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Case Report

Hemochromatosis Presenting with Ascites in a Newborn Infant

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ABSTRACT

Background: Although the incidence of neonatal hemochromatosis (NH) is not known exactly, it is one of the causes of acute liver failure in the newborns. NH is a rare iron metabolism disease characterized by excessive iron accumulation in the tissues that onsets in-utero. Here, a patient diagnosed with NH who developed ascites while investigating the etiology of cholestasis has been presented.

Case report: A 35-week-old premature female baby was referred us to investigate the etiology of cholestasis. She had a sibling who died at 34 days of age due to liver failure. Abdominal examination revealed a palpable liver 4 cm from the costal margin. On laboratory, aspartate transaminase was 111 U/L (range 9-80), alanine transaminase 62 U/L (range 8-32), total bilirubin 12.6 mg/dL, and direct bilirubin 5 mg/dL. Prothrombin time was 18.4 sec (range 10-14) and INR 1.86 (range 0.8-1.2). Magnetic resonance imaging revealed a diffuse reduction in liver density due to iron accumulation. Focal iron accumulation consistent with NH was observed in hepatocytes in liver biopsy. In the clinical follow-up, the patient developed abdominal distension. Abdominal ultrasonography showed excessive fluid accumulation in the abdominal cavity. Following intravenous immunoglobulin (1g/kg, single dose) and antioxidant cocktail, her abdominal distension subsided and liver function tests regressed. The patient has been discharged on the postnatal 67th day with planned liver transplantation.

Conclusion: Neonatal hemochromatosis should definitely be kept in mind in newborns with hepatic failure. As seen in this case, NH should also be considered in the differential diagnosis of ascites in newborn infants.

Keywords: Ascites, Acute liver failure, Neonatal cholestasis, Neonatal hemochromatosis

Introduction

Neonatal hemochromatosis (NH) is a very rare disease that onsets in the intrauterine period and leads to liver failure in the neonatal period as a result of intrahepatic iron accumulation. However, its incidence is not known exactly. NH is also called “neonatal iron storage disease” due to abnormal iron accumulation in intrahepatic and extrahepatic tissues and “congenital hemochromatosis” due to its antenatal onset (1). Siderosis is also seen in many organs other than the liver, such as the pancreas, heart, and small salivary glands (2). Prematurity, intrauterine growth retardation, and maternal oligohydramnios are seen in most of the patients (3). The disease manifests itself with coagulopathy, hypoglycemia, hypoalbuminemia, hypofibrinogenemia, thrombocytopenia, anemia, direct and indirect hyperbilirubinemia, which can be seen from the first day of life (4). In severe cases, the prognosis is usually very poor; the average life expectancy of such cases is limited to days to a few weeks (1). A female newborn patient with a diagnosis of NH who was referred to us to investigate the etiology of cholestasis and who developed ascites in her clinical follow-up, has been

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presented as an educational case.

Case report

A 35-week-old premature female baby, who was born by cesarean section as the 4th live birth from the 4th pregnancy of a 35-year-old mother, was admitted to the neonatal intensive care unit due to respiratory distress. The patient who developed cholestasis in her clinical follow-ups was referred to us for further examination and treatment. In her history, it was learned that a sibling born from the mother's first pregnancy died at 34 days of age due to liver failure. In the family history, there was a second degree cousin marriage between the parents. Her weight was 2100 g (50th centile), height 45 cm (25-50th centile), and head circumference 33 cm (25-50th centile). Abdominal examination revealed a palpable liver 4 cm from the costal margin. Cardiac examination revealed a 2/6 systolic murmur in the pulmonary focus, and echocardiographic examination showed atrial septal defect. Other systemic examinations including ophthalmological findings were normal. The baby's blood group was 0 Rh (-) and the direct Coombs test was negative. The initial laboratory results have been presented in Table 1. Blood amino acids, tandem mass, and urine organic acids tests for metabolic analysis were all normal. TORCH panel and alpha-1 antitrypsin tests were also normal. Serum ferritin was high (2530 ng/mL, range 25-200) and alpha fetoprotein value was normal (24760 ng/mL, range 105-226.000). Abdominal ultrasonography revealed hepatomegaly and edema in the gallbladder wall.

