden seizure characterised by abnormal hand movements and upward rolling of the eyeballs, lasting approximately 10 min. Initially the child was administered with injection midazolam to diminish the seizure. The child had fever for 1 day and cold and cough for 3 days, with no history of vomiting, abdominal pain and loose stools. The child's antenatal history included maternal fever at 3 months and breathing difficulty at 8 months of pregnancy. The natal history revealed a P2 L1 A1 status with a normal vaginal delivery at 3.9 kg and no NICU admission. Postnatally, the child was TORCH positive at 3 months of age with fever. Vaccinations were up to date until 7 months. Developmental milestones were delayed, with neck holding and bi-dextrous grasp not achieved. The patient had a past medical history of global developmental delay and was being evaluated for dystonic hepatosplenomegaly and jaundice. Tests indicated rubella positivity, for which ganciclovir treatment was initiated and continued for 5 months, then stopped at 8 months of age. At 8 months of age, the child was evaluated and was found to have global developmental delay, hepatosplenomegaly and dysmorphic features. Imaging studies including USG and MRI revealed hypomyelination in the corpus callosum, enlarged subarachnoid space and diffuse white matter hyperintensity.

On examination, the child was in the post-ictal phase, febrile and had pallor, abnormal coarse facies, fair hydration, a heart rate of 110/min, pulse rate of 36/min and SpO2 of 98% on oxygen. Cardiovascular examination revealed S1S2 with a systolic murmur. Respiratory examination showed bilateral air entry without added sounds. Abdominal examination indicated a soft abdomen, positive bowel sounds, abdominal distension and palpable liver and spleen extending 10 cm and 8 cm below the costal margin, respectively. Laboratory investigations revealed a haemoglobin level of 6.8 g/dL, indicating significant anaemia, which is concerning for a 1-year-old male child. Platelets were $132x10^3/\mu L$, slightly low. The total count was $5.1x10^3/\mu L$, within the normal range. RBC count was $3.54x10^6/\mu L$, reflecting the low haemoglobin. Total bilirubin was 1.7 mg/dL, with direct bilirubin at 0.50 mg/dL and indirect bilirubin at 1.2 mg/dL, suggesting mild hyperbilirubinemia. Liver enzymes SGOT and SGPT were 21 U/L and 23 U/L, respectively, which are within normal limits. Urea was 26 mg/dL, within the normal range and RBS was 96 mg/dL, indicating normal blood sugar levels. Immediate treatment

included a paracetamol suppository and tepid sponging for fever reduction, levetiracetam 90 mg IV BD for seizure control, ceftriaxone 400 mg IV BD for bacterial infection prophylaxis and IV fluids with DNS at 28 mL/hr for dehydration. General seizure management was conducted.

All these findings suggested a storage disorder, initiating further diagnostic investigations, including karyotyping, which confirmed the diagnosis of Niemann-Pick disease type A, a condition characterised by deficiency of acid sphingomyelinase, leading to the accumulation of sphingomyelin in various tissues. Long-term management includes ERT to supplement the deficient enzyme, aiming to reduce sphingomyelin accumulation, mitigate clinical symptoms and potentially slow disease progression. The child was referred to the Institute of Child Health and Hospital for Children (ICH) Egmore, a specialised center for ERT and multidisciplinary care, where regular ERT infusions and comprehensive supportive care will be provided to manage this complex condition effectively.

## DISCUSSION

Niemann-Pick disease includes two main metabolic disorders. The first category, due to ASM deficiency, encompasses types A and B. Type A appears in infancy with hepatosplenomegaly and severe central nervous system issues, often resulting in death by age two. Type B involves hepatosplenomegaly and lung pathology, usually sparing the CNS, allowing for varied progression and survival into adulthood. Intermediate phenotypes exist due to different ASM gene mutations. The second category, types C and D, affects cholesterol trafficking and primarily impacts the CNS.[16]

The genetic mutations involved in NPD have seven missense mutations and one frameshift mutation in the SMPD1 gene. These missense mutations varied in their impact on enzyme activity, with some resulting in less than 1% of wild-type activity and others maintaining up to 64%. The frameshift mutation led to a truncated enzyme with no functional activity. Type A patients had mutations with minimal residual activity, while type B patients had mutations with at least 5% residual activity.[17] These mutations in the SMPD1 gene result in the deficiency of enzyme ASM which leads to the accumulation of sphingomyelin in various tissues, particularly affecting the liver, spleen and brain. The accumulation causes severe organ dysfunction, with type A often presenting in infancy with profound neurological and hepatic symptoms and type B typically involving milder neurological effects but significant pulmonary issues such as interstitial lung disease and respiratory complications.[18]

In this case, the infant had NP-A, which is caused by a specific mutation in the SMPD1 gene. This gene mutation results in a significant deficiency of the enzyme ASM, leading to the accumulation of sphingomyelin in various tissues, including the liver, spleen and brain. The infant presented with typical symptoms of NP-A, including marked dystonic hepatosplenomegaly, jaundice and profound neurological involvement. Unfortunately, due to the aggressive nature of NP-A, the infant was recommended for ERT.

