The effect of prenatal and postnatal treatment with intravenous immunoglobulin on severity of neonatal hemochromatosis: the tale of two brothers (case report)

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Case report

Keywords: Neonatal hemochromatosis, Intravenous immunoglobulin, prenatal treatment

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Abstract

Background: Neonatal hemochromatosis (NH) is a rare condition that was the main reason for liver transplantation in infants. With the realization that NH results from the fetal complement-mediated liver injury, intravenous immunoglobulins (IVIG) were successfully introduced for the treatment.

Case Presentation: We present two cases of NH from the same family to illustrate the role of antenatal treatment with IVIG in alleviation and possible prevention of this serious morbidity.

Conclusion: A prenatal treatment and early postnatal administration of IVIG are effective ways to manage NH that help to reduce the severity of the symptoms, prevent liver failure and avoid the need for liver transplantation Keywords: Neonatal hemochromatosis, Intravenous immunoglobulin, prenatal treatment

Background:

Neonatal hemochromatosis (NH) is a rare condition that presents with early liver failure accompanied by hepatic and extrahepatic iron deposition (sideration)[1]. For many years NH was the main reason for liver transplantation in infants; supportive treatment with antioxidants and chelation was ineffective and associated with severe side effects[1 – 3]. With the realization that NH results from the fetal complement-mediated liver injury, intravenous immunoglobulins (IVIG) were successfully introduced for the treatment that subsequently resulted in increased survival rate and decreased need for liver transplantation[3.4].

We present two cases of NH from the same family to illustrate the role of antenatal treatment with IVIG in alleviation and possible prevention of this serious morbidity.

Case presentation:

Case 1
The mother of our patient was an asymptomatic gravida 4 para 2 woman with two previous term deliveries and one miscarriage at 12 weeks. She had regular prenatal follow up, her antenatal screening showed normal serology, and she denied any history of illnesses during pregnancy. Current pregnancy was uneventful until 28 weeks of gestational age (GA) when fetal ultrasound (US) showed severe oligohydramnios that rapidly progressed to the anhydramnios despite intact membranes. The infant was delivered by emergency caesarian section at 29 weeks due to BPP 0/8 and poor fetal tracing. Apgar scores at birth were 3, 7 and 7 at 1st, 5th and 10th minutes, respectively. The infant weighed 840 grams (8th percentile) and his initial physical examination was appropriate for the gestational age. He was intubated in the case room and received a surfactant for respiratory distress. During the next 24 hours, he remained on ventilatory support, and gradually developed hypoglycemia that was managed with glucose infusion. On his second day of life, the infant developed severe hypotension, thrombocytopenia, and progressive hypoxemia. His hypoglycemia precipitously worsens in spite of the increased glucose infusion rate (GIR). During this prolonged hypoglycemic episode a critical blood testing (insulin, cortisol, growth hormone, thyroid function, and lactate), a coagulation panel, and tests for possible metabolic

abnormalities were performed as well as a full sepsis workup (complete blood count, C-reactive protein level, blood culture, and cerebrospinal fluid analysis and culture). Treatment with antibiotics (ampicillin and gentamycin) was initiated. Initial blood tests showed leukopenia with normal platelets count, elevated liver enzymes, and evidence of coagulopathy. The next day, the patient's condition deteriorated. He developed progressive abdominal distension with clinical picture of ileus, his liver function precipitously worsened; coagulation tests showed disseminated intravascular coagulation (DIC) despite treatment with fresh frozen plasma, cryoprecipitate, platelets and vitamin K. His ferritin level was very high (2750 ng/mL), and he continues to have profound lactic acidosis (lowest lactate level was 7. 2 mmol/L and highest 15.1 mmol/L). The metabolic workup was reported as normal. Exploration laparotomy was performed for suspected necrotic bowel and showed mild ascites with multiple hemorrhages within the bowel wall. At the age of 3 days, the patient developed generalized tonic-clonic seizures that were refractory to the Phenobarbital, Phenytoin, and Levetiracetam. The patient remained hemodynamically unstable despite aggressive resuscitation and died at the age of 4 days.
An autopsy was performed and revealed abnormal, cirrhotic liver with nodular appearance, cholestasis and iron deposition in hepatocytes and Kupffer cells. Iron staining was found in thyroid, pancreas, mucous glands of upper respiratory tract and thymus. Hemorrhage within the lungs, cerebellum, lateral ventricles, subarachnoid were reported as well. Autopsy findings were consistent with the diagnosis of neonatal hemochromatosis (NH).

