

Early Diagnosis of Nieman–Pick Disease Type C and Rapid Response of Gelastic Cataplexy to Treatment With N-Acetyl-L-Leucine: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 3-year-old
Final Diagnosis: Niemann–Pick disease type C
Symptoms: Gelastic cataplexy • hepatosplenomegaly
Clinical Procedure: —
Specialty: Genetics • Neurology

Objective: Rare disease
Background: Niemann–Pick disease type C (NPC) is a rare, progressive neurodegenerative lysosomal storage disorder often diagnosed in childhood after the onset of neurological symptoms. Gelastic cataplexy – the sudden loss of muscle tone associated with laughter but remaining consciousness – is quite specific for NPC. This report describes the case of a 4-year-old boy with NPC presenting with gelastic cataplexy who responded to treatment with N-acetyl-L-leucine (NALL).

Case Report: We present the case of a patient who first presented in the genetics clinic due to hepatosplenomegaly, dysmorphic features, and milestone delay at 2 years old. He had a history of cholestatic jaundice and hepatosplenomegaly at 2 months old. Granulomatous hepatitis of unknown origin was diagnosed by liver biopsy, and then the cholestatic jaundice resolved. The diagnosis of NPC was made, confirmed by compound heterozygous missense likely pathogenic in *NPC1* (NM_000271.5): one known; c.2072C>T (p.Pro691Leu), and one novel; c.2805A>G (p.Ile935Met) at the age of 3 years. He then developed gelastic cataplexy at the age of 4 years, and a clinical improvement was observed within the first month after receiving NALL, including a significant decrease in cataplexy episodes, improved motor function, and reduced splenomegaly.

Conclusions: This case highlights the critical role of early genomic diagnosis in NPC, enabling prompt management of worsening neurological symptoms and potentially responding to treatment with NALL.

Keywords: Lysosomal Storage Diseases • Leucine • Hepatomegaly • Splenomegaly • Cataplexy • Genetics • Niemann–Pick Diseases • Hepatitis B • Catastrophic Illness • Case Reports • Genetics • Niemann–Pick Disease, Type C • Cataplexy • Whole Genome Sequencing • Case Reports

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Introduction

Niemann–Pick disease (NP), a lysosomal storage disease, is caused by precursor lipids that accumulate in the lysosomes of all tissues, such as the liver, spleen, lungs, and brain. The symptoms include hepatosplenomegaly, interstitial lung disease, and neurologic involvement, which is usually progressive [1]. Different enzyme deficiencies distinguish 3 main subtypes of NP, with type A (NPA) being the most severe form, and NP type B (NPB) being less severe. Both types are caused by acid sphingomyelinase deficiency, so the sphingomyelin (SM) precursor cannot be metabolized to ceramide and phosphocholine, leading to SM accumulation [1]. NP type C (NPC) is caused by a defect in cholesterol trafficking in lysosomes, resulting in the accumulation of multiple lipids, including cholesterol, glycosphingolipids, sphingosine, and sphingomyelin in lysosomes [2].

NP is a rare and progressive neurodegenerative lysosomal storage disorder with a prevalence varying from 1: 40,000 to 250,000 for NPA and NPB [1]; and 1: 45,000 to 212,000 live births for NPC [2–5]. However, underdiagnosis has been revealed by the proportion of patients with NPC who received treatment, which was only 1: 1,000,000 in the United States [6].

NPC intracellular cholesterol transporter 1 (*NPC1*) and NPC intracellular cholesterol transporter 2 (*NPC2*) are 2 genes responsible for the NPC1 and NPC2 proteins, respectively [7]. The function of NPC2 protein is to bind with free cholesterol in lysosomes before transferring to NPC1, which is a membrane protein [8]. Then, the NPC1 protein exports cholesterol from lysosomes to other organelles and plasma membranes [8]. Because the NPC1 protein is larger than NPC2, 95% of NPC is caused by *NPC1* mutations [2].