ERT for lysosomal storage diseases took years to refine. Early research using lipid-catabolising enzymes from human placenta showed potential in treating Fabry's and Gaucher's diseases. Production delays for galactosidase A and glucocerebrosidase hampered progress and modifications were required to target glucocerebrosidase to macrophages effectively. Once these targeted enzymes proved effective, recombinant versions made in Chinese-hamster-ovary cells were confirmed to be biologically equivalent.[19] In addition to ERT, Enzyme Enhancement Therapy (EET) uses small molecules known as 'pharmacological chaperones' to stabilise misfolded or unstable mutant enzymes with some residual function. This approach not only helps improve enzyme function but also holds promise for treating neurodegenerative lysosomal disorders, as these small molecules have the potential to cross the blood-brain barrier.[20]

Genetic mutations can disrupt the production of metabolic enzymes, leading to harmful substrate buildup and a lack of essential metabolites. ERT has become essential for treating these issues. Since the 1990s, ERT has been effective for rare lysosomal storage and metabolic disorders, with a dozen enzymes approved by the FDA. These enzymes are produced in mammalian, plant, or yeast cells to ensure effectiveness. Research continues to refine ERT by improving enzyme-cell interactions, reducing immune responses and addressing the blood-brain barrier. ERT has significantly improved patient quality of life and is a key treatment for genetic disorders.[21] ERT with Olipudase-alfa is effective and safe for pediatric patients with Acid Sphingomyelinase Deficiency (ASMD), a genetic disorder linked to SMPD1 gene mutations. It improves clinical outcomes such as hepatosplenomegaly, bone density, pulmonary infiltration, dyslipidemia and growth patterns. ERT also reduces Lyso-SM levels, a key biomarker for ASMD and shows improvements in liver stiffness and 6-min walking distance, though these biomarkers require further validation. Overall, ERT demonstrates significant benefits for ASMD management, with ongoing research needed to evaluate its impact on neurological involvement.[22]

However, ERT has several limitations, as it effectively reduces urinary glycosaminoglycans and decreases liver and spleen volume, it has limited impact on cartilaginous organs, bones and eyes due to poor tissue penetration. Additionally, ERT does not cross the blood-brain barrier, making it ineffective for addressing central nervous system symptoms. The high cost of ERT limits access, especially in countries with less affluent healthcare systems. Moreover, while all patients develop anti-ERT antibodies, only a few experiences drug-related adverse reactions and the potential impact of high-titre antibodies on ERT efficacy remains uncertain.[23,24]

## CONCLUSION

In conclusion, this case demonstrates the significant advancements in the management of Niemann-Pick Disease using Enzyme Replacement Therapy, which replaces deficient enzymes, improves patient outcomes and reduces disease progression. However, challenges such as limited tissue penetration, inability to cross the blood-brain barrier and high costs persist. Future studies should focus more on adjunctive therapies, such as enzyme enhancement therapy and recombinant enzymes, to offer more effective treatments. This case underscores the importance of early diagnosis and specialised care, highlighting the need for ongoing therapeutic strategies.

## ACKNOWLEDGEMENT

Authors would like to express sincere gratitude to all the physicians in the Department of Paediatrics at Government Medical College and Hospital, Nagapattinam, for their valuable guidance and support throughout the preparation of this case report.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Informed consent was obtained from the patient's legal guardian.

## CONFLICT OF INTEREST

The authors declare that there no conflict of interest.

## ABBREVIATIONS

**NPD:** Niemann Pick Disease; **ASM:** Acid Sphingo Myelinase; **NPC:** Niemann Pick Disease Type C; **NPA:** Niemann Pick Disease Type A; **ERT:** Enzyme Replacement Therapy; **HASM:** Human Acid Sphingomyelinase; **ASMD:** Acid Sphingomyelinase Deficiency; **EET:** Enzyme Enhancement Therapy; **NICU:** Neonatal Intensive Care Unit; **TORCH:** Toxoplasmosis, Others (Syphilis, Hepatitis B), Rubella, Cytomegalovirus, Herpes Simplex; **USG:** Ultrasound Sonography; **MRI:** Magnetic Resonance Imaging.

