

Case Report

Niemann-Pick disease type C-presenting as persistent neonatal jaundice: a rare case report

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ABSTRACT

Niemann-Pick disease (NPD) is an autosomal recessive lysosomal storage disorder caused by inherited deficiency of acid sphingomyelinase enzyme or its transport which leads to deposition of sphingomyelin and cholesterol in the lysosomes of reticuloendothelial system. It is characterized by failure to thrive, hepatosplenomegaly and neurodegenerative changes. There are four subgroups of Niemann-Pick disease, type A, B, C and D. Here authors are reporting a case of 5 months old female child presenting with persistent jaundice since neonatal period, progressive abdominal distention and failure to thrive. On examination patient had significant abdominal distension with moderate hepatosplenomegaly. On laboratory evaluation child diagnosed to have NPD type C. This case emphasizes the need to keep NPD in differential diagnosis of children presenting with persistent neonatal jaundice, hepatosplenomegaly, failure to thrive.

Keywords: Lipid storage disorder, Niemann-Pick disease, Persistent neonatal jaundice

INTRODUCTION

Niemann-Pick disease (NPD) is an autosomal recessive lysosomal storage disorder. It is caused by inherited deficiency of an enzyme, acid sphingomyelinase which leads to deposition of sphingomyelin and cholesterol within the lysosomes of reticuloendothelial cells of various organs.¹ It is characterized by failure to thrive, hepatosplenomegaly and neurodegenerative changes. NPD was first described by Albert Niemann in 1914. Ludwig Pick conclusively showed the tissues affected due to deposition of sphingomyelin in 1927, hence the name "Niemann-Pick disease". In 1958 Led Crocker reported that there was variability in age of onset, clinical presentation and he proposed a classification into four subgroups; types A, B, C and D.² Since the early 1980s, the Niemann-Pick disease has been divided into two main

entities, based on their metabolic defect.^{2,3} Acid sphingomyelinase (ASM) deficient Niemann-Pick disease which results from mutation in SMPD 1 gene and it includes type A and type B. Lipid trafficking defect corresponds to Niemann-Pick disease type C which results from mutations in NPC1 or NPC 2 gene. The term Niemann-Pick disease type D, a genetic isolated from Nova Scotia race, should no longer be used; it is shown to be a genetic variant of type C.^{4,5} NPD type A is acute neuropathic form usually proves fatal in infancy. Hepatosplenomegaly develops by age of 6 months. Developmental age does not progress beyond 12 months of age. A relentless neurodegenerative course with regression of milestones and seizures ensues and it usually results in death by age of 2 years. NPD type B is chronic non-neuropathic form observed in children and adults. Splenomegaly and pulmonary involvement are nervous system usually unaffected. The life expectancy

of NPD type B patient is highly variable depending on the severity of their symptoms.^{6,7} NPD type C is the most common sub-acute neuropathic form and is a progressive, irreversible disease caused by mutation in the genes NPC1 (95% of cases) or NPC2 (~4% of cases). The age of onset ranges from the perinatal period until late adult age. Clinical manifestations include jaundice, ataxia, quadriparesis, seizures, hepatosplenomegaly.⁷

CASE REPORT

A 5 months old female infant, first born of 3rd degree consanguineous marriage, late preterm (36 weeks), delivered by LSCS, 1.75kg at birth. Child was brought with complaints of persistent jaundice since 2nd day of life and progressive abdominal distention since the age of 2 months. History of poor weight gain and developmental delay were present. No history of convulsions, hematemesis, melena.

On general examination child is icteric, pallor present. All vital parameters were stable. Anthropometrically child is severely underweight. On per abdominal examination, liver was palpable for 7cm below right costal margin and it was firm, non-tender with sharp borders. Spleen was enlarged by 10cm from left costal margin along its long axis (Figure 1).



Figure 1: Picture showing massive hepatosplenomegaly.

There are no signs of free fluid in the abdomen. There was diminished deep tendon reflexes with decreased muscle tone in all four limbs. CVS and respiratory system examination were unremarkable. Ophthalmic examination was normal (no cherry red spot). Complete blood picture showed hemoglobin-8g/dl. Total count and differential counts were within normal range. Platelet count was normal. Peripheral smear was suggestive of hypochromic anemia. LFT showed Serum total bilirubin

25.23mg/dl, direct bilirubin 17.4mg/dl. SGOT-660U/L, SGPT- 340U/L, serum alkaline phosphatase 594U/L, S. albumin-2.52g/dl. PT-72.2secs, INR-6.5, Urea-36mg/dl, creatinin was 0.39mg/dl. Total cholesterol 125mg/dl, triglycerides-202 mg/dl, HDL cholesterol-6mg/dl. Alphafeto protein levels-219780 ng/dl. Urine examination was normal. USG abdomen showed moderate hepatosplenomegaly and bilateral nephromegaly with medullary cyst. Chest X-ray was normal. Liver biopsy showed chronic hepatitis with bridging fibrosis suggestive of metabolic etiology (storage disorder). Gene analysis showed homozygous missense variation in exon 2 of the NPC2 gene on chromosome 14, which is confirmatory of Niemann-Pick disease type C2.

