Case report: Successful treatment of neonatal hemochromatosis with exchange transfusion and intravenous immunoglobulin

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Abstract:

Background: Neonatal hemochromatosis (NH) is a rare disorder. It is the most common cause of acute liver failure in neonates. The NH is a significant mortality and morbidity risks. Some neonates are stillborn and most others die within the first weeks or months of life. The prevalence of NH in Thai people is very low. The recurrence rate in families is nearly 80%.

Objective: To present the successful treatment of neonatal hemochromatosis in a Thai with exchange transfusion and intravenous immunoglobulin and review the English language literature.

Method: A 14 days old boy who was born into a Thai family with no previous pregnancy presented neonatal hemochromatosis. He developed persistent jaundice, hepatosplenomegaly caused severe liver failure since birth.

Result: Diagnosis of NH was made by detecting high serum ferritin level, alpha-fetoprotein along with demonstrating iron deposition in hepatic tissues by magnetic resonance imaging (MRI) and lip , buccal tissues (minor salivary gland), liver showed siderosis, which supported the diagnosis of NH. The successful treatment was exchange transfusion and three doses of intravenous immunoglobulin.

Conclusion: The diagnosis of NH requires tissue analysis to assess extrahepatic siderosis (EHS) and early treatment with exchange

transfusion and intravenous immunoglobulin can prevent before liver transplantation and serious morbidity and mortality.

Keywords: acute liver failure, gestational alloimmune liver disease, neonatal hemochromatosis, exchange transfusion, intravenous immunoglobulin, extrahepatic siderosis.

Introduction

Neonatal hemochromatosis (NH) is a rare, severe liver disorder associated with extrahepatic siderosis (EHS) sparing the reticuloendothelial system and fetal death or neonatal liver failure. Previously NH was described as an inborn error of iron metabolism.[1] NH is no known disease incidence. NH is fetal liver injury causes disturbed fetal iron homeostasis resulting in fetal iron overload, rather than iron overload causing fetal liver injury.[2,3,4] The mortality rate is more than 60%. Presence of an affected older sibling is a risk factor for NH. There have been no reports of racial or gender predilections, and there is no known genetic factor for NH. Clinical symptoms can occur in utero or in the immediate postnatal period. A gestational disease with transplacental transfer of maternal Ig G antibodies targeting the fetal liver resulting in immune injury. The alloimmune target is believed to be a fetal hepatocyte cell surface antigen, with subsequent complement activation resulting in severe loss of hepatocytes and fetal iron overload.[5] NH refers to the clinical diagnosis of hepatic failure that is largely caused by gestational alloimmune liver disease (GALD). NH should be suspected in all neonates with signs of severe liver disease and in unexplained cases of fetal demise in the late second or third trimester.[6] The treatment with exchange transfusion, intravenous immunoglobulin (IVIG) has been successfully used, along with antioxidants, iron chelator without liver transplantation.

Case description:

A Thai male infant was born at 34+6 weeks gestational age to a 27-year-old G2 P1 healthy mother. The infant was delivered by caesarean section due to prolong PROM (96hr) with polyhydramnios. The infant was apgar scores of 9 and 10 at 1 and 5 minutes, respectively. The infant was vigorous at birth. His birth weight was 2,600 g. The maternal

