

## Two Cases of Niemann-Pick Disease Type C Presenting with Neonatal Cholestasis: Case Reports

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### ABSTRACT

**Background and Objective:** Niemann-Pick type C is a rare lysosomal storage disorder causing cholesterol intracellular transport deficiency. Typically found in children, it causes neurological deterioration and age-related symptoms. In this article, two cases of Niemann-Pick type C1 with cholestasis and another case with a compound heterozygous mutation that included Niemann-Pick type D are presented. Although neonatal diseases are the most common cause of early cholestasis, this report emphasizes the importance of considering storage disease in cholestasis.

**Case Report:** A 34-day-old female baby born to a third-degree married couple at 38 weeks gestation presented with cholestatic jaundice. Whole-exome sequencing suggested an NPC1 gene mutation and Niemann-Pick type C. A 35-day-old female baby born at 39 weeks gestation presented with ecchymotic patches, decreased feed acceptance, greenish discoloration of the eyes, high-color urine, and firm hepatosplenomegaly. The child was worked up for conjugated hyperbilirubinemia and a liver biopsy in favor of Niemann-Pick disease. Whole exome sequencing showed an NPC1 gene heterozygous mutation, suggesting Niemann-Pick disease types C and D.

**Conclusion:** Pediatricians should consider Niemann-Pick disease in neonates with persistent cholestasis.

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## Introduction

Neimann-Pick is a fatal inherited metabolic disorder with a global incidence of 1 in 89,000 to 1 in 120,000 live births. It is classified as sphingolipidosis, which involves the accumulation of sphingolipids in the brain, liver, lung, spleen, and bone marrow <sup>[1]</sup>.

Niemann-Pick type C (NPC) is an autosomal recessive lipid storage disorder caused by mutations in either the NPC1 or NPC2 genes. Mutations in these genes are linked to aberrant endosomal-lysosomal trafficking, resulting in the lysosome accumulation of numerous tissue-specific lipids <sup>[2]</sup>. NPC disease has a clinical spectrum ranging from a neonatal, fast-developing, deadly ailment to an adult-onset chronic neurodegenerative disease. The metabolic base of type 'C' remained an enigma for a long time and is not yet fully elucidated, despite a reclassification of the disease as a cellular lipid trafficking disorder. Initial manifestations can be hepatic, neurological, or psychiatric. Approximately 45% and 65% of NPC cases have neonatal liver disease <sup>[2]</sup>. NPC accounts for 7-8% of cases of neonatal cholestasis <sup>[3]</sup>. Prolonged neonatal cholestatic icterus associated with progressive hepatosplenomegaly is the most common sign, with spontaneous resolution by 2–4 months of age, followed by rapid fatal liver failure in about 10% of cases without any neurological signs. In infants and young children, isolated hepatosplenomegaly may be the only sign of the disease. The most common presentation (about 60-70% of the cases) is late infantile and juvenile neurologic onset <sup>[1]</sup>. In this study, we present two cases of Niemann-Pick type C1 with early cholestasis and liver failure. In one case, we found a novel mutation; in another case, we noticed a compound heterozygous mutation that also included Niemann-Pick type D.

## Case Report 1

A term female baby was admitted to Niloufer Hospital on the tenth day of life with complaints of abdominal distension, greenish discoloration of the body, and passing dark-colored urine. The baby was born to a mother in a third-degree consanguineous marriage with an uneventful antenatal history. The

baby was delivered by a lower segment Cesarean section (LSCS) because of oligohydramnios at 38 weeks of gestational age. The baby's birth weight was 2.5 kg, and the baby presented with jaundice on the second day of life. The baby was admitted on the fourth day of life in a private hospital and was discharged after two days of phototherapy.

Upon examination, the baby presented with microcephaly (a head circumference of 32cm, < 3rd percentile), a normal weight and length for gestational age, an icterus, and a distended abdomen with palpable firm hepatosplenomegaly (figure 1).

A total serum bilirubin was obtained, which showed direct hyperbilirubinemia. Total serum bilirubin (TSB) was 21.4 mg/dl, direct bilirubin (DB) was 9.3 mg/dl, and indirect bilirubin (IB) was 12.1 mg/dl. A provisional diagnosis of cholestatic jaundice with hepatosplenomegaly was made, and the child was further investigated. The patient was given supportive care, such as ursodeoxycholic acid (UDCA) and fat-soluble vitamins.