The clinical spectrum of NPC is highly heterogeneous, ranging from neonatal liver dysfunction to adolescent- or adult-onset neuropsychiatric and motor symptoms [9]. A hallmark neurological symptom of NPC is vertical supranuclear gaze palsy, often accompanied by cerebellar ataxia, dystonia, cognitive decline, and psychiatric disturbances [2,9]. Most cases are diagnosed in childhood after the onset of neurological symptoms. During the infantile period, hepatic manifestations are the only ones that occur [10]; therefore, a liver biopsy may be a key diagnostic clue.

Gelastic cataplexy is a rare manifestation characterized by a brief, sudden episode of generalized loss of muscle tone, leading to a fall while remaining conscious, typically triggered by laughter. This symptom is specific to NPC [11], but needs to be differentiated from atonic seizures, fainting, or narcolepsy [12]. Apart from NPC, cataplexy can also occur in Coffin–Lowry syndrome [13].

Current disease-modifying treatment options for NPC are limited. Miglustat is a substrate-reduction therapy that slows neurodegenerative processes and results in either an improved or stable clinical course [14,15], but has only been approved in some regions [16], and is also cost-prohibitive in developing countries. Recently, N-acetyl-L-leucine (NALL), also known as levacetylleucine, is a derivative of the essential amino acid leucine; it has emerged as a potential therapeutic agent and has been approved for improving neurological symptoms and quality of life in patients with NPC [17,18]. NALL can cross the blood–brain barrier, and possibly activate cerebral glucose metabolism in the cerebellum [19], improving neuronal signaling and circuits, reducing neuroinflammation, activating the enzyme control pathway of adenosine triphosphate (ATP) production, and leading to enhanced lysosomal function by improving lysosomal fusion and trafficking [16,18,19]. While its long-term disease-modifying effects remain under investigation, rapid symptomatic relief, particularly of cerebellar and vestibular symptoms, was observed in early studies [17,18]. Therefore, the U.S. Food and Drug Administration (FDA) approved Aqneursa® (NALL) in September 2024 for the treatment of neurological symptoms in NPC [16]. However, no specific effect on gelastic cataplexy has been reported.

Here, we report the case of a patient who received a diagnosis of NPC by a molecular genetic test before presenting with gelastic cataplexy, which is a well-known symptom characteristic of NPC. Furthermore, the effectiveness of NALL was demonstrated, resulting rapid improvement of gelastic cataplexy.

Case Report

This study was approved by the Human Research Ethics Committee of Thammasat University (Medicine) (MTU-EC-PE-0-304/67). Written informed consent was obtained from the patient's parents. This patient was not enrolled in any clinical trials.

