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CASE REPORTS

NEONATAL HEMOCHROMATOSIS - A FULMINANT CAUSE OF NEONATAL CHOLESTASIS

Drishti Tolani[1], Javed Ahmed[2], Khushnuma Mullanfiroze[1], Ira Shah[1,2].

[1]Pediatric Liver Clinic, B. J. Wadia Hospital for Children, Mumbai, Maharashtra, India,
[2]Pediatric Department, Nanavati Hospital, Mumbai, Maharashtra, India.

ABSTRACT

Neonatal hemochromatosis (NH) due to Gestational alloimmune liver disease (GALD) is a rare form of fulminant liver disease of unknown cause characterized by diffuse deposition of iron in the liver and extra hepatic sites without any evidence of increased iron intake. Neonatal cholestasis is characterized by persistent elevation of conjugated bilirubin. It can be caused by infections, biliary atresia, by toxins or by metabolic disorders of the liver. GALD is rarely reported as a cause of fulminant neonatal cholestasis. We present three cases of infants who presented with neonatal cholestasis and were found to have NH as well.

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Case Report

Neonatal hemochromatosis (NH) is a rare and severe disorder characterized by excessive iron deposition in liver and extra hepatic sites. It is characterized by neonatal liver failure with an in utero onset.[1] Gestational alloimmune liver disease (GALD) is a leading cause of NH. The pregnancy may be complicated either by oligohyraminous or growth retardation and sometimes may cause stillbirth.[2] Neonatal cholestasis is defined as the prolonged elevation of serum levels of conjugated bilirubin beyond the first 14 days of life. The overall incidence of neonatal cholestasis is estimated to be 1 in every 2500 live births.[3] The most common causes of neonatal cholestasis include biliary tract anomalies of which biliary atresia is the commonest, metabolic disorders of the liver, infections or it may be idiopathic.[4] A study has shown metabolic disorders of the liver to contribute to 8.6% of the total cases of neonatal cholestasis.[5] Amongst the metabolic disorders causing neonatal cholestasis, alpha-1-antitrypsin deficiency is the commonest; others include tyrosinemia, galactosemia, and hypothyroidism, inborn errors of bile acid metabolism, Alagille syndrome. Though NH can cause neonatal cholestasis, however it is not listed as a common metabolic cause of neonatal cholestasis.[6] We report three cases of infants who fit the diagnostic criteria for NH and were found to have fulminant neonatal cholestasis without evidence of any other etiology of cholestasis.

Case 1: A 1 month old boy born of non consanguineous marriage presented with jaundice and high coloured urine since birth, progressive abdominal distension for 15 days and blood in stools since yesterday. There is no clay coloured stools. Mother had no fever or rash during pregnancy. On examination, there is jaundice with anasarca and splenomegaly. Child was altered with left sided hemiparesis. Investigations are depicted in Table 1. Ultrasound abdomen (USG) showed splenomegaly. Urine aminoacidogram showed increased cysteine. Serum alpha fetoprotein was normal. TORCH titres were negative. Triglycerides were normal and Fibrinogen was< 45 ng/ml. He was treated with fresh frozen plasma, lactulose, metronidazole and intravenous fluids. Child subsequently died next day before any further tests could be done.

Case 2: A 2 day old newborn was referred to for evaluation of conjugated hyperbilirubinemia. He was born of a full term normal delivery of a non-consanguineous marriage. He weighed 3.5 kg and had cried immediately after birth. On examination, he was deeply jaundiced with hepatosplenomegaly. Investigations are depicted in Table 1. Serum bilirubin kept fluctuating between 31.5 to 54.40 mg/dl throughout the admission. TORCH serology was negative. Blood and urine culture were negative. Serum triglycerides (150 mg/dl) and fibrinogen (262 mg/dl) were normal. Total serum iron was high (238 mg/dl, Normal - 76-198 g/dl) with total iron binding capacity (TIBC) of 289g/dl (Normal - 262-474 g/dl) and reduced transferrin saturation (24.7%, Normal - 25-35%). MRI of abdomen showed iron deposits in liver and spleen but not in the pancreas. He was started on N -acetylcysteine, Vitamin E, prostaglandin E, deferoxamine, fresh frozen plasma but he continued to remain jaundiced and stared developing edema and ascitis on day 4 of admission along with increasing serum ferritin. He developed respiratory distress and had to be ventilated following which he died due to a pulmonary bleed on Day 5 of hospitalization. Intravenous immunoglobulin (IVIG) could not be given due to non-affordability. Postmortem, parents refused a liver biopsy or a buccal biopsy.