Upon evaluation, the mother and baby blood groups were A-positive. The white blood cell count was 5,540/mm<sup>3</sup>, hemoglobin 13.0 g/dL, platelet count 411,000/mm<sup>3</sup>, C-reactive protein (CRP) 4 mg/dl, cholesterol 173 mg/dL, albumin 2.79 g/dL (ref. 3.3–5.2 g/dL), bile acids 122.6 µmol/L (ref. 0–6.0 µmol/L), prothrombin time international normalized ratio (PT-INR) 1.3, activated partial thromboplastin time (aPTT) 54.9 sec, and ammonia 95 µg/dL (27.2–102.0 µg/dL). The baby had elevated alkaline phosphatase (ALP) at 818 IU/L, serum glutamic-oxaloacetic transaminase (SGOT) at 69.4 U/L, serum glutamate pyruvate transaminase (SGPT) at 35 IU/L, and gamma-glutamyl transferase (GGT) at 204 U/L (Table 1). Chest radiography revealed no pulmonary infiltrates.

The ultrasonogram of the abdomen was suggestive of a subscapular lesion measuring 10\*8 mm in the liver. A Contrast-Enhanced Computed Tomography (CECT) of the abdomen revealed the lesion to be a hemangioma with no post-contrast enhancement, and the gallbladder was distended. TSH, T3, and T4 levels were normal [TSH was 5.03 uIU/ml (0.35–5.5), T3 was 1.25 ng/ml (0.6–1.81), and T4 was 9.7 ug/Dl (4.5–11)]. The TORCH

profile was normal except for cytomegalovirus (CMV).

CMV IgG was positive with a positive titer, but the CMV DNA PCR of the urine sample was negative. Serological markers for hepatitis A, B, and C were not detected. A hepatobiliary iminodiacetic acid (HIDA) scan showed a normal liver with adequate hepatic function and visualization of subhepatic drains (ruling out biliary atresia). Metabolic screening was normal. Urine for reducing substances was normal. Suspected storage disorders were considered. A fundoscopy was normal. The parents were refused a liver and bone marrow biopsy. Whole-exome sequencing was done. The report was suggestive of a novel NPC1 gene mutation, exon 4 c.337\_340 homozygous duplication. Some investigations related to cholestasis were postponed for financial reasons, while the diagnosis was confirmed. In this case, the parents were left without any notification or medical advice, which is why parental genetic tests were not done.

**Table 1. Laboratory values of case 2**

Lab Parameter	Result	Reference Range
Serum Albumin	2.9g/dL	3.3–5.2 g/dL
TSH	5.03 uIU/ml	0.35–5.5 uIU/ml
T3	1.25 ng/ml	0.6–1.81ng/ml
T4	9.7 ug/dl	4.5–11 g/dl
CRP	4 mg/dL	< 6 mg/dl
PT-INR	13.6	12.7 to 15.4Sec
aPTT	54.9 sec	31–54 Sec
ammonia	95 µg/dL	(27.2–102.0 µg/dL)
ALP	818IU/L	30–120 IU/L
SGOT	69.4U/L	4–36 IU/L
SGPT	35IU/L	5 to 30 IU/L
GGT	204U/L	6–50 IU/L
bile acids	122.6 mol/L	(0–6.0 mol/L)
Serum Cholesterol	173 mg/dL	75–180 mg/dL

## Case Report 2

A 35-day-old female baby presented with a greenish discoloration, decreased acceptance of feeds for up to eight days, and ecchymotic patches all over her body from one day onwards. The mother also stated that her baby passed strongly colored urine that stained the diapers, but had no clay-colored stools. The baby had similar complaints on the 18th day of life for which she

received a vitamin K injection and fresh frozen plasma (FFP) transfusion at a private hospital and was discharged the next day.

The baby was third in birth order, born to a non-consanguineously married couple with no significant antenatal history. The baby was delivered at 39 weeks of gestation by normal vaginal delivery with a birth weight of 3 kg. There is no significant family history of infantile deaths. The mother's two previous male babies were healthy. On examination, anthropometry was age-appropriate. The baby had severe pallor, icterus, ecchymotic patches all over the body, and firm hepatosplenomegaly with a tense anterior fontanelle (figure 2). A provisional diagnosis of acute liver failure with hepatosplenomegaly and intracranial bleeding was made, and a further line of management was initiated.