In the clinical follow-up, the patient developed feeding intolerance and abdominal distension (Figure 1). Antibiotic treatment was started because the C-reactive protein value was high. Excess fluid accumulation in the abdominal cavity was observed on direct abdominal X-ray (Figure 2).

Table 1. The patient's initial laboratory results

Laboratory parameter	Result	Normal Range
Hemoglobin	9.4 g/dL	14-24
White blood cell	$4.34x10^3/mm^3$	9.0-30.00
Platelet	$51x10^3/mm^3$	150-400
Urea	14 mg/dL	3-12
Creatinine	0.34 mg/dL	0.55 ± 0.24
Aspartate transaminase	111 U/L	9-80
Alanine transaminase	62 U/L	8-32
Total bilirubin	12.6 mg/dL	
Direct bilirubin	5 mg/dL	
Albumin	2.7 g/dL	2.5-3.9
Ammonia	107 µmol/L	< 110 µmol/L
Prothrombin time	18.4 sec	10-14
International normalized ratio	1.86	0.8-1.2
Activated partial thromboplastin time	47 sec	25-45
Fibrinogen	228 mg/dL	200-400

Figure 1. General appearance of the patient. Note the abdominal distension

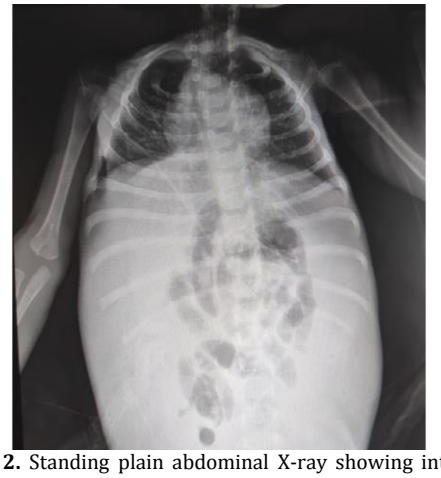

Figure 2. Standing plain abdominal X-ray showing intestinal loops gathered in the midline due to ascites

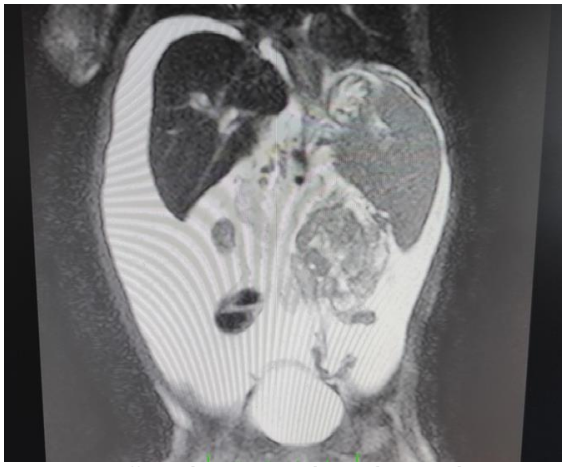

Figure 3. Diffuse decrease in liver density due to iron accumulation on T2-weighed abdominal magnetic resonance imaging

and then on abdominal ultrasonography. Then, diagnostic paracentesis has been performed; paracentesis fluid was in favor of transudate. Microbiological evaluation of peritoneal fluid was unremarkable. T2-weighted magnetic resonance imaging (MRI) of the abdomen revealed a diffuse reduction in liver density due to iron accumulation (Figure. 3). Since the buccal mucosal biopsy was normal, the patient underwent liver biopsy, which revealed focal iron accumulation in hepatocytes consistent with NH (Figure 4).