history is unremarkable but DCIP test is positive. Family history haven't evidence for chronic liver disease, jaundice, hepatosplenomegaly, parental consanguinity and metabolic disorders. However, after birth, the infant is noted to have jaundice and hepatosplenomegaly. The infant is admitted to the NICU at province hospital. Physical examination are marked jaundice, SEM grade II at LLPSB, liver 1 FB BRCM, spleen 3 FB BLCM, hemangioma at abdomen and back size 0.5x0.5cm. His liver function blood test is total bilirubin 25.3 mg/dL, direct bilirubin 13.3 mg/dL, AST 287 U/L, ALT 85 U/L, ALP 407 U/L and coagulogram is prothrombin time (PT) 20.4 sec, partial thromboplastin time (PTT) 87.3 sec, international normalized ratio (INR) 1.94, after he received several fresh frozen plasma and vitamin K intravenous. He was clinical not improve then the infant was transfered to the NICU at Naresuan University for 14 days old. A 14 days of age , infant of physical examination was 2.36 kg (10-25 th percentile) of weight, length was 46 cm (10-25 th percentile), head circumference was 33 cm (50 th percentile), vital sign (body temperature, pulse rate, respiratory rate and blood pressure) were within normal limit. Heart was no active precordium, no heaving, no thrill, normal S1 S2, SEM gr. II at LUPSB. Abdomen was small hemangioma 0.3 x 0.2 cm, no distension, active bowel sound, soft, liver 1 FB below Rt. costal margin, spleen 3 FB below Left costal margin. The other system examinations were normal. The laboratory values of the infant showed total protein 4.0 g/dL, Albumin 2.4 mg/dL, globulin 1.6 g/dL, total bilirubin 18.23 mg/dL, direct bilirubin 11.35 mg/dL, AST 155 U/L, ALT 60 U/L, ALP 884 U/L, GGT 36 U/L, PT 16 sec, PTT 59.6 sec, INR 1.4, fibrinogen 155 mg/dL. Complete blood count showed white blood cell 8410 cell/L, Hct 34.1 %, platelet 221,000 cell/uL, N 39.9%, L 40.5 %, monocyte 10.2 %, eosinophile 9.2%, basophile 0.2%. Mother and patient's blood group were B Rh+ and O

Rh+, respectively. Reticulocyte count 2.04% and G6PD level were normal. TORCH titers were negative. The initial differentials diagnosis are infection, inborn error metabolism and metabolic liver disease. Despite the initial treatment were started cefotaxime and ampicillin intravenous although change infant formula was lactose free because screening urine benedict test was positive. Later, additional laboratory data showed urine PCR for CMV: negative, parvovirus B19 IgG,IgM : negative, EBV IgG,IgM : negative, VDRL: non-reactive, Serum PCR for HSV1,HSV2 : negative, CMV viral load less than 150 copies/mL, HBsAg : negative, HBsAb : negative, AntiHCV : negative, AntiHBc Ig M, blood sugar 84 mg/dL, NH_3 level 36 µmol/l, Lactate 17.8 mg/dL, uric acid 1.8 mg/dL, cholesterol 128 mg/dL, triglyceride 43 mg/dL, LDH 240 U/L, eyes examination were no chorioretinitis, no cataract, no KF ring, anterior embryotoxon, Film skull and long bone: no skull calcification, no osteolytic lesion, no butterfly spine, Ultrasound whole abdomen was resulted the liver is normal in size and echogenicity without focal lesion. There are multiple portohepatic shunt scattering in both lobe of liver. There is no bile duct dilatation, The triangular cord sign is negative, normal distended gallbladder without internal echo, The spleen, pancrease and both kidneys appear normal, no ascites is seen. Serum ferritin 3361 ng/mL, serum alpha-fetoprotein 77,539 ng/mL, Iron 98.6 ug/dL, UIBC 0 ng/dL, TIBC 98.6 ug/dL, Transferrin Saturation : 100%, normal plasma amino acid ,negative blood for metabolic comprehensive screening and urine organic acid, respectively. At this point, neonatal hemochromatosis was considered as a developing diagnosis. Factor V 44% (70-130), Factor VII 18% (60-140) . Left buccal mucosa punch biopsy for age 15 days old showed no pathologic change, Lower lip punch biopsy revealed mild hemosiderosis in minor salivary gland. A 16 days old, Liver biopsy showed giant cell hepatitis with moderate

accumulation of iron pigments, suggestive of hemochromatosis. But hepatocytes don't demonstrated using immunohistochemical staining for C5b-9 to identify accumulations of the membrane attack complex in hepatocytes and giant cells because this test isn't available. MRI whole abdomen and thyroid were limited and showed diffused decrease T2-signal intensity of the liver with loss of signal intensity on the in-phase SPGR, suggestive of iron depositional disease or hemochromatosis. Therefore, A 18 days of age ; double volume exchange transfusion was initiated in order to remove possible maternal alloantibodies along with first dose intravenous immunoglobulin (IVIG) and administering anti oxidant cocktail and iron chelation were vitamin E 25 IU/kg/day, N-acetylcysteine 200 mg/kg/day x 21 doses started between at age 28-35 days old, Selenium 3 mcq/kg/day orally during the period of hospitalization, started at age 41 days old. Desferoxamine 30 mg/kg/day intravenous until serum ferritin < 500 ng/mL started between at age 39-45 days old. Eye and ear examination before received desferoxamine. Despite the treatments above, this infant was decreased jaundice but bilirubin level and coagulopathy revealed no normal level. Subsequently, he was received second and third doses IVIG at age 22, 29 days old, respectively. And the resulted blood for liver function test , coagulopathy, alpha-fetoprotein and ferritin are improve then as showed as table 1

Last, the heart disease was demonstrated by echocardiography. It was resulted small PDA and follow up echocardiography before discharge, It didn't appeared PDA. Nowadays, his growth and development is normal.