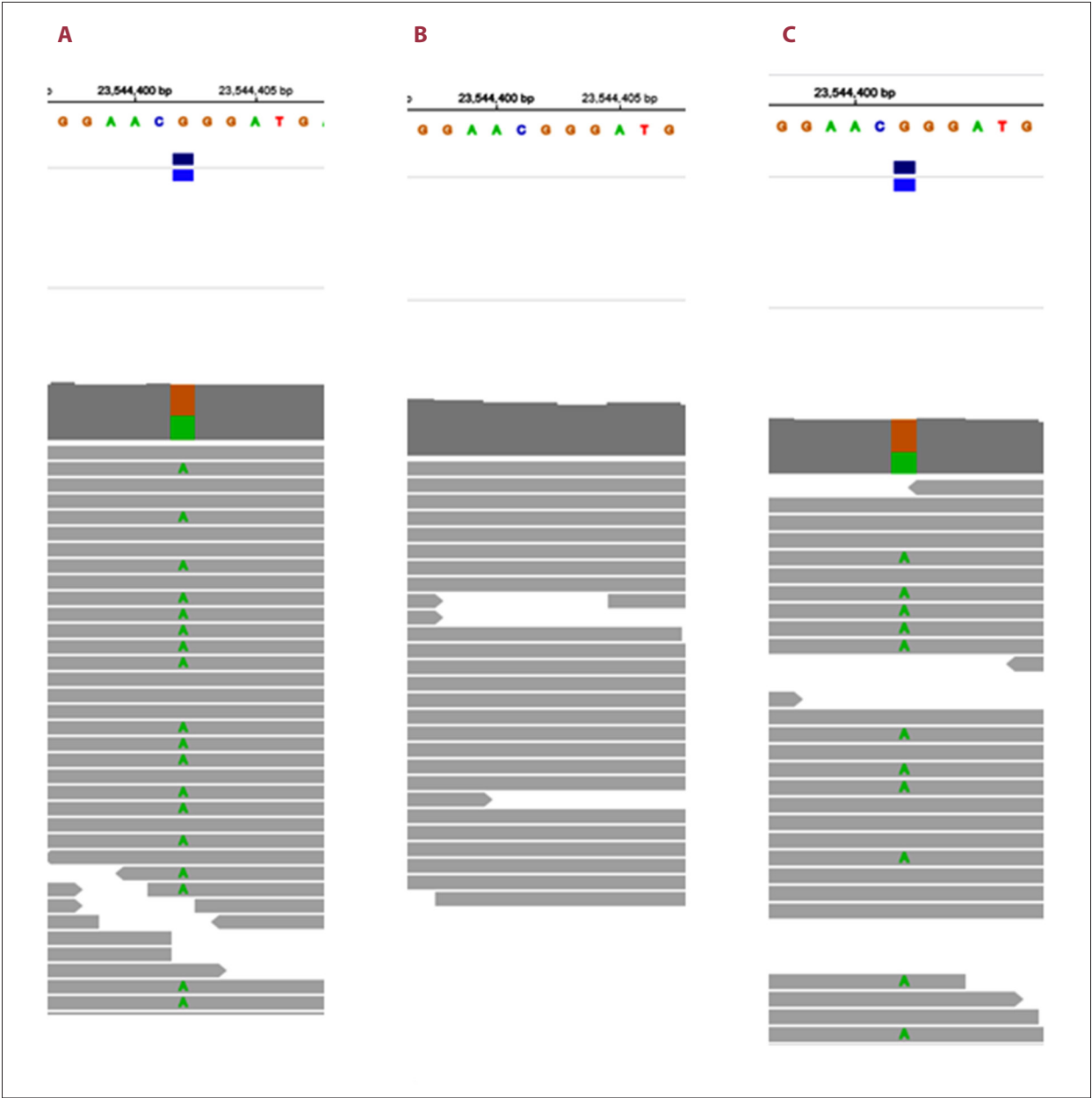
The patient was the first child of non-consanguineous parents, born at 38 weeks of gestation by elective cesarean delivery. The prenatal ultrasound revealed a calcified placenta. His birth weight was 2310 g (in the 3rd percentile), body length was 48 cm (in the 10th to 50th percentile), head circumference was 32 cm (in the 10th percentile), and the Apgar scores at 1 and 5 minutes after birth were 9 and 10, respectively. At 4 days of age, he received phototherapy for 1 day for neonatal jaundice. His total bilirubin (TB) was 13 mg/dL (222 μmol/L) and decreased to 6.9 mg/dL (118 μmol/L) on the next day.

At 2 months old, he presented with cholestatic jaundice. He was exclusively breastfed. His stool and urine color were yellow. Physical examination revealed a body weight of 4.7 kg (in

the 25th percentile), body length of 57 cm (in the 50th percentile), jaundice, liver 2 cm below the right costal margin with a span of 7 cm, and spleen 7 cm below the left costal margin. The liver function test results were as follows: total bilirubin (TB) 137, direct bilirubin (DB) 67 $\mu\text{mol/L}$, aspartate aminotransferase (AST) 2.26, alanine transaminase (ALT) 0.58 ukat/L , albumin 39, globulin 18 g/L , alkaline phosphatase (ALP) 16 ukat/L , and gamma-glutamyl transferase (GGT) 6951 ngat/L . Complete blood count, coagulogram, and thyroid function test results were normal. Abdominal ultrasound demonstrated a hyperechogenic lesion in the liver, with hepatosplenomegaly, and a liver biopsy revealed granulomatous hepatitis of unknown origin but negative for *Mycobacterium tuberculosis*, and the dihydrorhodamine

test result was negative for chronic granulomatous disease. Immune deficiency was also ruled out by a normal number of lymphocytes, lymphoid subpopulation, and immunoglobulins.