The laboratory tests revealed an Hb of 6.5 g/dl, platelets of 4.2 ks, and a PT of 30 sec. INR 3.7 aPTT was 100 sec. An injection of vitamin K IV was administered. PRBC and FFP (fresh frozen plasma) were transfused until normalization of the above laboratory parameters. A brain CT scan revealed a right frontotemporal EDH (extra-dural hemorrhage) with falcine extension and a midline shift of 4 mm. A neurosurgeon was consulted, and the child was managed conservatively. Liver function tests revealed a TSB of 14.2 mg/dl, a DB of 6.7 mg/dl, an IB of 7.73 mg/dl, an SGOT of 50 U/L, an SGPT of 170.7 U/L, an ALP of 238 U/L, and a GGT of 117 U/L (Table 2).

After initial stabilization, the child was worked up for the cause of conjugated hyperbilirubinemia. The ultrasonogram of the abdomen was suggestive of multiple hypoechoic areas in the liver with moderate splenomegaly. Serology for viral hepatitis and TORCH showed negative titers. An HIDA scan was suggestive of normal biliary function. Suspecting a storage disorder, we conducted a liver biopsy that showed individual hepatocytes with markedly enlarged vacuolated cytoplasm, focal giant cell transformation of hepatocytes, a few hepatocytes showing intra-cytoplasmic brown pigment, periportal inflammatory infiltrates, focal cholestasis, and occasional bile pigments. A PAS stain showed focal positivity, suggesting a storage

disorder of the liver. Whole exome sequencing showed pathogenic NPC1 gene mutation on exon 24 c.3718 G > A, suggesting NPC, and on exon 18 A > G C.2769 A > G, suggestive of Niemann-Pick disease type D. In both cases, the clone-by-clone sequencing method was used in whole-genome sequencing (WGS), which was performed in a private laboratory in Hyderabad with government funding.

A bone marrow aspiration was not performed because a liver biopsy and WGS confirmed the diagnosis, and the complete blood count (CBP) was also normal, which is usually not in favor of bone marrow infiltration. The baby is now three months old and regular supportive treatment is given.

**Table 2. Laboratory values of case 2**

Lab Parameter	Result	Reference Range
Hb	6.5mg/dL	13mg/dl-16m g/dL
Platelets	4.5 Lakhs	1.5-5 Lakhs
PT	30 Sec	0.6-1.81ng/ml
a PTT	100 Sec	4.5-11 g/dl
CRP	4 mg/dL	< 6 mg/dl
TSB	14.2mg/dl,	12.7 to 15.4Sec
DB	6.7mg/dl,	31-54 Sec
IDB	7.73mg/dl	(27.2-102.0 µg/dL)
ALP	818IU/L	30-120 IU/L
SGOT	508U/L	4-36 IU/L
SGPT	170.7U/L	5 to 30 IU/L
GGT	117 IU/L.	6-50 IU/L



**Figure 1. Case 1 at the time of admission with hepatosplenomegaly**



**Figure 2. Case 2 at the time of admission with abdominal distention**

## Discussion

The incidence of Niemann-Pick disease type C (NPC) was reported to be approximately 1/100,000–1/120,000 live births, but it increased after genetic tests became more common [4]. Types A and B of Niemann-Pick disease occur when the body lacks the enzymes necessary to break down sphingomyelin, causing a buildup of toxic amounts of sphingomyelin, a fatty substance found in every cell of the body. Niemann-Pick type C disease is characterized by the impaired ability of the body to metabolize cholesterol and other lipids, which is caused by a deficiency in either NPC1 or NPC2 proteins. Defects in the NPC1 gene account for approximately 95% of patients, while NPC2 is the cause in approximately 5% of reported cases. Type A, the most severe form begins in early infancy and is most common in Jewish families. Additional symptoms encompass the occurrence of severe brain damage by the age of 6 months, with affected individuals exhibiting a limited life expectancy of no more than 18 months. Type B, also referred to as juvenile-onset, manifests with symptoms such as ataxia and peripheral neuropathy, while the central nervous system is typically unaffected. Children with type B can live relatively long lives but may require supplemental oxygen due to lung damage. Type C, a genetic disorder, is associated with significant neurological complications, including impaired vertical and horizontal eye movements,



visual impairment, gait disturbances, hearing impairment, hepatosplenomegaly, jaundice, seizures, dementia, dysarthria, liver diseases, sleeping disorders and the potential for premature mortality during childhood or adulthood [5].