Table 1 Laboratory results of the patients

Age	TP	Alb	Glo	TB	DB	AST	ALT	ALP	PT	PTT	INR	WBC	Plt	Hct

Day 14	4.0	2.4	1.6	18.23	11.35	155	60	884	16	59.6	1.4	8410	221,000	34.1
Day 16	3.8	2.5	1.3	15.73	10.35	89	40	565	16	69.5	1.4			
Day 18	3.5	3.1	0.4	12.35	9.42	69	24	372	17.4	72.6	1.53	5,510	151,000	30.3
Day 18	3.9	2.8	1.1	5.11	4.13	37	10	114	15.7	40.5	1.38	3,950		
Day 19	4.2	2.6	1.6	8.28	6.45	86	21	231	18.5	53.6	1.62			
Day 20	4.5	2.9	1.6	10.85	7.78	137	30	279	18.6	59.8	1.63		85,000	33.1
Day 22	4.5	3.1	1.4	10.99	8.20	166	31	291	19.6	73.9	1.72			
Day 27	4.8	2.7	2.1	16.32	12.48	197	69	373	18	83	1.58	7,650	278,000	31.1
Day 33	5.3	3.1	2.2	18.71	13.86	157	67	683	13.9	47.7	1.23	9,950	384,000	31.5
Day 47	5.0	3.2	1.8	12	9.31	175	51	524	13.3	47.5	1.17	10,840	536,000	28.2
Day 62	5.4	4.0	1.4	9.09	7.18	88	44	513	11.9	39.2	1.05	9,280	388,000	29.2
Day 92	4.6	3.3	1.3	2.44	2.11	50	28	381	12.7	39.10	1.12	6,580	284,000	27.2

IVIG Double volume exchange transfusion

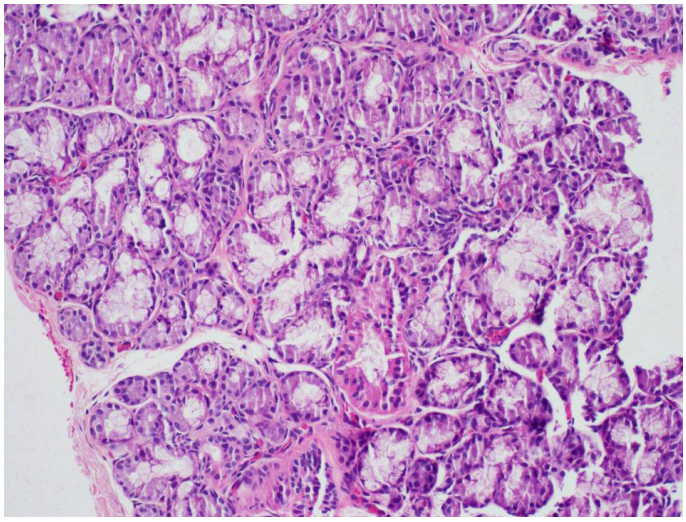
Table 1 continuation

Age	Alpha Fetoprotein	Ferritin
Day 14	77,539	3,361
Day17	54,565	-
Day 21	-	1,935
Day 31	45,491	3,623
Day 109	291.9	189.2

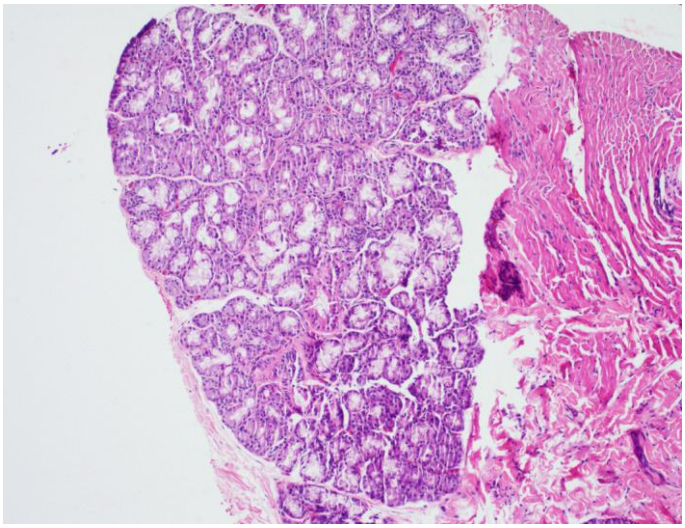
Prussian blue stain at minor salivary gland