Case 3: A 2 ½ months old boy, first by birth order, born of non-consangineous marriage presented

Address for Correspondance: Dr Drishti Tolani, Division of Pediatric Cardiology, The Children's Hospital of Michigan, Detroit, MI, USA.
Email: drishtolani@hotmail.com

Table 1. Investigations of all the patients

Investigations	Patient 1	Patient 2	Patient 3
Hemoglobin (gm/dl)	10.1	13.3	6.9
White cell count (cells/cumm)	5,700	26190	8500
Platelets (cells/cumm)	62,000	5000	22000
Bilirubin (mg/dl) (direct)	26.1 (9.3)	41.9 (31.8)	5.9 (3.4)
SGOT (IU/L)	236	258	405
SGPT (IU/L)	73	257	265
Total proteins (gm/dl)	4.5	5.3	2.7
Albumin (gm/dl)	2.7	2.3	1.0
Prothombin time (sec)	Prolonged	22.8	>60
Partial thromboplastin time (sec)	Prolonged	35.8	>120
Alkaline phosphatase (IU/L)		160	397
GGTP (IU/dl)		40	415
Ammonia (mmol/L)	305	-	120
Thyroid function tests	Normal	Normal	
Serum Ferritin (mg/dl)	10,915	3980 (increased to 5400 after 3 days)	4511

with progressive abdominal distension and jaundice of four days. Child was also feeding poorly, was irritable & was passing clay coloured stools. There was no history of bleeding from any site, lethargy or convulsions. Antenatally mother was diagnosed to have oligohydramnios during the last trimester. Child had been diagnosed with hypoxic ischemic encephalopathy (HIE) stage I during the immediate postnatal period though the child had developed normally this far. The child had not thrived well (Birth weight 2.5 kg & current weight 3.4 kg). On examination, he had jaundice, pallor, hepatosplenomegaly with brisk deep tendon reflexes. Investigations are depicted in Table 1. Urine examination showed 2+ albuminuria and 4+ sugar with simultaneous blood sugar of 204 mg/dl. GALT enzyme levels were normal. Urine aminoacidogram was normal and urine and plasma succinyl acetone levels were normal. Serum alphafeto protein level was 16,069 microgm/L. USG & MRI of the liver were not undertaken in view of unstable clinical condition. He was started on N -acetylcysteine, Vitamin E, deferoxamine but he died within 24 hours of admission to the hospital. Postmortem liver biopsy showed preserved architecture, with no necrosis or inflammation. Prussian blue staining showed hemosiderin in kuffper cells.

Discussion

NH is a rare disorder and in literature >100 cases have been reported however very little information about the exact incidence of the disease is available.[2] However it has been reported as the most common cause of liver failure in infants.[2,7] The exact etiology and pathogenesis of NH is yet unknown. It is often considered as a syndrome caused by various primary etiologies including infection, genetic, metabolic diseases and toxic insults. The most recent and common hypothesis for NH is that it is a consequence of GALD.[7] NH may arise from non-GALD etiologies, including perinatal infection, trisomy 21, mitochondrial DNA depletion due to deoxyguanosine kinase deficiency (DGUOK gene mutations), bile acid synthetic defect (SRD5B1 mutations), GRACILE syndrome (BCS1L mutation), myofibromatosis, tricho-hepato-enteric syndrome, and Martinez–Frias syndrome.[8] The infants commonly present with symptoms of liver failure and usually also of multiorgan failure.[7] NH is characterized by hepatocellular failure often appearing from the first day of life along hypoglycemia,marked coagulopathy, hypoalbuminemia and edema with or without ascites and oliguria.[7,9] Jaundice commonly develops a few days after birth and in most infants, there is significant elevations in the levels of both conjugated and unconjugated bilirubin.[7] No other disease of the newborn demonstrates the combination of liver disease and extra hepatic siderosis[7]; therefore, these two findings together are diagnostic of neonatal hemochromatosis. In literature, a case report of two siblings suffering from neonatal haemachromatosis has been reported both of whom had symptoms of cholestatic jaundice and hepatoslenomegaly which appeared after 30 days and caused progressive liver failure leading to their death within a few months.[8] In all our patients, serum ferritin was elevated and in our third patient, liver biopsy was suggestive of iron deposition. We were not able to depict extrahepatic iron deposition in first and third patient, but the second patient did have iron deposition in spleen on MRI apart from hepatic deposition. In the third case the mother in addition presented with oligohydraminous.

The outcome of neonatal cholestasis is increased by prompt diagnosis and treatement of the underlying etiology.[6] The initial medical treatment plan for neonatal hemachromatosis included combination of cheating agents and antioxidants.[1] Based on the alloimmune mechanism, treatment of GALD has switched from

conventional cocktail therapy to the combination of exchange transfusion (ET) and IVIG while saving liver transplantation for refractory cases. ET acts to remove existing reactive antibody, and IVIG blocks antibody-induced complement activation.[10] Overall neonatal hemochromatosis has a poor prognosis. Studies have been successfully reported that maternal treatment with high doses of immunoglobulins during pregnancy drastically improves the prognosis of neonatal hemochromatosis in future pregnancies.[11] This treatment is based upon the recent hypothesis of an alloimmune mechanism for the development of the disease and involves treatment with immunoglobulins on a weekly basis from the 18th week of gestation till term.[11]

Conclusion

Neonatal hemachromatosis can be considered as a cause of fulminant neonatal cholestasis. Prompt diagnosis and treatment is necessary in such cases.

Compliance with Ethical Standards

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