His cholestatic jaundice was treated by ursodeoxycholic acid and vitamin A, D, E, and K supplements. At 4 months old, his jaundice was resolved, and a liver function test revealed TB 24, DB 12 $\mu\text{mol/L}$, AST 1.59, ALT 0.71 ukat/L , albumin 38, globulin 24 g/L , ALP 5.6 ukat/L , and GGT 8152 ngat/L . He has been followed for hepatosplenomegaly and granulomatous disease; at 18 months old, his liver function test result was within normal range, including a GGT of 467 ngat/L . However, delayed development of walking and speaking was noticed.



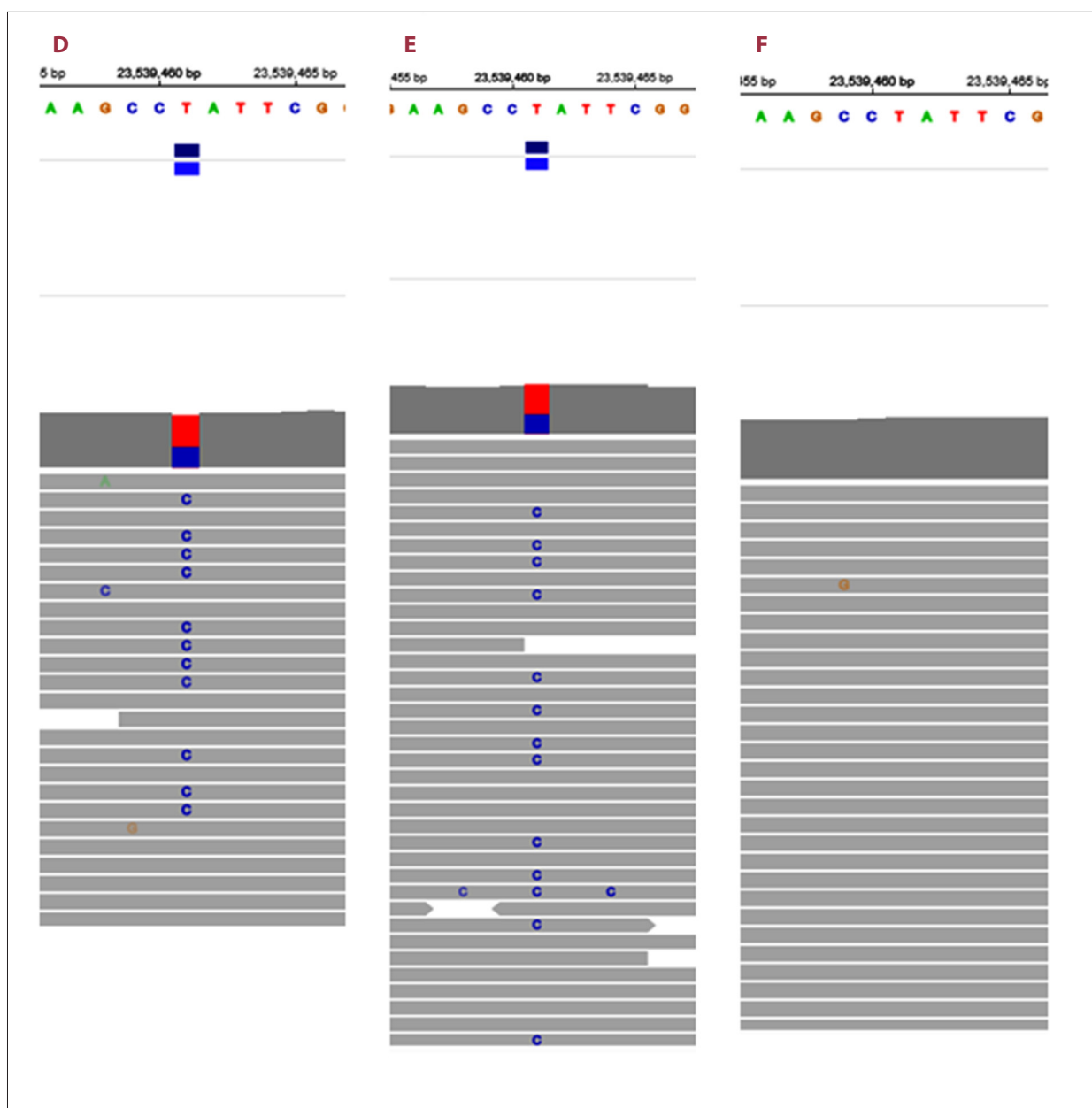


Figure 1. Integrative Genomics Viewer file view illustrating compound heterozygous likely pathogenic variants in the *NPC1* gene (NM_000271.5). The c.2072C>T (chr18-23544402 G>A) in our patient (A) and his mother (C), wild-type in his father (B), and c.2805A>G (chr18-23539461 T>C) in our patient (D) and his father (E), and wild-type in his mother (F).

He was seen in the genetics clinic at the age of 2 years; his weight, height, and head circumference were in the 25th to 50th percentile. Frontal bossing, midface hypoplasia, full lips, and hepatosplenomegaly (liver 3 cm below the right costal margin with a span of 8 cm and spleen 4 cm below the left costal margin) were observed. Enzyme testing for glucocerebrosidase and acid sphingomyelinase was sent for screening of Gaucher and Niemann–Pick type A and B, and the results were negative.

Whole-genome sequencing (trio) was performed by the Genomics Thailand project, a government-funded initiative during 2019–2023 that involves 22 universities and regional hospitals throughout Thailand, which has processed sequencing for the genomic database of 50,000 Thai people [20]. Genomic DNA was extracted from the patient's peripheral blood and his parents using the magnetic beads method and subsequently sequenced for whole-genome sequencing on the BGI DNBSEQ-T7 sequencing platform, achieving an average coverage depth of 30×. Variant calling was conducted using GATK