Left buccal mucosa punch biopsy (old of age 15 days) : -no pathologic change

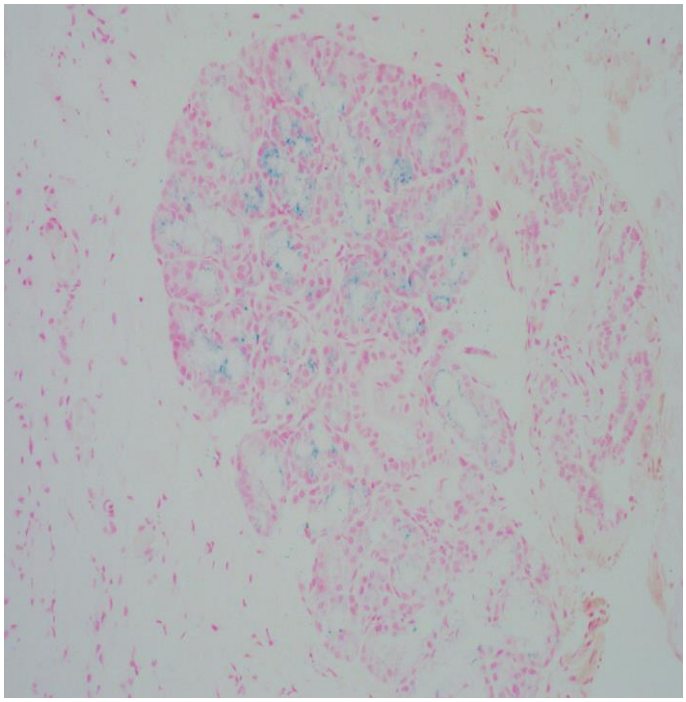
Lower lip punch biopsy (old of age 15 days) **Mild hemosiderosis in minor salivary gland**