Intravenous immunoglobulin (IVIG, 1 g/kg single dose) and antioxidant cocktail (N-acetyl cysteine, desferrioxamine, selenium, vitamin E, prostaglandin E1) treatment has been initiated to the patient, who had previously been given ursodeoxycholic acid and vitamin supplements. Following this treatment, abdominal distension decreased and liver function tests regressed. The patient has been discharged on the postnatal 67th day with planned liver transplantation. The patient, who is waiting for liver transplantation, is now 21 months old and her outpatient follow-up continues. Written informed consent for publication has been obtained from the patient's parents.

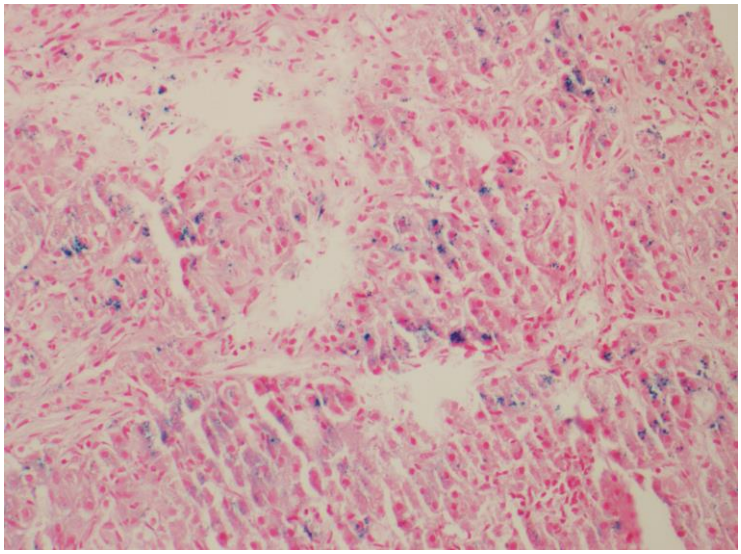

Figure 4. Iron accumulation in the liver (Prussian blue, x400 original magnification)

Discussion

Inborn error of metabolism, viral and perinatal infections, hypotension, shock, hematological disorders, congenital leukemia and familial hemophagocytic lymphohistiocytosis in neonatal period may cause liver failure in early childhood.

Liver failure in the first 30 days of life is rare and the proportion of neonates in liver transplantation is 2%. However, among these patients, NH is one of the most common causes of liver failure. Liver failure occurs after a few weeks due to metabolic and infectious diseases, while NH presents earlier due to its in-utero onset (1,5).

Neonatal hemochromatosis was first described in 1957 and higher than 100 cases have been reported. Although its etiopathogenesis cannot be fully explained, it has an aggressive course and poor prognosis (5). The disease is called "neonatal iron storage disease" due to abnormal iron accumulation in the liver and other tissues, and "congenital hemochromatosis" due to its antenatal onset. In addition to extensive iron accumulation in the liver, NH is characterized by extrahepatic siderosis, which can affect many other organs such as the heart, pancreas, and small salivary glands (1,6).

Gestational alloimmune liver disease (GALD) has been identified as the cause of fetal liver injury resulting in NH. Gestational alloimmune liver disease is an immunoglobulin G (IgG)-mediated disorder like other maternofetal alloimmune diseases. Maternal IgG antibodies are actively transported to the fetus via the placenta at the 12th gestational week, when neonatal Fc receptors are first expressed. However, although there are IgG antibodies against the paternal blood cells in gestational alloimmune diseases such as Rh and/or ABO incompatibility and alloimmune thrombocytopenia, those are directly against fetal hepatocytes in GALD. In NH, hepatocyte cell surface antigen appears to be an alloimmune target. This process explains the mechanism of liver failure caused by excessive iron accumulation in the damaged fetal liver by alloimmunization (7).

