

NEONATAL HEMOCHROMATOSIS: A RARE CASE REPORT WITH CONSANGUINITY

Sandeep Mude^{1**} , Bhushan Miraje^{1*}, Vijay Gavade¹, Uday S. Patil^{2*}, Rajendra S. Patil².

^{**1}Resident Masai Childrens Hospital, Kolhapur, Maharashtra, India

^{*1}Pediatric Hepatologist (Teaching faculty), Masai Childrens Hospital, Kolhapur, Maharashtra, India

¹Consultant Neonatologist, Masai Childrens Hospital, Kolhapur, Maharashtra, India

^{2*}Superintendent & HOD, Masai Childrens Hospital, Kolhapur, Maharashtra, India

²MD, Department of Pathology, Ambika Lab, NABL Accredited (NBR MC3332), Kolhapur, Maharashtra, India.

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Corresponding author: Sandeep Mude, <https://orcid.org/0000-0002-4425-0381>

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Abstract

Background: Neonatal hemochromatosis (NH) is a rare and severe liver disease of mainly intra-uterine onset, characterized by neonatal liver failure, hepatic and extrahepatic iron acquisition. NH is also called as Gestational alloimmune liver disease (GALD). This leads to an altered iron metabolism with resulting siderosis, multi-organ failure and infants may be stillborn or present with advance, overwhelming liver disease. The disease represents the most common cause of liver failure in neonates and is also the most common indication for neonatal liver transplantation. We present a neonate who died at 15 days of age and who was found to have massive iron overload in the liver. Initial treatment consisted of chelation therapy and antioxidants, but lack of laboratory and clinical improvement led to an exchange transfusion followed by intravenous immunoglobulin (IVIG). Irrespective of all above treatment no improvement of general condition of the patient. The unfavourable course of the disease is described in this case report.

Introduction

Acute liver failure (ALF) is relatively rare condition in neonates. In the year 1957 Cottier¹ first described a clinical picture in neonates comparable to hemochromatosis. Since then this rare medical condition is known as neonatal hemochromatosis (NH). Etiological factors include metabolic, infectious and haematological disorders, congenital vascular, heart abnormalities and drugs. Clinical presentation usually starts in utero² and recent investigations suggest a gestational alloimmune genesis of liver failure on the basis of an alloantibody-mediated liver injury, leading to an altered iron metabolism with resulting siderosis.^{3,4,5}

Treatment options are limited and the prognosis of NH remains generally poor.^{6,7} Success rates of 10 to 20% are reported for medical treatment, which consists of antioxidants and an iron chelator. Early treatment may be beneficial in those patients who present with milder phenotypes. Nevertheless, this benefit is discussed controversially in the literature.^{7,8}

In cases of more severe acute liver failure and in non-responders, liver transplantation is the state-of-the-art therapy (survival rates of 50%).^{6,7}

Since 2009 a new therapy regimen has been introduced in NH patients: in order to eliminate the suspected alloantibodies, which induce NH, an exchange transfusion

(ET) is performed followed by a single administration of intravenous immunoglobulin (IVIG).^{5,9}

We report a case of NH, which we treated with ET/IVIG early after diagnosis. Before this treatment the patient was already listed for high-urgency liver transplantation.

Case:

Newborn is the first child of consanguineous parents. The mother is 24 years of age primi, without any history of miscarriage. There are no further chronic or liver diseases and no metabolic disorders in the family history. The female infant was born by caesarean delivery at 38 weeks of gestation. Birth weight was 2600 g (3rd to 50th centile), length 48 cm (3rd to 50th centile) and head circumference 33.5 cm (3rd to 10th centile). Apgar scores were 5 at 2 min and 9 at 5 min.

On the third day of life mother noticed increase work of breathing and abdominal distention gradually and progressed to intermittent grunting in next 72hr. Then infant developed severe jaundice, persistent hypoglycemia, ascites and progressive oxygen requirements and ventilation. Thus shifted to our tertiary care neonatal unit on day ten. For initial values of coagulation and liver function parameters. Thus having metabolic acidosis and respiratory alkalosis, very highly elevated ferritin levels, hyperbilirubinemia, thrombocytopenia and liver failure made the diagnosis for NH most likely.