minor salivary gland ย้อม H&E

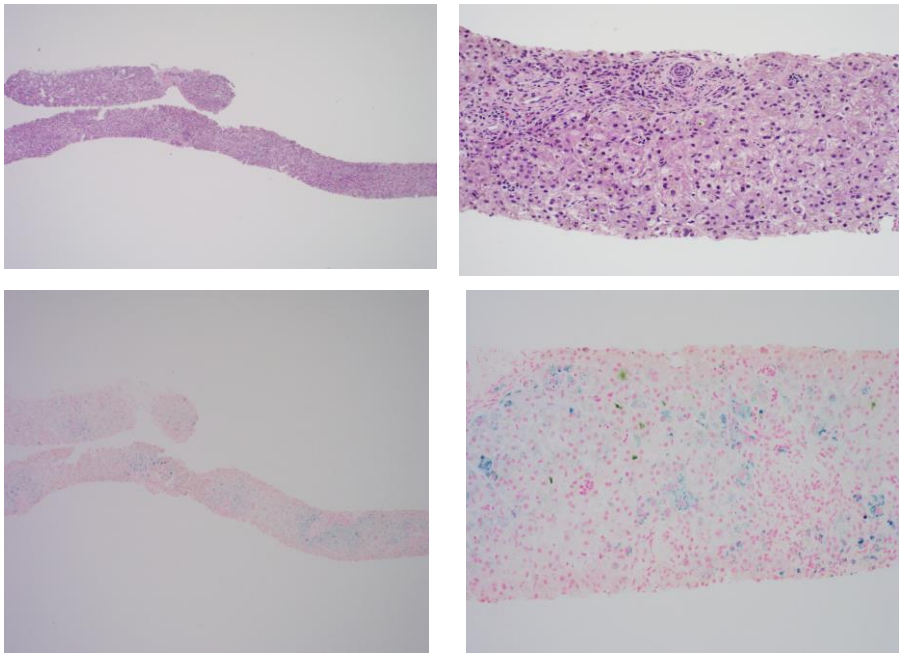


minor salivary gland ; H&E stain

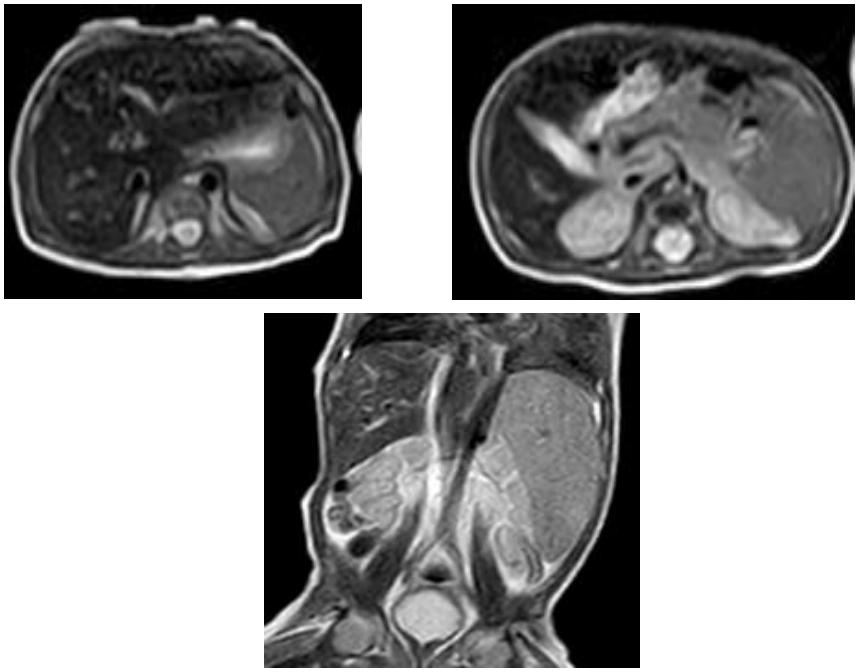


Lower lip punch biopsy ; **Prussian blue** stain seen **hemosiderosis**

Liver biopsy



MRI whole abdomen



MRI whole abdomen: Diffused decrease T2-signal intensity of the liver with loss of signal intensity on the in-phase SPGR, suggestive of iron depositional disease or hemochromatosis.

Discussion

NH is a rare condition, with published articles consisting mostly of isolated case reports or small series. There is a high mortality despite treatment. NH is accompanied by severe fetal liver injury, and one of its most common presentations is late second and third trimester fetal loss as evidenced by the gestational histories of women who have had a baby diagnosed with NH.[6] Pathogenesis of NH, like other maternofetal alloimmune disease, is mediated by immunoglobulin G (Ig G) maternal Ig G antibodies are actively transported across the placenta to the fetus starting around the 12 th week of gestation when the neonatal crystallizable fragment receptor (FcRn) is first expressed. These Ig G antibodies serve to provide the fetus with humoral immunity as the fetal and newborn adaptive

immune system is immature and incapable of warding off infection.[7] There are two possibilities to consider in regard to the mechanism of siderosis in NH. The first possibility is that the fetus becomes iron-loaded due to poor control of iron flux across the placenta. Fetal hepcidin is involved in regulating placental ferroportin function, which is intimately involved in regulating maternal-fetal iron flux. It is reasonable to speculate that reduced hepcidin synthesis in the severely injured liver could lead to poor regulation of ferroportin in the placenta and to iron overload. The failure to regulate ferroportin could also contribute to the observed lack of macrophage and Kupffer cell iron. The second possibility has an abnormal discrete deposition of iron in tissue with severe liver injury, the central repository and distribution apparatus for iron in the fetus is impaired. The tissues showing siderosis are those with a propensity to take up non-transferrin-bound iron from plasma.[8] The clinical presentation of NH can be seen with complications of pregnancy such as intrauterine growth retardation, oligohydramnios, placental edema and sometime polyhydramnios. [6,8,9,10] The mechanism of recurrent neonatal hemochromatosis affecting the fetus. In alloimmunity, the fetal target antigen to the maternal circulation is required , as well as lack of the antigen in the maternal repertoire of 'self-antigen', the fetus expresses a dominant paternal allele for blood group antigens expressed on erythrocytes (hydrops fetalis) or platalets (alloimmune thrombocytopenia) that many normal mothers lack. A rare cause is for the mother to have a homozygous genetic deficiency results in her not expressing a common species-related protein and developing an immune response to a fetus expressing that protein from the normal paternal allele. Last mechanism of alloimmune disease involves sensitization to a fetal antigen that differs from the isoform expressed in mature individuals.[11] The pregnancy frequently ends with stillborn infants or infants who are premature or small for gestational age. In this case, history of previous pregnancy was normal child but this infant had history of polyhydramnios. Initial presentations, which were found soon after birth included cholestasis, anemia, hepatosplenomegaly,