DISCUSSION

NPD type C is a rare autosomal recessive lipid storage disorder, usually characterized by hepatosplenomegaly and severe progressive neurological dysfunction. The estimated incidence of NP-C is 1 in 120,000 live births.⁸ It occurs as a result of mutation in the NPC1 gene in the majority of patients (95%) and NPC2 gene (4%) which code for their respective proteins, NPC1 and NPC2.⁹ The two proteins are believed to be involved in transport of intracellular cholesterol. Dysfunction of these proteins leads to impaired intracellular trafficking and accumulation of unesterified cholesterol in lysosomes and late endosomes.¹⁰ Prognosis in patients with NPC disease depends on age of onset of the disease and life expectancy ranges from a few days to several decades.

NPC is best classified according to age of onset of neurological manifestations as follow:¹¹

1. Visceral- neurodegenerative form
 - Early- infantile (<2 years)
2. Neurodegenerative form
 - Late infantile (2-6 years)
 - Juvenile form (6-15 years)
3. Psychiatric-neurodegenerative form
 - Adult (>15 years)

Niemann-Pick disease type C can manifest in the pre/perineonatal age group primarily as liver disease with persistent neonatal jaundice, hepatosplenomegaly and failure to thrive. In some cases, acute liver failure with or without pulmonary disease. Early infantile form presents with neurological manifestations like delay in developmental motor milestones, hypotonia. Hepatosplenomegaly and/or neonatal prolonged jaundice almost always present. Vertical supranuclear gaze palsy (VSGP) may be present.

Late infantile form presents with ataxia, frequent falling, sensory deafness, dysarthria with delayed speech and impaired pronunciation. Focal or generalized seizures, cataplexy and vertical supranuclear gaze palsy (VSGP) are usually present.

Juvenile form presents with learning disability, decrease in scholastic performance with difficulties in writing with impaired attention and behavioral problems. Coordination problems (clumsiness, frequent falls, progressive ataxia and dystonia), VSGP may present.

Organomegaly is not usually present. Adolescent and adult onset NPC patients presents with cognitive impairment, higher rates of psychiatric illness and neurological manifestations. VSGP present.^{4,11}

Table 1: Clinical manifestations of NP-C disease by age group.³

Age <4 years	Age 4-16 years	Age >16 years
Splenomegaly (>50%) Prolonged neonatal unexplained or cholestasis jaundice (>50%) Delay of the developmental milestones (>50%) Infantile hypotonia Dystonia Dysarthria/dysphagia	Dystonia Vertical supranuclear gaze palsy Dysarthria/dysphagia Seizures, delayed development milestones, gelastic cataplexy, and ataxia Cognitive decline Splenomegaly	Vertical supranuclear gaze palsy Dystonia, Dysarthria/dysphagia Ataxia Cognitive decline Psychotic symptoms, treatment resistant Psychiatric symptoms, disruptive or aggressive behavior, and other psychiatric disorders
Majority of domain symptoms Visceral + neurological	Majority of domain symptoms Neurological + psychiatric Visceral + neurological Visceral + psychiatric	Majority of domain symptoms Psychiatric + Neurological

Apart from clinical findings, histopathological examination of bone marrow, liver and spleen showing foamy cells can help to establish the diagnosis. Filippin staining of cultured skin fibroblasts is the historical gold standard method to establish diagnosis but it is no longer considered as first line test for diagnosis of NPC.¹² Gene sequencing of NPC1 and NPC2 is currently the most universally acceptable diagnostic technique to confirm Neimann-Pick disease type C.¹³

This child presented with persistent jaundice since neonatal period, failure to thrive, and hepatosplenomegaly. Initial investigation was suggestive of liver failure of metabolic etiology. Diagnosis of NPD type C was made by molecular genetic sequencing. There is no curative therapy for NPC exist.

Symptomatic treatment may be effective in the management of seizures, dystonia and cataplexy. Miglustat is the first disease specific approved therapy for the treatment of neurological manifestations and should be initiated at the earliest signs of neurological manifestations.³

CONCLUSION

NPD should be considered in differential diagnosis of infants presenting with persistent jaundice, hepatosplenomegaly and failure to thrive. Miglustat is the only approved treatment available and should be started at the first sight of neurological symptoms in order to slow down the irreversible neurological damage. Molecular genetic testing, genetic counselling and prenatal diagnosis should be emphasized to reduce the burden of the disease in the community.

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