Neonatal hemochromatosis

Case series from Bahrain

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ABSTRACT

الأهداف: مراجعة الأعراض السريرية، وطرق التشخيص، والاستجابة للعلاج، ونتائج الرضع المدخلين إلى قسم الأطفال بمركز السلمانية الطبي المشخصين بداء ترسب الأصبغة الدموية لحديثي الولادة.

الطريقة: أجريت الدراسة بأثر رجعي للحالات المصابة بداء ترسب الأصبغة الدموية لحديثي الولادة والذين تم تشخيصهم خلال الفترة من مارس 2008م حتى مايو 2011م. واستند التشخيص لقياس مستوى الحديد والفيريتين وبروتين ألفا الجنيني في الدم، وخزعات الكبد والشدق وتصوير البطن بالرنين المغناطيسي.

النتائج: أظهرت الدراسة وجود 10 رضع (8 ذكور و2إناث) مصابين. إثنان لديهم تأخر في النمو الجنيني. وستة خدج. متوسط الوزن عند الولادة 1700غرام ومتوسط العمر عند ظهور الأعراض 16 يوماً وعند التشخيص 23 يوماً. ولوحظت عند مريضين صلة القرابة بين الأبوين. أما الأعراض فكانت تضخم الكبد، والطحال لخمسة، والحبن لثلاثة، ونقص سكر الدم لستة مرضى. جميع المرضى لديهم مستويات مرتفعة من الفيريتين وطول زمن البروثرومبين. كان لدى 9 مرضى مستويات عالية للحديد والبروتين الجنيني ألفا في الدم. أظهر التصوير بالرنين المغناطيسي زيادة ترسب حديد الكبد عند 8 مرضى. خزعة الكبد أظهرت دلالة على المرض في 3 مرضى ولطخت خزعات الشدق إيجابياً للحديد في مريض. تلقى 8 مرضى العلاج بمضادات الأكسدة ونجوا وتوفي اثنان.

خاتمة: داء ترسب الأصبغة الدموية لحديثي الولادة من أمراض الكبد النادرة، مع تفاوت الأعراض السريرية. ارتفاع الفيريتين وبروتين ألفا الجنيني في الدم تساعد على تأكيد التشخيص بعد استبعاد الأسباب الأخرى لفشل الكبد. كما أن استخدام مضادات الأكسدة يحسن النتيجة النهائية.

Objectives: To review clinical presentations, diagnosis, response to treatment, and outcome of infants with neonatal hemochromatosis (NH).

Methods: This is a retrospective review of all cases admitted to the Pediatric Department at Salmaniya Medical Center, Manama, Bahrain between March 2008 and May 2011. The diagnosis was based on serum iron and ferritin, alpha-fetoprotein levels (AFP), liver and buccal biopsies, and abdominal MRI scan.

Results: Ten patients (8 males and 2 females) were diagnosed with NH. Two patients were intrauterine growth restriction (IUGR) and 6 were preterm. The median birth weight was 1.700 grams. The median age at presentation was 16 days, and at diagnosis was 23 days. Two patients had positive consanguinity. Clinical presentations of the infants were hepatosplenomegaly (n=5), ascites (n=3), and hypoglycemia (n=6). All patients had raised ferritin levels, prolonged prothrombin time, and 9 patients had high serum iron and serum AFP. Abdominal MRI showed iron overload in the liver (n=8). Liver biopsies showed evidence of hemochromatosis (n=3). Buccal biopsies stained positive for iron (n=1). Eight patients received antioxidant therapy and survived. Two patients passed away.

Conclusions: Neonatal hemochromatosis is a rare liver disease of newborns with a spectrum of clinical severity. Elevated serum ferritin and AFP support the diagnosis after excluding other causes of neonatal liver failure. The use of antioxidant therapy helps to improve the outcome.