## REFERENCES

1. Parker, J. N., and Parker, P. M. (Eds.).Niemann:Pick disease: A bibliography and dictionary for physicians, patients and genome researchers. 2007. ICON Health Publications.
2. McGovern MM, Lippa N, Bagiella E, Schuchman EH, Desnick RJ, Wasserstein MP. Morbidity and mortality in type B Niemann-Pick disease. Genet Med Open. 2013;15(8):618-23, doi: 10.1038/gim.2013.4.
3. Eskes EC, Sjouke B, Vaz FM, Goorden SM, van Kuilenburg AB, Aerts JM, *et al.* Biochemical and imaging parameters in acid sphingomyelinase deficiency: Potential utility as biomarkers. Mol Genet Metab. 2020;130(1):16-26, doi: 10.1016/j.ymgme.2020.02.002.
4. Bianconi SE, Hammond DI, Farhat NY, Do AD, Jenkins K, Cougnoux A, *et al.* Evaluation of age of death in Niemann:Pick disease, type C: Utility of disease support group websites to understand natural history. Mol Genet Metab. 2019;126(4):466-9, doi: 10.1016/j.ymgme.2019.02.004.
5. Thurm A, Chlebowski C, Joseph L, Farmer C, Adedipe D, Weiss M, *et al.* Neurodevelopmental characterization of young children diagnosed with Niemann:Pick disease, type C1. J Dev Behav Pediatr. 2020;41(5):388-96, doi: 10.1097/DBP.0000000000000785.
6. Guillemot N, Troadec C, de Villemeur TB, Clément A, Fauroux B. Lung disease in Niemann-Pick disease. Pediatr Pulmonol. 2007;42(12):1207-14.
7. Kresojević N, Mandić-Stojmenović G, Dobričić V, Petrović I, Brajković L, Stefanova E, *et al.* Very late-onset Niemann Pick Type C disease: example of progressive supranuclear palsy look-alike disorder. Mov Disord Clin Pract. 2020;7(2):211, doi: 10.1002/mdc3.12892.
8. Patterson M. Niemann:Pick Disease Type C. In: GeneReviews®. University of Washington, Seattle, Seattle (WA); 1993. PMID: 20301473.
9. Zheng Z, Cheng C, Zhao W, Feng Q, Li C, Lou T. Case Report Renal failure and ascites in a patient with Niemann:Pick disease: case report and literature review. Int J Clin Exp Me. 2016;9:4800-4.
10. Bajwa H, Azhar W. Niemann:Pick Disease. [Updated 2023 Mar 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024:. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556129/
11. Patterson MC, Clayton P, Gissen P, Anheim M, Bauer P, Bonnot O, *et al.* Recommendations for the detection and diagnosis of Niemann:Pick disease type C: An update. Neurol Clin Pract. 2017;7(6):499-511, doi: 10.1212/CPJ.0000000000000399.
12. Vanier MT, Gissen P, Bauer P, Coll MJ, Burlina A, Hendriksz CJ, *et al.* Diagnostic tests for Niemann:Pick disease type C (NP:C): A critical review. Mol Genet Metab. 2016;118(4):244-54, doi: 10.1016/j.ymgme.2016.06.004.
13. Macauley SL, Sands MS. Promising CNS:directed enzyme replacement therapy for lysosomal storage diseases. Exp Neurol. 2009;218(1):5, doi: 10.1016%2Fj.expneurol.2009.03.040.
14. Rappaport J, Garnacho C, Muro S. Clathrin:Mediated Endocytosis Is Impaired in Type A-B Niemann-Pick Disease Model Cells and Can Be Restored by ICAM:1:Mediated Enzyme Replacement. Mol Pharm. 2014;11(8):2887-95, doi: 10.1021/mp500241y.
15. Schaible P. Modifying enzyme replacement therapy-A perspective. J Cell Mol Med. 2023;27(2):165-73, doi: 10.1111/jcmm.17653.
16. Schuchman EH, Wasserstein MP. Types A and B niemann:pick disease. Best Pract Res Clin Endocrinol Metab. 2015;29(2):237-47, doi: 10.1016/j.beem.2014.10.002.
17. Desnick JP, Kim J, He X, Wasserstein MP, Simonaro CM, Schuchman EH. Identification and characterization of eight novel SMPD1 mutations causing types A and B Niemann:Pick disease. Mol Med. 2010;16:316-21, doi: 10.2119/molmed.2010.00017.
18. 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;14(2):211, doi: 10.3390/biom14020211.
19. Brady RO, Schiffmann R. Enzyme:replacement therapy for metabolic storage disorders. Lancet Neurol. 2004;3(12):752-6, doi: 10.1016/S1474: 4422(04)00938:X.
20. Desnick RJ. Enzyme replacement and enhancement therapies for lysosomal diseases. J Inherit Metab Dis. 2004;27(3):385-410, doi: 10.1023/B:BOLI.0000031101.12838.c6.
21. Marchetti M, Faggiano S, Mozzarelli A. Enzyme replacement therapy for genetic disorders associated with enzyme deficiency. Curr Med Chem. 2022;29(3):489-525, doi: 10.2174/0929867328666210526144654.
22. Pan YW, Tsai MC, Yang CY, Yu WH, Wang B, Yang YJ, *et al.* Enzyme replacement therapy for children with acid sphingomyelinase deficiency in the real world: a single center experience in Taiwan. Mol Genet Metab Rep. 2023;34:100957, doi: 10.1016/j.ymgmr.2023.100957.
23. Concolino D, Deodato F, Parini R. Enzyme replacement therapy: efficacy and limitations. Ital J Pediatr. 2018;44:117-26, doi: 10.1186/s13052: 018:0562:1.
24. Wraith JE. Limitations of enzyme replacement therapy: current and future. J Inherit Metab Dis. 2006;29(2-3):442-7, doi: 10.1007/s10545: 006:0239:6.

**Cite this article:** Vignesh V, Kalaivani S, Lokeshvaran D, Aswin J, Abinish DG. A Rare Case of Type A Niemann-Pick Disease and its Treatment Approaches. Indian J Pharmacy Practice. 2025;18(2):239-42.