TEST	31/10/19	1/11/19	3/11/19
HB/TLC/PLT	12.6/20,760/1,04,000	10.5/15,100/1,060,00	11.6/7550/44,000
PT/APTT/INR	>80/120/6.2	>120/>180/1.29	40/46/3.1
SGOT/SGPT		4840/1411	—/402.1
Sr.AMMONIA/LACTATE		348/120.5	
Sr.NA/K/CL		130/6/99	120.1/—/—
Sr.CREATININE/B.UREA		1.58/88.5	0.6/—

TORCH	-ve IgM
Sr.KETONE	0.1
Sr.TRIGLY	91.6
Sr.FERRITIN	>100000
URINE R/M	NORMAL
Sr.CREATININE	0.6
BLOOD CULTURE	-ve
Sr.BIL T/D	9/2.9
Sr.ALBUMIN	3.40
FIBRINOGEN LEVEL	<1.0

Patient ID : b/o anannya baing		
pH	7.289	L
pCO ₂	18.8 Torr	L
pO ₂	91.7 Torr	
Na	104.4 mmol/L	L
K	5.51 mmol/L	H
Ca	0.50 mmol/L	?
Hb	10.6 g/dL	L
Temp	37.0 °C	
FI02	21.0 %	
BP	70/1.0 Torr	
HCO ₃ -act	8.7 mmol/L	
HCO ₃ -std	13.0 mmol/L	
BE(ef)	-17.9 mmol/L	
BE(B)	-15.8 mmol/L	
BB	30.3 mmol/L	
atCO ₂ (P)	9.3 mmol/L	
Hct	31.2 %	
sO ₂ (est)	96.8 %	
Ca(7, 4)	*** mmol/L	
pO ₂ (A-a)	24.4 Torr	

Other possibilities for differential diagnosis (sepsis, galactosemia, thyrocinemia, HLH, neonatal lupus erythematosus and less likely α -1 antitrypsin deficiency) could be excluded clinically or by urine and blood testing.

From the first day of admission, daily administration of fresh frozen plasma was mandatory in order to keep coagulation parameters in measureable ranges and avoid spontaneous bleeding. On day 12 of life the administration

of a chelation-antioxidant therapy (deferoxamine ($40 \text{ mg}^{-1} \text{ kg}^{-1}$ per day), vitamin E ($30 \text{ IU}^{-1} \text{ kg}^{-1}$ per day) and acetylcysteine ($150 \text{ mg}^{-1} \text{ kg}^{-1}$ per day) was started. Prostaglandin E1 had not been administered due to potential adverse effects. This treatment did not appear to be of any benefit for the patient.

Thus suspecting NH liver biopsy, buccal mucosa was taken, x ray showing cardiomegaly

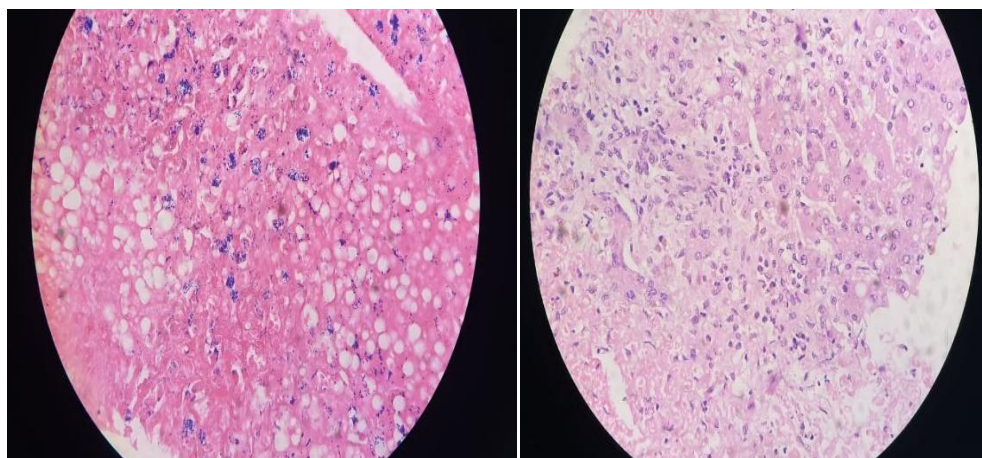


Figure 1:

Fig.1. liver biopsies with Perls Prussian blue staining shows a characteristic pattern of iron accumulates predominantly in hepatocytes and biliary epithelial cells.