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Neonatal hemochromatosis (NH) is a rare[1] perinatal disorder defined as severe liver disease associated intrahepatic and extra hepatic siderosis presenting in utero or in early neonatal age.[2] It can be thought of as a form of fulminant hepatic failure.[3] Though it is rare, NH may be one of the most common causes of liver failure in the neonatal period.[4] The etiology and pathogenesis of NH are still unknown[4] and the mechanism of liver damage and diffuse siderosis are not fully understood.[5] Recent reviews have provided evidence that many cases of NH are due to maternal alloimmunity directed at the fetal liver.[4,6] Elevated serum ferritin (>800ng/ml), low transferrin, and hypersaturation of available transferrin are characteristics of NH.[7] The diagnosis can be confirmed by magnetic resonance imaging (MRI) and histology of liver or buccal mucosa.[7] Although liver transplantation holds the greatest promise for these patients, antioxidant therapy may be beneficial in the milder phenotypes.[7] Liver disease attributed to siderosis has not recurred in survivors to date.[3] More than 100 cases of NH have been described,[7] but hardly any centers reported more than few patients with this disease.[2,8] The aim of this study is to review the clinical presentations, diagnosis, response to medical therapy, and outcome of infants admitted to our center and diagnosed to have NH.

Methods. The inclusion criteria were any infant admitted to the Pediatric Department, Salmaniya Medical Complex (SMC), Kingdom of Bahrain, between March 2008 and May 2011 and diagnosed to have NH. The detailed informations on NH were collected from literatures searched through PubMed, Medline and Ovid search engines. Neonatal hemochromatosis was found in 10 infants and no patient was excluded. A retrospective review of their medical records, histopathology, and radiological reports was performed. Patients' demographic data were collected. The diagnosis of those patients was based on the combination of hepatic dysfunction (acute liver failure), raised serum iron, raised serum ferritin concentration (>1000 microgram/l), high transferrin saturation, reduced transferrin, high AFP, increase iron on liver (intrahepatic) and buccal biopsies (extra hepatic siderosis). Abdominal magnetic resonance imaging 1-Tesla scan (Siemens, Erlangen, Germany) was used as a confirmatory test. Other causes of neonatal liver failure including intrauterine viral hepatitis, biliary atresia, α1-antitrypsin deficiency, tyrosinemia, galactosemia, zellweger's syndrome, bile acids, and mitochondrial disorders were excluded. The patients received standard supportive treatment along with an iron chelating/antioxidant cocktail therapy. The cocktail therapy consisted of desferrioxamine 30 mg/kg/day intravenous (IV) infusion, which was continued until ferritin levels decreased below 500μg/l, N-acetylcysteine 200 mg/kg/day IV infusion for 17-21 days, prostaglandin E1 0.4-0.6 μg/kg/hour IV infusion for 2-4 weeks, oral vitamin E 25 IU/kg/day for 6-8 weeks, and selenium 3 μg/kg/day IV for hospitalization length. Patients' outcomes were assessed and followed on a regular basis every 3 months with the liver function test and serum ferritin level. If the patient survive despite disease insult without the need for liver transplantation this was considered as good outcome. However, death or requirement of liver transplantation is considered as poor outcomes.

Ethical consideration. The study was in accordance with the principles of Helsinki Declaration and was ethically approved by the Secondary Care Medical Research Subcommittee, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain.

Statistical analysis. The patients' data were analyzed using Microsoft Excel 2010. The frequencies and percentages were calculated. Group data were presented as medians and ranges.

Results. Ten infants (8 males and 2 females) were included in the study (**Table 1**). Six patients were Bahrainis, 2 Yemenis and 2 Indians. The mother of patient 2 had hepatitis C (HCV), but the baby was HCV RNA negative. Two patients were IUGR (20%), one with oligohydramnious and one with polyhydraminous. There were one set of twins (patients 7 and 8) and twin A (patient 4) of another set. The pregnancy of patient 5 was complicated by gestational diabetes, while the mother of patient 6 had pregnancy induced hypertension and hypothyroidism. Six patients were delivered normally and 4 by lower segment cesarian section. Abortions were noted in 3 of the 9 families (33.3%) and one family had a history of stillbirth (n=3; 11.1%). Six patients were preterm (60%). The median gestational age was 32 weeks (range 26-40 weeks), and median birth weight was 1.700 grams (range 820-4100 grams). The median age at presentation was 16 days (range birth to 90 days). The median age at diagnosis was 23 days (range 9-120 days). Two families had marital consanguinity (patients 3 and 5), one with a 2-month-old infant who died because of liver disease (patient 3). Five patients had hepatosplenomegaly and one had only hepatomegaly. Ascites was present in 3 cases; one was diagnosed antenatally by ultrasound (patient 6). Hypoglycemia was noted in 6 patients. Nine out of the 10 patients had associated features.

