Neonatal hemochromatosis: a case report with unique presentation

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Acute liver failure (ALF) is a relatively rare condition in neonates, and early diagnosis and treatment are crucial for the treatable conditions. Neonatal hemochromatosis (NH) is a rare clinical condition that is clinically defined as severe neonatal liver disease associated with hepatic and extrahepatic iron deposition in a distribution similar to that seen in hereditary hemochromatosis. Although a few cases have been reported with spontaneous remission, early and aggressive medical treatment is essential for improving the outcome. Despite aggressive treatment, some patients may require liver transplantation. We report a five-day-old male infant with NH and associated Duarte variant galactosemia, renal tubulopathy and hypertyrosinemia, who was successfully treated with combination medical treatment. Combination therapy may reduce the need for liver transplantation in infants with NH. Early diagnosis and aggressive treatment are important as in galactosemia or tyrosinemia for the outcome. Thus, NH may be listed as a treatable cause of ALF in neonates.

Key words: acute liver failure, newborn, hemochromatosis, hypertyrosinemia, treatment.

Acute liver failure (ALF) is a relatively rare condition in neonates. Etiological factors include metabolic, infectious and hematological disorders, congenital vascular/heart abnormalities and drugs¹. Onset of liver failure may differ, in that metabolic disorders or infectious disease may produce liver failure in weeks to months after birth, whereas some diseases may affect the fetus². As in adults and older children, the main symptoms are jaundice and encephalopathy, which is very difficult to diagnose and prove in neonates. Early diagnosis and treatment are crucial for the treatable conditions such as galactosemia, tyrosinemia and fatty acid oxidation defects, since identification of these disorders may lead to clinical improvement if treatment is initiated quickly.

Neonatal hemochromatosis (NH), neonatal iron storage disease, is a rare clinical condition that is clinically defined as severe neonatal liver disease associated with hepatic and extrahepatic iron deposition in a distribution similar to that seen in hereditary hemochromatosis³. Apart from iron deposition, perinatal onset and alloimmune liver injury are distinctive features of NH from other causes of ALF in the newborn period⁴. Although a few cases have been reported with spontaneous remission, early and aggressive medical treatment is essential for improving the outcome. Despite aggressive treatment, some patients may require liver transplantation³.

The diagnosis of NH is made by laboratory (elevated ferritin and transferrin saturation and alpha-fetoprotein), clinical (ALF and hypoglycemia) and radiological (iron deposition in the liver and extrahepatic sites) findings in addition to exclusion of other causes of neonatal-onset ALF³. Some laboratory findings such as hyperphenylalaninemia, hypermethioninemia and hypertyrosinemia and some clinical conditions such as renal tubular dysgenesis, tricho-hepato-enteric syndrome have been reported in association with NH³,⁵.
In this manuscript, we report a typical case of NH and associated Duarte variant galactosemia, renal tubulopathy and hypertryrosinemia who was successfully treated with combination medical treatment. We discuss the associated conditions, medical treatment options and outcome of NH.

Case Report

A five-day-old male infant was admitted to our neonatal unit with the complaints of umbilical hemorrhage and jaundice. He was born from a gravida 2, para 1 (G2P1) mother at 38 weeks of gestation. There was no parental consanguinity or family history of metabolic disorders or liver disease. The first pregnancy was terminated with curettage in the early period. The current patient had a birth weight and length of 3150 g and 50 cm, respectively. He was breastfed and there was no history of vomiting, diarrhea, pale-colored stool, or convulsion. Physical examination revealed jaundice and mild ascites. No hepatosplenomegaly or dysmorphic feature was observed.