acute neonatal liver failure. Therefore, progressive cholestasis, hepatosplenomegaly, although clinical feature of NH include hypoglycemia, marked coagulopathy, hypoalbuminemia with edema, ascites and oliguria.[2] The presenting finding are those of liver failure and usually multiorgan failure. Affected infants are frequently diagnosed as having overwhelming sepsis of the infant even with negative cultures.[6] The possible causes of acute neonatal liver failure were TORCH infection, Parvovirus B 19, tyrosinemia, galactosemia, familial hemophagocytic syndrome, NH, Niemann-Pick disease type C and Glycogen storage disease type IV. Eyes examination were no chorioretinitis, no cataract, no KF ring, anterior ambryotoxon for excluded rubella, CMV, syphilis infection, wilson disease, galactosemia and alagille disease , We report an infant with a diagnosis of NH. The diagnosis is based on the clinical features of acute liver failure. The investigations which supported diagnosis of NH, were very high levels of serum ferritin (usually > 800 ng/mL), alpha- fetoprotein (AFP; usually > 100,000 to 600,000 ng/mL) but normal newborn values <80,000 ng/mL [8,12,13] and hypersaturation but low levels of factor V, VII (usually less than 10% of normal), fibrinogen, transferrin and hypoalbuminemia (usually less than 2 g/dL). Whitington PF[8], reported biochemical evidence suggests that 80% of infants were affected elevated serum AFP range 100,820 to 670,000 ng/mL and /or elevated serum ferritin range 1250 to 15,948 ng/mL. Recent data indicate that increased ferritin levels alone are insufficient for diagnosis, as ferritin is an acute phase reactant and may be increased in infants with liver failure from other causes.[14,15]

Although, demonstration of iron deposition in the liver from MRI along with excluding other diseases. The absence of iron deposit in heart and pancreas from the MRI cannot exclude NH. But specificity MRI of the liver, pancreas, spleen and heart for NH demonstrated the iron deposits are in the heart, pancreas, exocrine and endocrine organs, intestines, and gastric and salivary glands.[11] Hepatic siderosis is not specific for NH. Likewise, hepatic histology showed increase iron stores sparing the reticuloendothelial system, and evidence of extrahepatic

siderosis, although lip biopsy revealed iron in salivary glands for confirm diagnosis of NH. The usual liver histology of NH showed extensive fibrosis with or without nodular regeneration and hepatic siderosis. [16] It is not always possible to make the diagnosis before death or liver transplantation because of the difficulties in confirming liver histology in infants with abnormal coagulation. In this case can lip, buccal mucosa minor salivary gland and liver biopsy for confirm diagnosis as a result as above. The treatment of NH have extremely literatures. In the past, a cocktail of antioxidants and iron chelator was survived rates as low as 10-20%. [2,17] There therapy to reduce the oxidative (extra-) hepatic injury due to iron overload. In patients studied by Murray and Kowdley [18] and Sigurdsson et al. [19] chelation-antioxidant therapy was not efficacious. However, iron chelators have significant side-effects and are not indicated in infants with documented NH without significant hepatic dysfunction. But study of Grabhorn et al. [20] Published treatment of severe NH by exclusive chelation-antioxidant therapy was survival rates of up to 80% . Annagur A et al.,[6] reported four cases of NH. The patients were supported with blood components. Therefore, all patients received IVIG dose 1 g/Kg., N-acetyl cysteine, selenium, vitamin E and C as antioxidant and desferroxamine treatment (Table 2) was started to decrease ferritin level. One of the patient had chelation-antioxidant treatment died within the first week of hospitalization. Overall treatment success is stated to be around 10-20%. Jimenez-Rivera C. et al. 2014,[21] this research presented successful treatment of neonatal hemochromatosis was treated by exchange transfusion and three doses intravenous immunoglobulin (IVIG) (1 g/kg) and reports of infants treated with exchange transfusion and IVIG that survival without liver transplantation improved tremendously. [22] Same our infant. The mechanism of double volume exchange transfusion is initiate in order to remove possible maternal alloantibodies, IVIG (1 g/Kg) is used to block antibody action and interfere with complement activation. Other researches, NH was treated by IVIG 2 g/kg with double volume exchange transfusion on day 8 led to rapid improvement in liver function and follow-up at the