Laboratory features at presentation. Thrombocytopenia was noted in 5 (50%) (**Table 2**). All patients developed cholestatic jaundice (direct bilirubin more than 20% of total bilirubin) and 8 patients had high alanine aminotransferase (80%). Median prothrombin time was 17.5 seconds (range 11-60 seconds). Serum iron concentration was high in 9 patients (median 30 μmol/l; range 18-49 μmol/l; normal range 6-27μmol/l). All patients had raised serum ferritin levels (median 2562 μg/l; range 1185-8568 μg/l; normal range 52-421μg/l). Transferrin saturation was performed in 7 patients and the median was 86% (range 46.1-127.2%), 2 patients tested after antioxidant therapy (patients 1 and 4). Serum AFP levels were very high in all 9 tested patients (median >5845μg/ml; range 324.5 to >35350 μg/ml; normal range 15.7-146.5 μg/ml).

Histology results. Neonatal hemochromatosis was confirmed on histological examination. Liver biopsy was carried out for one patient (patient 2) and consented postmortem autopsies were carried out in 2 (patients 3 and 5). The histology examination revealed evidence of cholestasis, ballooned hepatocytes, mild bile ducts proliferation, and moderate to severe hemosiderin deposition (**Figure 1**). In patient 2, no fibrosis was found in the liver biopsy, while both autopsies showed mild focal to prominent fibrosis in patients 5 and 3, respectively. The parents of patient 9 refused liver biopsy. Buccal biopsies were performed in 8 patients, but only patient one stained positive for iron (**Figure 2**).

No salivary glands were found in one buccal biopsy (patient 10). Eight patients underwent abdominal MRI scan. Diffuse low signal intensity of the liver, indicating iron overload, was seen in all scans. Three of those patients show evidence of iron overload in the pancreas (**Figure 3**).

Antioxidant cocktail therapy and outcome. Eight patients received antioxidant therapy as per protocol. The median age of starting antioxidant therapy was 28 days (range 9-102 days). Eight patients (80%) survived with normal liver function tests after 2-4 years of follow up. Two patients passed away. Patient 3 died at the 40th postnatal day, 3 weeks after the initiation of cocktail therapy, while patient 5 died at the age of 21 days before starting the cocktail therapy. Patient 7 showed spontaneous improvement. On follow up, patient 2, although his hepatic enzymes and serum ferritin normalized, he developed hepato-pulmonary syndrome at the age of 2 years and 9 months, and he was sent for cardiology assessment, but he lost follow up. Patient 9, who underwent exchange transfusion because of an associated indirect hyperbilirubinemia, survived with chronic liver disease, hepatosplenomegaly, portal hypertension, and ascites. He was waiting for an overseas living-related liver transplant. No patient received intravenous immunoglobulins (IVIG).

Table 1 - Pregnancy and clinical picture at presentation of 10 patients with neonatal hemochromatosis.