Initial laboratory examination revealed hemoglobin 14.1 g/dl, white blood cells 8600/mm³ and thrombocytes 142000/mm³. Serum glucose was 29 mg/dl, aspartate aminotransferase 797 U/L (10-38), alanine aminotransferase 130 U/L (10-41), total/direct bilirubin 15.6/9.3 mg/dl, gamma glutamyl transferase 22 U/L (5-61), alkaline phosphatase 1198 U/L (35-130), and albumin 2.6 g/dl (3.4-4.8). Coagulation parameters showed that prothrombin time was 27.3 seconds and international normalized ratio (INR) was 3.54. Fibrinogen level was 125 mg/dl (200-400). Blood gas analysis was normal. Serum ammonia and lactate levels were 27 Umol/L (15-55) and 26.5 mg/dl (4.5-19.8), respectively. Urine analysis revealed pH 5.5 and density 1005, and protein and glucose were negative. Urinary reducing substance was slightly positive. Tubular phosphate reabsorption was 75% (65% in the second examination). The lipid profile was normal. Ophthalmic examination for cataract was negative. Echocardiography revealed secundum type atrial septal defect.

Serum alpha-fetoprotein level was 350,900 ng/ml (normal range: 50000-100000 ng/ml), and tandem mass and urinary organic and amino acids were sent for metabolic examination. Alpha-1 antitrypsin level was <20 ng/ml (90-200 ng/ml), but alpha-1 antitrypsin deficiency was ruled out by MM genotype. Studies for infectious diseases including viral hepatitis B, hepatitis C, cytomegalovirus, Epstein-Barr virus, adenovirus, and herpes simplex virus were non-diagnostic.

The iron panel was studied for neonatal NH and revealed high ferritin levels: 21769 ng/ml and 21960 ng/ml (normal range: 47-554 ng/ml) in the second examination, and transferrin saturation was 99%. Abdominal magnetic resonance imaging (MRI) examination documented decreased T2 signal intensity of hepatic parenchyma and pancreas relative to the spleen, suggesting hemochromatosis (Fig. 1).

A diagnosis of NH was made based on clinical (hypoglycemia and ALF), laboratory (high ferritin and transferrin saturation) and radiological examination (decreased T2 signal intensity of hepatic parenchyma and pancreas) in addition to the exclusion of other etiologies. However, the abnormal clotting profile precluded the confirmation of diagnosis by liver biopsy.

Exchange transfusion was performed for NH with the objective of removing maternal alloantibodies, followed by intravenous immunoglobulin (IVIG) administration (1 g/kg). A prominent decrease was observed in ferritin levels (decrease to 1000 ng/ml) and coagulation parameters within three
days, but they began to increase thereafter. He was listed for liver transplantation due to severe coagulopathy (INR: 2.24 despite 3 fresh frozen plasma/per day) and cholestasis (total bilirubin: 16 mg/dl). As a last resort, an antioxidant cocktail including vitamin E (25 IU/kg/day, orally), N-acetylcysteine (100 mg/kg, intravenously) and selenium (3 µg/kg, orally) in addition to deferoxamine (30 mg/kg/day, intravenously) was begun. Ferritin levels begin to decrease gradually and were <500 ng/ml at the end of three weeks. Coagulopathy and cholestasis were improved, and the patient was discharged on day 35 (Fig. 2).

During the hospitalization period, plasma and urine amino acid profile and urinary organic acids analysis were reported. Only plasma tyrosine level was high [749 uM (normal: 13-200)], but other metabolites including methionine and phenylalanine were within the normal limits. Urine amino acid profiles revealed generalized aminoaciduria. On the other hand, one week later, urine succinylacetone was reported as negative. Based on these findings, we ruled out tyrosinemia. Plasma acylcarnitine profile was also normal. Erythrocyte galactose-1-phosphate uridylyltransferase level was low [1.93 U/g Hb (>3.0)] and total galactose level was high [18 mg/dl (<10)]. During this period, the patient was fed with lactose-free diet for three days, thereafter discontinued because of absence of cataract, negative urinary reducing substance and absence of GALT mutation analysis for the classic galactosemia (Q188R, N314D and S135L). He only had Duarte variant (D2) (homozygote N314D mutation).

The patient is now 6 months of age and is being followed in the outpatient pediatric hepatology clinic in good condition. Ferritin levels were 267 ng/ml, liver enzymes were mildly increased and liver function tests were normal at the final visit. Liver biopsy revealed mild fibrosis and mild cholestasis with multinuclear hepatocyte formation and negativity for iron staining (Fig. 3).