Case 2
After confirming the diagnosis of NH, parents were counseled about the risks of morbidity in the next pregnancy and explained that the probability of the next infant to be lethally affected is greater than 90%. However, they were informed that the severity of NH could be considerably alleviated by antenatal IVIG treatment.
The next spontaneous singleton pregnancy occurred 26 months later, and the mother was under close surveillance of high-risk maternity services from 10 weeks of gestation. Preventive treatment with IVIG was initiated at 14 weeks of pregnancy until the end of gestation. The pregnancy was uneventful, and multiple fetal ultrasounds were reassuring. At 39 + 5 weeks of GA, a male infant was born by spontaneous vaginal delivery. Apgar scores at birth were 7 and 9 at 1st and 5th minutes, respectively. The infant weighed 3275 grams, and his physical examination was unremarkable. He was admitted to NICU for the management of possible neonatal hemochromatosis. His course at NICU was notable for transient hypoglycemia that was treated with intravenous glucose and moderately deranged coagulation profile: low fibrinogen, slightly increased INR, and elevated ferritin (950 ng/mL). Although the patient remained asymptomatic, treatment with IVIG 1 g/kg was started immediately. Vitamin E 40 units twice a day was added after consultation with a pediatric gastroenterologist. Following treatment, the patient showed rapid laboratory improvement: fibrinogen (90 mg/dL to 175 mg/dL), INR (2.68 to 1.1), and ferritin (950 ng/mL to 510 ng/mL). The patient was discharged home on day 20 of life with planned follow-up with pediatrician and gastroenterologist.

Discussion And Conclusion

NH is a rare but often life-threatening clinical condition, and untreated it is uniformly lethal[1-3]. Although the inheritance of NH remains unclear, the recurrence of NH in families with one affected child is about 90%[3,5]. Current clinical evidence explains NH as a maternofetal alloimmune disorder, so this condition is congenital but not hereditary[3,4]. NH starts at 14 weeks of pregnancy when maternal IgG began to cross placenta and bind to fetal hepatocytes causing complement-mediated hepatocyte injury[5-7]. The discovery of the alloimmune etiology of NH advanced prevention, timely diagnosis, and treatment of this condition[5.6].

It is well described in the literature that a woman could have multiple unaffected infants before having an infant with NH[1-3,6,7]. In our case, the mother had two healthy children before the miscarriage, and afterward, an infant with severe NH was born. This fact could be explained by the time-lapse between exposure, sensitization, and production of IgG antibodies against the fetal antigen[7,8].

While the majority of NH affected infants present with acute liver failure within hours after delivery, some could have isolated symptoms of hypoglycemia, coagulopathy, or hyperbilirubinemia at birth[7.9]. Without early and aggressive medical treatment these infants usually deteriorate within the first week of life[10,11]. The intrauterine growth restriction, oligohydramnios, prematurity are common co-foundings in infants with NH[11,12].

This diagnosis without family history could be a challenge. Laboratory evaluation is usually significant for hyperbilirubinemia, hypoglycemia, and deranged coagulation factors. Iron studies reveal high serum ferritin levels (>800 ng/mL) which is a sensitive but not specific indicator for NH[1,5,11]. Placental pathology findings are none-specific for NH, and consist of edematous placental villi[2].

In the first presented case combination of being small-for-gestational-age, having highly elevated ferritin levels, and liver failure made the diagnosis for NH most likely, and buccal biopsy was considered as a confirmation test, however, rapid clinical deterioration makes it unfeasible. The autopsy confirmed the suspected diagnosis of NH and provided with the necessary information for further counseling.

Since the Introduction of IVIG preventive therapy, mortality and morbidity rate among neonates with NH decreased dramatically[7,8,9]. Feldman and Whitington (2013) developed an effective protocol of NH prevention, with the use of IVIG at 14 weeks, 16 weeks, and 18 weeks, and then weekly until the end of pregnancy in mothers with a history of fetal or neonatal hemochromatosis[3]. They reported good outcomes in 99 % of cases[3]. Several studies support this approach and report similar effectiveness[6.8.9]. In situations when mothers were unable to receive preventive therapy with IVIG, exchange transfusion, IVIG, and chelation-antioxidant therapy remain the treatment choices for the neonates with NH[5,9].

In our second case, the mother received preventive therapy with IVIG that helped to preserve pregnancy until term (previously, she had a miscarriage and preterm birth at 29 weeks). This infant was born appropriate for gestational age and was clinically asymptomatic. His laboratory findings (elevated ferritin, deranged coagulation profile) on the first day of life were suggestive of impaired liver function, so,

IVIG was administrated aiming to reduce the ongoing hepatocyte injury. We believe that the early use of IVIG in this patient helped to preserve hepatocytes and normalize liver function. His hospital course was straightforward, he was observed for 3 weeks and discharged home with no active concerns.

A prenatal treatment and early postnatal administration of IVIG are effective ways to manage NH that help to reduce the severity of the symptoms, prevent liver failure and avoid the need for liver transplantation.

Abbreviations

Congenital hepatoblastoma (CH), Neonatal Intensive Care Unit (NICU), Magnetic Resonance Imaging (MRI)

Declarations

Declarations: Ethics approval and consent to participate: no ethics approval required, informed consent from the patient received

Consent for publication: Written informed consent was obtained from the patient‘s parents for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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