4.0 against the human genome reference GRCh38. Variants were annotated using the Variant Effect Predictor (VEP) version 110, dbNSFP version 4.4a, and in Thai genome databases (<https://thaiger.genomicsthailand.com>). The variant classification was performed using a modified version of the “Tool for Assessment and Prioritisation in Exome Studies” (TAPES) [21]. Trio analysis was conducted using GENMOD, a tool designed for annotating and analyzing genomic variations. The VCF file was uploaded to Franklin Genoox® to aid in variant interpretation. Variants with a minor allele frequency of less than 0.01% in the Genome Aggregation Database (gnomAD) were analyzed. Pathogenic interpretations were made based on the American College of Medical Genetics and Genomics (ACMG) classification for pathogenicity [22].

Compound heterozygous missense variants in *NPC1* (NM_000271.5) were detected. One was c.2072C>T (p.Pro691Leu), a likely pathogenic variant based on ACMG classification as PM1, PM2, PM3, PM5, PP2, PP3, and PP5 reported previously in patients with NPC, juvenile type [7,23,24], and inherited from his mother. Another was c.2805A>G (p.Ile935Met), a novel likely pathogenic variant based on ACMG classification as PM1, PM2, PM3, PP2, and inherited from his father (Figure 1). Neither variant was observed in gnomAD (available at <https://gnomad.broadinstitute.org>) or Thai genome databases (available at <https://thaiger.genomicsthailand.com>).

At the age of 3 years, when the genetic result was known, his delayed developmental milestones had improved, and he could talk in sentences and walk quickly. At 4 years old, he began exhibiting sudden episodes of muscular collapse precipitated specifically by laughter, with retained consciousness and postural slumping, which is characteristic of gelastic cataplexy. He had frequent episodes (more than 5 times/day), unstable gait, and frequent falls, with marked splenomegaly. NALL was initiated at age 4.5 years, and a notable clinical improvement was observed within 1 month, including a significant decrease in cataplexy episodes, reduced splenomegaly, and improved motor function, active movement, and walking.