Discussion
In this manuscript, we report a newborn with NH successfully managed with medical treatment. Additionally, he had renal tubulopathy and high tyrosine levels that led us to suspect the diagnosis of NH. Although elevated ferritin levels and transferrin saturation, iron deposition in the liver and pancreas and additional findings support the diagnosis of NH, hepatic iron deposition may also be seen in bile acid synthesis defects, neonatal lupus, echovirus infections, mitochondrial cytopathy, and tyrosinemia. Additionally, high alpha-fetoprotein levels, high tyrosine levels and tubulopathy supported the diagnosis of tyrosinemia. Nevertheless, urine succinylacetone was reported as negative. Mackay et al. reported that elevated tyrosine and methionine levels, particularly an increased tyrosine/serine ratio, should alert the physician for NH after excluding the inborn errors of metabolism during newborn screening programs. ALF, hypoglycemia and tubulopathy may be seen in classical galactosemia, but absence of cataract and GALT mutation in addition to negative urinary reducing substance ruled out the diagnosis. This patient had Duarte variant (D2)
galactosemia. It is a mild to asymptomatic condition that results from partial impairment of galactose-1-phosphate uridylyltransferase. Tubulopathy is uncommon in these patients.

Although we did not perform renal biopsy, we thought that the renal tubulopathy in our patient was mainly related with NH. It was shown that severe proximal tubular dysgenesis due to decreased hepatic angiotensinogen synthesis may be seen in NH.

Medical treatment must be initiated as early as possible after the diagnosis of NH is made. Although spontaneous remission has been reported in a few cases, most infants do not survive without treatment. Medical treatment includes antioxidant cocktail in addition to iron chelator, IVIG and double volume exchange transfusion. Patients unresponsive to these treatment options must be listed for liver transplantation.

Maternal alloimmunity directed to the fetal liver hepatocytes is the main hypothesis for NH. Therefore, double volume exchange transfusion and/or IVIG may have lessened the severity of liver injury. Rand et al. compared the effect of exchange transfusion and/or IVIG with their historical patients who received antioxidant-chelator therapy, and they found that exchange transfusion and/or IVIG improved the outcome (75% vs. 17%) and reduced the need for liver transplantation in infants with NH. Early treatment is the major prognostic factor for the outcome. However, we performed exchange transfusion and IVIG in our patient within the first week of life, and we only had a transient response. It may be related to the fact that our case had more severe disease (high ferritin and INR levels) compared to the cases of Rand et al.

The success of antioxidant cocktail with iron chelator has been reported as 10-20%. Some authors reported that this treatment regimen has no effect especially in severe cases, and additionally, it has been suggested that the use of iron chelator may potentiate bacterial growth. Contrary to previous reports, Grabhorn et al. reported 16 infants with NH, and 4 of 5 patients survived with exclusive antioxidant-chelator therapy. However, none of these studies are randomized controlled studies, and it is therefore impossible to make a definite decision about the effectiveness of antioxidant-chelator therapy. After exchange transfusion and IVIG, we listed the patient for liver transplantation and prescribed antioxidant-chelator therapy as a last resort. Clinical and laboratory improvement was achieved within two weeks, and the patient was discharged from the hospital on day 35. In our opinion, after removing or neutralizing antibodies with exchange transfusion and IVIG, antioxidant-chelator therapy protects against oxidant injury more effectively.

Liver transplantation is the last option for patients who do not respond to medical therapy. Rodrigues et al. reported King’s College experience about liver transplantation in NH, and long-term survival was found as 50%. Cadaveric donor for an infant is very limited in our country, although living-related liver transplantation is quite difficult in small infants.

In conclusion, although it cannot be concluded from a single case report, exchange transfusion and IVIG followed by antioxidant-chelator therapy may be used for NH when cadaveric donors are limited. Combination therapy may reduce the need for liver transplantation in infants with NH. Early diagnosis and aggressive treatment are important for the outcome as in galactosemia or tyrosinemia. Thus, NH may be listed as a treatable cause of ALF in neonates.

REFERENCES