During pregnancy, type C can manifest as hydrops, one of the clinical symptoms. In infancy, the most prevalent visceral symptoms include hepatosplenomegaly, jaundice, and pulmonary infiltrates. Neurological manifestations have exhibited increased prominence during the later stages of infancy [6]. Earlier, the onset of neurological symptoms led to a shorter lifespan, with most individuals dying between 10 and 25 years of age. In our reports, both cases were characterized by the presence of cholestasis. Hildreth A reported a case of a male child at 7 weeks of age, which was considered the youngest case at the time. However, in our study, we present a case that occurred even earlier [7]. Wang NL et al. found that vacuolated Kupfer cells can help in the early diagnosis of NPC in neonatal cholestasis [8]. Park SW reported a similar case to our second case in a 15-day-old Korean child who had progressive liver failure and gastrointestinal bleeding and died. After the individual's demise, a neonatal cholestasis panel was conducted, which led to the diagnosis of NPC [9]. Bulut FD reported a 16-day-old male baby who was presented with transient cholestasis and was admitted at 8 months with neurological symptoms [10].

In our study, both children developed hepatosplenomegaly, and in the second case, the child suffered from liver failure with ecchymosis. However, Gumus et al. observed in their retrospective single-center study that not only liver causes but also pulmonary causes can lead to neonatal death in neonates [11]. Staretz-Chacham O conducted a study involving a cohort of 12 patients, of whom nine exhibited pulmonary complications such as pneumonia, wheezing, and interstitial lung disease necessitating the use of oxygen support [12].

Surmeli-Onay O reported a case study involving a patient with nonketotic hyperglycinemia (NPC) who presented with hydrops fetalis, perinatal ascites, and hepatosplenomegaly [13]. Seker Yilmaz concluded that identifying mutations determining

NPC will help predict disease progression and structure future clinical trials of novel therapies [14]. In the initial case, the frameshift variant had not been previously documented or reported to the best of our knowledge and sources. The gene variant in the second case was already reported as pathogenic and usually had a poor prognosis. Degtyareva AV (year) highlighted in their case report that the presence of visceral symptoms serves as a crucial diagnostic indicator for the early infantile variant of Niemann-Pick disease type C [15]. Meher Lad et al. reported a 22-year-old female patient with a progressive neurological syndrome characterized by seizures, cataplexy, supra-nuclear vertical gaze palsy, cognitive decline, and swallowing difficulties, which were undefined, highlighting the involvement of the cerebrum, basal ganglia, cerebellum, and brain stem. The patient was considered to have cerebral palsy in childhood [16].

The definitive method for diagnosing NPC is demonstrating undetectable or low rates of cholesterol esterification accompanied by excess storage of free cholesterol through filipin staining in cultured fibroblasts or by detecting pathogenic mutations. Kraus et al. reported that serum alpha-fetoprotein (AFP) and liver anti-CD68 immunostaining levels were useful in diagnosing the disease within the first four months of life [17].

Miglustat, a glucosylceramide synthetase inhibitor approved for the treatment of Gaucher's disease, may delay the onset of neurological symptoms. The investigation agents employed in this study encompassed various techniques such as hematopoietic stem cell transplantation, intrauterine stem cell transfer, intracerebral transfer of neural progenitor cells (in mouse models), as well as the administration of vorinostat, N-acetyl-l-leucine, and arimoclomol [18]. Modin L reported that liver transplantation is not very successful in treating NPC [19]. Counseling was provided to the parents regarding genetic tests for the second case, but they refused. Dietary restrictions do not prevent the accumulation of lipids in cells and tissues.

## Conclusion

In early neonatal cholestasis, Niemann-Pick disease type C should be considered. The first case

underscores the genomic expansion of the disease. The second case demonstrates that the presence of consanguinity in the parents is not a prerequisite for the occurrence of the expected inborn errors of metabolism. Furthermore, it highlights the possibility of a single patient presenting with a combination of various types of disease. The prognosis was unfavorable, as it necessitated multiple therapies.

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## Ethical approval

This study obtained Ethics Committee approval.

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## Conflict of interest

There are no conflicts of interest.

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