After NH delivery, there is a 60-80% probability of giving birth with NH again in other subsequent pregnancies of the mothers. In pregnant women who had healthy children before, the rate of recurrence of the disease increases again after delivery with NH. In addition, it has been found that the disease can also recur in children of the same woman from different partners (8). Based on these data, NH is considered a congenital and familial disease, but not an inherited disorder. In our patient, the symptoms of the disease appeared immediately after birth and the history of a sibling who died with a similar disease is consistent with this definition.

While siderosis is mostly seen in hepatocytes in NH, Kupffer cells are relatively spared. However, siderosis may also occur in non-hepatic tissues. Among these, the follicular epithelium of the thyroid, myocardium, pancreatic acinar epithelium, respiratory system and small salivary glands in the oronasopharynx are the most affected tissues (9). Oral mucosal biopsy is a common approach to demonstrate glandular tissue siderosis. In a study, hemosiderosis was demonstrated in the acinar epithelial cells of the minor salivary glands in all 30 cases of autopsy-proven NH (10). In another study, it is recommended to use oral mucosal biopsy to confirm the diagnosis in cases that clinical and laboratory findings are compatible with NH (11). However, oral mucosal biopsy was normal in our patient.

In the diagnosis of NH, the magnetic susceptibility difference of normal and iron-loaded tissue on T2-weighted MRI may show siderosis, especially in the liver and pancreas. Therefore, MRI is specific and sensitive in detecting iron accumulation. As seen in the case presented here, a decrease in signal in the liver and pancreas is typically seen in MRI in hemochromatosis (12). MRI is an efficient and non-invasive method for the quantitative evaluation of iron accumulation. However, only 60% of NH patients are diagnosed with MRI (13).

Babies with NH are generally premature or small for gestational age. Intrauterine growth retardation, oligohydramnios, placental edema and sometimes polyhydramnios may occur during pregnancy (14). Laboratory findings of the disease include hypoglycemia, coagulopathy, hypoalbuminemia, edema, ascites, oliguria, low serum fibrinogen level, thrombocytopenia and anemia. The patients have clinical signs of culture-negative sepsis. Jaundice is seen in the first few days postnatally. Most patients have both direct and indirect bilirubin elevations. Serum total bilirubin level often exceeds 30 mg/dL in untreated patients. Low serum transaminase levels, which are proportional to the degree of liver damage, are characteristic of the disease (1). Similarly, our patient had a history of premature birth and low birth weight, and had both indirect and direct hyperbilirubinemia, coagulopathy, thrombocytopenia and anemia at the time of admission. During clinical follow-up, the patient developed clinical signs of culture-negative sepsis and ascites.

NH is a disease with a poor prognosis that is difficult to treat. The success rate of current treatments is generally low. Treatment with an

antioxidant cocktail (vitamin E, N-acetylcysteine, selenium, prostaglandin E1), known as antioxidant therapy, and desferroxamine as an iron chelator are frequently used in treatment (2). It has been reported that the rate of treatment success varies between 10-20% with this protocol (9). On the other hand, the success rate of chelation-antioxidant therapy applied by Grabhorn et al. (15) in 14 patients diagnosed with NH is 25%. In a different study, it was reported that there were cases with spontaneous recovery (16). In addition, after it was determined that the pathophysiology of NH was associated with GALD, a treatment protocol was developed that includes double volume blood exchange with the aim of eliminating reactive autoantibodies, and then administering IVIG at a dose of 1 g/kg in order to block the antibody-induced complement activity (13). We did not perform exchange transfusion in our patient; however, IVIG and cocktail treatment was given.

Conclusion

NH is a rare but important disease of the newborn that often onsets in-utero and causes liver failure in the first few months postnatally. NH should definitely be kept in mind in newborn patients with hepatic failure. To our knowledge, our patient is the first newborn patient who developed ascites due to NH.

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None.

Conflicts of interest

The authors declared no conflict of interest.

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