Case Report

Neonatal presentation of Niemann-Pick disease type C2- A rare case report.

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Abstract

Niemann Pick type C [NP-C] disease is a rare neurodegenerative lysosomal storage disorder marked by an accumulation of unesterified cholesterol in the lysosomal system. It has autosomal recessive inheritance caused by mutations in NPC1 and NPC2 genes. The broad clinical spectrum ranges from a prenatal severe manifestation to an adult-onset chronic neurodegenerative disease. The manifestations in the perinatal period and infancy are predominantly visceral, with hepatosplenomegaly, jaundice, and pulmonary infiltrates (in some instances). Patients with NP-C usually do not show neurological manifestations during the neonatal period. Herein we present a case of neonatal cholestasis with hepatosplenomegaly and anaemia, which was diagnosed as Niemann Pick disease type C2. Thus, NP-C is an important differential diagnosis of neonatal cholestasis in the presence of visceromegaly.

Keywords: Hepatomegaly, Cholestasis, Storage disorder, Neonate

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Introduction

Niemann-Pick disease (NPD) is a heterogeneous group of lipid storage disorders, with a common presentation of hepato-splenomegaly with or without neurological involvement [1,2]. It consists of two types namely, acid sphingomyelinase (ASM) deficiencies, including types A, B and intermediate forms, and lipid trafficking defect, corresponding to Niemann-Pick type C (NP-C) [3]. NP-C is a rare autosomal recessive neurovisceral lipid storage disorder, with an incidence of 1 in 120,000 live births which is characterized by the accumulation of unesterified cholesterol in the lysosomal/late endosomal system presenting as progressive, disabling neurological symptoms and premature death in most patients [4, 5]. Presentation of cases in the perinatal period and infancy are predominantly visceral, while from late infancy onward it is neurological [1]. Molecular genetic study is preferred for diagnosis. Herein, we describe a neonate with NPC-2 presented with cholestatic jaundice, anaemia, progressive hepatosplenomegaly and history of sibling death due to cholestasis.

Case Report: 28 days old full term, 2.6 kg, female baby with uneventful antenatal and birth history presented with jaundice since 10 days and an episode of convulsion 2 days before. The baby also had a refusal to feed, and decreased activity**.** History of death of elder male sibling at 2.5 months due to cholestasis was present. The baby has been admitted to another hospital

and received antibiotics, antiepileptic and a dose of Vit K. On admission, the baby was icteric, pale with depressed sensorium and bulging anterior fontanelle. The baby had a firm non-tender 4 cm hepatomegaly and 2 cm of spleen was palpable. The baby was started on oxygen, Intravenous Fluid, and intravenous antibiotics Cefotaxime and amikacin. The haemoglobin concentration of the baby was found to be 7 g/dl hence a pack of red cell transfusion was given. Orogastric tube feeds were started the next day. Arterial blood gas, Septic screening, Cerebrospinal fluid analysis, cranial Ultrasonography, ophthalmic evaluation, 2-Decho, Xray Chest was normal. Ultrasonography abdomen showed hepatosplenomegaly with the liver measuring 5.9 cm, spleen 5.4 cm and normal gall bladder. Hepatoportal doppler was suggestive of liver parenchymal disease. MRI brain revealed a left cerebral infarct with no evidence of haemorrhage, midline shift or uncal herniation. Serial Liver function tests showed increasing cholestasis. (Table 1) Hepatosplenomegaly was increasing. (Figure 1) Genetic study was suggestive of Niemann Pick disease type C2 with compound heterozygous variants with deletion of NPC2 gene located in exon 3 on chromosome 14. Genetic counselling was done, baby eventually discharged and referred for bone marrow transplant.

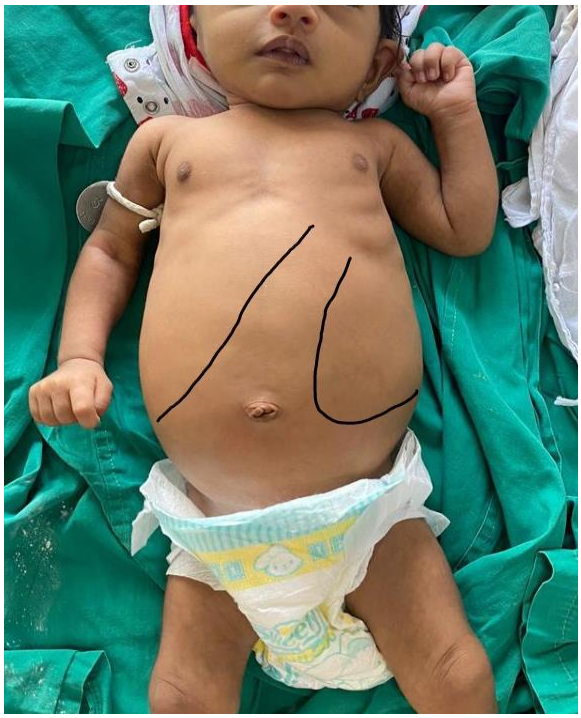

Figure 1: Abdominal distention due to hepatosplenomegaly

Table 1: Haematological and biochemical parameters of the patient.