Discussion

This is the first case report to demonstrate the efficacy of NALL in a patient with gelastic cataplexy from NPC, who was diagnosed prior to the onset of classic phenotypes, including neurological regression, clumsiness, gait disturbances, and impaired vertical gaze [2]. With the advent of next-generation sequencing, diagnoses have been made in infancy. Cholestasis is the first reported symptom of NPC, which presents in half of infantile-onset cases. When hepatosplenomegaly (or hepatomegaly/splenomegaly) presents with cholestasis, the likelihood of NPC diagnosis increases to 30% [10].

While molecular genetic results demonstrated compound heterozygous likely pathogenic variants in *NPC1* in patients without neurological deterioration, interpreting these variants and their clinical correlation requires caution. Both likely pathogenic variants, p.Pro691Leu, in a sterol-sensing domain, and another novel variant, p.Ile935Met, in a cysteine-rich loop with a RING-finger motif domain, are the crucial domains in *NPC1* [2], and both variants are missense, which are the most common pathogenic/likely pathogenic variants in *NPC1* [25].

Gelastical cataplexy is a classic neurological manifestation of Niemann–Pick disease type C, with an estimated prevalence of approximately 50% among affected individuals during childhood or adolescence [11]. Therefore, when diagnosing NPC before neurological symptoms and neurodegeneration features arise, early recognition and management can be started immediately.

Our patient had a rapid and significant improvement in gelastic cataplexy after receiving NALL, accompanied by more active movement, walking, running, and climbing, and a reduction in splenomegaly. A case report showed the efficacy of miglustat in complete resolution of gelastic cataplexy within 6 months of treatment [26]. No previous studies have specifically addressed the efficacy of NALL for treatment of gelastic cataplexy. Previous studies demonstrated improvement in ataxia, as measured by the Scale for the Assessment and Rating of Ataxia (SARA) scores, after NALL use for 12 weeks [17,18]. This swift clinical response supports emerging data suggesting that NALL can provide acute symptomatic relief in NPC, in addition to its long-term neuroprotective potential. Notably, this case report reinforces the efficacy of NALL for treating cataplexy, highlighting documented short-term benefits and thus expanding the potential scope of its therapeutic effects. However, long-term outcomes need to be monitored.

Conclusions

Our patient’s clinical manifestations over time illustrate the classic presentation of NPC from infancy to childhood, including gelastic cataplexy, and emphasize the utility of treatment using NALL, which resulted in rapid symptomatic relief and has potential neuroprotective effects. This report shows the critical role in early diagnosis of NPC and enabling timely treatment, potentially leading to improved outcomes.

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Institution Where Work Was Done

Thammasat University Hospital, Pathumthani and Faculty of Medicine, Thammasat University, Pathumthani, Thailand.

Patient Consent

The patient's parents consented to publication of this case report.

References:

1. Bajwa H, Azhar W. Niemann–Pick disease. [Updated 2023 Mar 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK556129/>
2. Vanier MT. Niemann–Pick disease type C. *Orphanet J Rare Dis*. 2010;5:16
3. Labrecque M, Touma L, Bh  rer C, et al. Estimated prevalence of Niemann–Pick type C disease in Quebec. *Sci Rep*. 2021;11(1):22621.
4. Pinto R, Caseiro C, Lemos M, et al. Prevalence of lysosomal storage diseases in Portugal. *Eur J Hum Genet*. 2004;12(2):87-92
5. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. *JAMA*. 1999;281(3):249-54
6. Burton BK, Ellis AG, Orr B, et al. Estimating the prevalence of Niemann–Pick disease type C (NPC) in the United States. *Mol Genet Metab*. 2021;134(1-2):182-87
7. Park WD, O'Brien JF, Lundquist PA, et al. Identification of 58 novel mutations in Niemann–Pick disease type C: Correlation with biochemical phenotype and importance of PTC1-like domains in NPC1. *Hum Mutat*. 2003;22(4):313-25
8. Pfeffer SR. NPC intracellular cholesterol transporter 1 (NPC1)-mediated cholesterol export from lysosomes. *J Biol Chem*. 2019; 294(5):1706-9
9. Bremova-Ertl T, Patterson M. Niemann–Pick disease type C. 2000 Jan 26 [updated 2025 Nov 20]. In: Adam MP, Bick S, Mirzaa GM, et al, editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025
10. L  pez de Frutos L, Cebolla JJ, de Castro-Or  s I, et al. Neonatal cholestasis and Niemann–Pick type C disease: A literature review. *Clin Res Hepatol Gastroenterol*. 2021;45(6):101757
11. Yazdi N, Fasano A, Lang AE, Rohani M. Gelastic cataplexy in Niemann–Pick type C. *Mov Disord Clin Pract*. 2019;6(6):498-99
12. Yang Z, Liu X, Dong X, et al. Epilepsy and narcolepsy-cataplexy in a child. *J Child Neurol*. 2012;27(6):807-10
13. Stephenson JB, Hoffman MC, Russell AJ, et al. The movement disorders of Coffin–Lowry syndrome. *Brain Dev*. 2005; 27(2):108-13
14. Pineda M, Walterfang M, Patterson MC. Miglustat in Niemann–Pick disease type C patients: A review. *Orphanet J Rare Dis*. 2018;13(1):140
15. Patterson MC, Garver WS, Giugliani R, et al. Long-term survival outcomes of patients with Niemann–Pick disease type C receiving miglustat treatment: A large retrospective observational study. *J Inher Metab Dis*. 2020;43(5):1060-69
16. Noor R, Qazi MS. FDA approves Miplyffa and Aqneursa: A new era in treatment of Niemann–Pick disease type C. *J Rare Dis*. 2025;4(1):14
17. Bremova-Ertl T, Ramaswami U, Brands M, et al. Trial of N-acetyl-L-leucine in Niemann–Pick disease type C. *N Engl J Med*. 2024;390(5):421-31
18. Patterson MC, Ramaswami U, Donald A, et al. Disease-modifying, neuro-protective effect of N-acetyl-L-leucine in adult and pediatric patients with Niemann–Pick disease type C. *Neurol*. 2025;105(1):e213589
19. Fields T, M. Bremova T, Billington I, et al. N-acetyl-L-leucine for Niemann–Pick type C: A multinational double-blind randomized placebo-controlled crossover study. *Trials*. 2023;24(1):361
20. Sukasem C, Biswas M, Lungchukiet P, Sangtian M. Clinical pharmacogenomics implementation in Thailand: A dream come true. *Pharmacogenomics*. 2023;24(6):297-301
21. Xavier A, Scott RJ, Talseth-Palmer BA. TAPES: A tool for assessment and prioritisation in exome studies. *PLoS Comput Biol*. 2019;15(10):e1007453
22. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-24
23. Jahnova H, Dvorakova L, Vlaskova H, et al. Observational, retrospective study of a large cohort of patients with Niemann–Pick disease type C in the Czech Republic: A surprisingly stable diagnostic rate spanning almost 40 years. *Orphanet J Rare Dis*. 2014;9:140
24. Musalkova D, Majer F, Kuchar L, et al. Transcript, protein, metabolite and cellular studies in skin fibroblasts demonstrate variable pathogenic impacts of NPC1 mutations. *Orphanet J Rare Dis*. 2020;15(1):85
25. Guatibonza Moreno P, Pardo LM, Pereira C, et al. At a glance: The largest Niemann–Pick type C1 cohort with 602 patients diagnosed over 15 years. *Eur J Hum Genet*. 2023;31(10):1108-16
26. Zarowski M, Steinborn B, Gurda B, et al. Treatment of cataplexy in Niemann–Pick disease type C with the use of miglustat. *Eur J Paediatr Neurol*. 2011;15(1):84-87

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