age of 8 months showed normal development and near normal liver function along with repeat MRI abdomen showed no signs of iron deposition in the liver, pancreas, or adrenal gland.[23] Timpani G. et al described in 2007 , NH was treated with two exchange transfusions at the age 1 and 5 days then followed by rapid clinical and laboratory improvement. [17] Exchange transplantation/ IVIG therapy appears to improve the outcome of NH should be considered as early as possible for treatment of this serious condition. Some of the side effects of IVIG reported include fever, hypotension, hypoglycemia and necrotizing enterocolitis then should be monitored closely and if some components of the antioxidant/chelation combination provide added benefit.[24] Flynn DM et al.,[15] reported the NH should be started on an antioxidant cocktail while the diagnosis is being confirmed. If there is no response to treatment within 48-72 hours, the infant should be listed early for liver transplantation.[15] Although, Feldman AG et al., in 2013[7] described infant with NH should be given one dose of IVIG afterthat the infant has not improved an exchange transfusion should be performed followed by administration of a second dose of IVIG. Normalization of the international normalized ratio (INR) may take 4-6 weeks as this therapy.[7] Lopriore E et al.,[2] reported outcome treatment without liver transplantation improved from 17% to 75%. But some report presented NH often leads to liver transplantation in the first 3 months of life.[8] Liver transplantation remains a necessity for many patients with NH who are refractory to medical management. Sheflin-Findling S et al.[25] reports liver transplantation has a high rate of graft loss and death.

The prognosis of NH is variable and generally poor. Conflicting results have been reported about the efficacy of a medical treatment comprising of a cocktail of antioxidants and an iron chelator. In recent years, the prognosis with medical therapy has improved as researchers have elucidated that the mechanism of liver damage is most likely related to an alloimmune process [4]

Table 2 The cocktail for treating neonatal hemochromatosis [6,12]

Drug	Dose

N-Acetyl cysteine	200 mg/kg/day, divided three times daily, by mouth for 17-21 doses
Vitamin E	25 IU/kg/day, divided twice daily, by month for 8 week
Selenium	3 µg/kg/day, iv by continuous infusion for length of hospitalization
Prostaglandin E1	0.4 µg/kg/hour iv increasing to 0.6 over 3-4 hour. The infusion is maintained for 10 days
Deferoxamine	30 mg/kg/day, iv infused over 8 hour until the serum ferritin < 500 µg/L

Conclusion:

Treatment of this fatal disorder has focused on supportive treatment for acute liver failure and liver transplantation, which may be successful in some cases, and more recently on the use of antioxidant treatment. Although Flynn DM et al.[15] reported three children underwent liver transplantation, which was only successful in one patient and comparison of outcome with or without antioxidant treatment resulted antioxidant treatment improved outcome in two children, but these children had less severe disease and their antioxidant treatment was started earlier than in those who didn't survive. The Whitington PF, et al.[26], Lopriore E, et al.[2] The published, in subsequent pregnancies of a woman after giving birth to an affected baby that a very high recurrence rate estimated at 90% led to the 'alloimmune hypothesis' and subsequently to the discovery of GALD. Then it's important for prevention for next pregnancy by maternal treatment with high-dose (1 g/kg body weight , maximum 60 g) intravenous immunoglobulin (IVIG) at 14 weeks, 16 weeks, and then weekly from the 18 th week of pregnancy until the end of gestation.[7,10,27] These guidelines have been successes of this prevention. Then good outcome in 99% of cases. The prognosis of NH was universally reported as extremely poor. Antenatal management using high dose IVIG prevents recurrence of NH in subsequent pregnancies and

postnatal management using exchange transfusions, and IVIG improves the rate of survival without liver transplantation.

Conflicts of interest

All authors have none to declare.

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