Investigation	Result (normal range)
Haemoglobin	7.7 (14-18) g/dL
Total Leucocyte count	9.41 (4.5-11) $X10^3$ /ml
platelet count	2.67 (1.5-4) X 10^6/ ml
Serum Sodium [Na+]	125 (135-145) mEq/L
Potassium [K+]	5.6 (3.5-5.5) mEq/L
Ionic calcium	1.11 (1-1.3) mmoL/L
Serum glutamate oxaloacetate transaminase	101 (10 -35) U/L
Serum glutamate puruvic transaminase	39 (13-40) U/L
Alkaline phosphatase	1121 (35-130) IU/L
Total bilirubin	7.9 (5-15) mg/dl)
Direct bilirubin	4.5 mg/dl
Serum albumin	3.1 (3.5-5) mg/dl
γ-Glutaryltransferase	121 (5-40) U/L
Seum Lactate	1.60 (<2) mml/L
Serum Ammonia	127 (48-137) ug/dl
Serum Lactate Dehydrogenase	540 (140 -280) U/L
Serum Ferritin	698 (12-300) ng/ml
Internalised Normalised Ratio	1.4

Discussion:

Our case was very rare as the presentation is perinatal. Gradual increase in hepatosplenomegaly was the clue towards the suspicion of storage disorder. Niemann-Pick disease type C (NP-C) is caused by mutations in the NPC1 (~95% of cases), NPC2 (~4% of cases) and possibly other as yet unidentified genes (~1% of cases).[1] Apart from few babies who die at birth, or in the first 6 months of life from hepatic or respiratory failure, all patients ultimately will develop a progressive and fatal neurological disease [2]. The combined presentation of visceral, neurological and psychiatric manifestations should therefore lead to the consideration of NP-C.[3] Based on the appearance of neurological symptoms NP-C presentations are categorized as early-infantile (2 months–2 years of age), late-infantile (2–6 years of age), juvenile (6–12 years of age), adolescent/adult (>12 years of age). The perinatal form (up to 2 months) is characterised by systemic symptoms only [3, 4].

NP-C cases in pre/perinatal period can have fetal hydrops or fetal ascites [2]. Neonates can have transient jaundice to severe cholestasis without neurological manifestations [5,6]. Presence of isolated spleno- or hepatosplenomegaly should raise suspicion of NP-C [6,7]. In neonate and young infants, Niemann-Pick disease type C must be differentiated from idiopathic

neonatal hepatitis, biliary atresia, congenital TORCH infections, malignancies, tyrosinemia type I, alpha 1 antitrypsin deficiency and storage disorders [7, 8]. B. Yerushalmi et al.in his study has observed that NPC was the most common (7.5%) metabolic/genetic disorder presenting as neonatal cholestasis during a 2-year period. Neurologic abnormalities also developed by 12 to 24 months of life including mild hypotonia and delay in gross motor skills [9]. Narayana et al reported a case of 5 months old female child presenting with persistent neonatal jaundice diagnosed as NPC with homozygous missense variation in exon 2 of the NPC2 gene [10].

Imrie et al, observed a total of 146 patients with NP-C amongst which 116 had at least one identified, disease-causing NP-C gene mutation, 114 had NPC1 and 2 cases had NPC2 mutations. 6 patients had an early, non-neurological neonatal onset form of NP-C with hepatic disease [4]. Our patient had a neonatal presentation with cholestatic jaundice, anaemia and splenohepatomegaly with a significant history of sibling death due to cholestatic liver disease. The progressive increase in splenohepatomegaly and deteriorating liver functions narrowed down the differential diagnosis to storage disorders. A genetic study confirmed the diagnosis of Niemann-Pick disease type C2.

In the absence of cholestasis or hypersplenism cases of NPC, may have normal results for routine lab studies. [9,10] Filippin staining of cultured skin fibroblasts is the historical gold standard test is no longer considered as a first line test for the diagnosis [10]. Other tests, including tissue biopsies and tissue lipid analysis, are now rarely needed. Mutation analysis of NPC1 and NPC2 genes is mandatory to confirm the diagnosis of NPC as a carrier case and as a prenatal diagnosis [10]. MRI of the brain is usually normal until the late stages of the illness and can show marked atrophy cerebellar vermis, thinning of the corpus callosum [1].

To date, management remains largely symptomatic [2]. Miglustat (N-butyldeoxynojirimycin), a substrate reduction therapy, is the only licensed disease-modifying medicine which may benefit only in cases with neurological manifestations [2]. Hematopoietic stem cell transplantation is an emerging therapy in NPC2 patients [2].

The lifespan of the patients varies between a few days until over 60 years of age, although a majority of cases die between 10 and 25 years of age. [2] The systemic disease can be fatal in early infancy with majority of babies die due to severe pulmonary insufficiency. [2]

Consent

Written informed consent was obtained from the mother of the baby for publishing medical information and photograph of the baby.

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