Fig.2. CXR showing cardiomegaly

Which eventually confirmed the diagnosis of NH. Thus, on day 13 full double volume exchange transfusion according to Rand *et al.*¹⁰ was performed, followed by the administration of IVIG (1 gm/kg). Both, ET and IVIG were tolerated well. In the following days the general condition of the patient not improved and liver synthetic function not stabilized and started to slowly deteriorated. Thus diagnosis was conformed as NH with excess accumulation of iron in hepatocytes. Next plan of treatment is liver

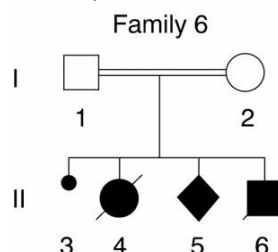


Figure: 2

transplantation. Patient listed for liver transplantation but unfortunately patient deteriorated and died on day 15.

Discussion

Consanguinity was observed in only one family (family 6) which was of Asian descent but produced all four offspring affected (one stillbirth, three neonatal deaths)¹²



NH remains a severe, life threatening and often lethal multiorgan disorder of iron metabolism.¹¹ It manifests at birth or during the first week of life with severe hepatic failure and alloimmune genesis on the basis of an alloantibody-mediated process has been suggested.^{3,5,7} Diagnosis is confirmed by the demonstration of extra hepaticsiderosis.

This diagnosis remains a challenge in early stages. In the late 1990's in many cases of NH diagnosis was only possible by taking the family history of affected children revealing that a sibling already died of liver disease.⁸ Nowadays, early diagnosis is feasible by exclusion of differential diagnosis and confirmation with a biopsy of oral mucosa.

After the introduction of antioxidant therapy, liver transplantation appeared to be a potential cure. In 2007 Timpani *et al.*⁵ were the first to report a case of a patient with NH whose positive outcome could have been related to having been given an exchange transfusion, followed by Escolano-Margrit *et al.*⁹ Rand *et al.*¹⁰ compared 13 newborns treated with IVIG/ET to historical controls 2 years later. In this regimen double volume exchange transfusion is intended to remove >90% of alloimmune antibodies and IVIG is given in order to displace specific reactive IgG. Outcome of the IVIG/ET cohort appeared to be significantly improved with 75% who did not need liver transplantation compared with 17% in the historical control group. Similar to our patient, many patients of this study group were treated with both chelation-antioxidant therapy and IVIG/ET. These results suggest, along with our case report, that the chelation-antioxidant combination seems to be of little help in severe cases of NH.^{6,8,10}

In our neonate, the course of disease remains rapid deterioration. ET/IVIG administration, which should eliminate the ongoing loss of hepatocyte function to permit survival, was safe and well tolerated. Initially ET/IVIG showed improved the patient's general condition and liver synthetic function, but due to massive iron deposition in liver, heart, endocrine organs with multiorgan failure baby was died.

Conclusion

Thus NH seems to be a gestation alloimmune disease, and reoccurrence of severe neonatal hemochromatosis in at-risk pregnancies may be reduced by maternal treatment with weekly (beginning gestational age 18wk) high-dose intravenous immunoglobulin (1gm/kg) during gestation. After birth, affected neonates are treated with exchange

transfusion and intravenous immunoglobulin, which improves survival and reduced the need for transplantation. As repeated affected neonates in the same family are common. We also describe a consanguineous family with four affected members and the occurrence of disease in one of three non-identical triplets as well as in maternal half sibs.

Early application of ET/IVIG is a feasible and effective treatment in NH to potentially prevent liver transplantation and allows a positive impact on the course of the disease.

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