Clinical picture	Patient's number									
	1	2	3	4	5	6	7	8	9	10
Gender	Male	Male	Male	Male	Female	Male	Male	Male	Male	Female
Pregnancy	Normal	HCV positive	IUGR, Oligo-hydramnious	Twin A	GDM	PIH, Hypo-thyroidism	Diaminiotic-monochorionic placenta	Diaminiotic-monochorionic placenta	Normal	IUGR, Poly-hydraminous
Abortion	-	-	1 (1 stillbirth)	1	-	-	-	-	-	1
Gestational age (weeks)	36	39	32	27	40	39	26	26	40	30
Birth weight (kg)	2.67	3.05	1.64	0.92	3.01	2.62	0.82	0.9	4.1	1.7
Age at presentation(days)	3	16	16	90	14	24	90	66	26	At birth
Age at diagnosis(days)	9	23	16	102	19	34	120	90	42	12
Consanguinity	No	No	2nd degree	No	Yes	No	-	-	No	No
Hepato-splenomegaly	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes
Ascites	No	No	Yes	No	Yes	Yes	No	No	No	No
Hypoglycemia	Yes	No	Yes	Yes	Yes	Yes	-	-	No	Yes
Associated features	DCM, PDA	Mild PPS	Bilateral extra renal pelvis	RDS	No	ileal atresia	RDS, sepsis	RDS, PDA	UTI	DCM hypotonia

HCV - Hepatitis C virus, IUGR - intrauterine growth retardation, GDM - gestational diabetes mellitus, PIH - pregnancy induced hypertension, DCM - dilated cardiomyopathy, PDA - patent ductus arteriosus, PPS - peripheral pulmonary stenosis, RDS - respiratory distress syndrome, UTI - urinary tract infection

Table 2 - Laboratory features at presentation of 10 patients with neonatal hemochromatosis:

Laboratory test	Normal values	Patient's number									
		1	2	3	4	5	6	7	8	9	10
Hb (g/dl)	13-16.5	11.8	13.8	11.2	10.1	9.3	9.5	11.4	13.5	10.7	13.3
Platelets	140-440 (10^9 /l)	392	58	38	236	8	103	347	87	362	178
Bilirubin (umol/l)	<18	396/258	302/238	238/52	149/101	257/182	145/105	71/46	476/336	125/107	778/523
Protein (g/l)	64-82	47	45	41	41	45	56	43	65	54	54
Alb/Glob (g/l)	35-50/15-30	22/25	23/22	25/16	26/15	24/21	34/22	24/19	32/33	29/25	30/24
AF (u/l)	150-420	215	434	663	365	269	336	500	974	539	169
ALT (u/l)	30-60	27	484	22	98	81	206	25	306	372	170
GGT (u/l)	<185	121	40	21	83	99	183	129	64	83	93
NH3 (umol/l)	64-100	-	-	-	57.9	125	74.4	-	49	38.7	-
Fibrinogen(mg/dl)	173-365	-	285	-	-	101	94	-	-	142	96
INR	0.9-1.2	1.1	1.0	3.4	1.5	4.9	1.9	1.2	1.6	1.4	1.1
PT/PTT (s)	11-15/25-35	13/36	11/27	41/62	18/44	60/-	24/47	14/33	19/40	17/32	13/36
S. Iron (umol/l)	6-27	33	34	29	18	29	37	25 (max 35)	31	25 (max >35)	49
S. ferritin (µg/l)	52-421	2702	1619	1242	1185	1830	3873.8	2422	2948	3121	8568
Max. ferritin	-	4098	6536	6536	1753	1830	3873.8	2422	11041	6022	8568
Transferrin (g/l)	2.2-3.5	2.53	1.48	1.85	0.82	-	-	-	0.95	1.04	1.49
TIBC (umol/l)	-	47.6	37.9	34.8	21	-	-	-	24.3	26.66	38.2
Transferrin saturation	%	*46.1	89.5	86.02	*66	-	-	-	127.2	93.75	78.5
S. AFP (µg/ml)	15.7–146.5	>35350	> 35350	> 35350	> 35350	-	> 5845	>5845	> 5845	> 5845	324.5

Hb - hemoglobin,T/D - total/direct bilirubin, Alb/Glob - albumin/globulin, AF - alkaline phosphatase, ALT - alanine aminotransferase, GGT - gamma glutamyltransferase, NH3 - ammonia, INR - international normalized ratio, PT/PTT(s) - prothrombin time/partial thromboplastin time (in seconds), TIBC - total iron binding capacity, *after cocktail therapy, S. AFP - serum alpha fetoprotein.

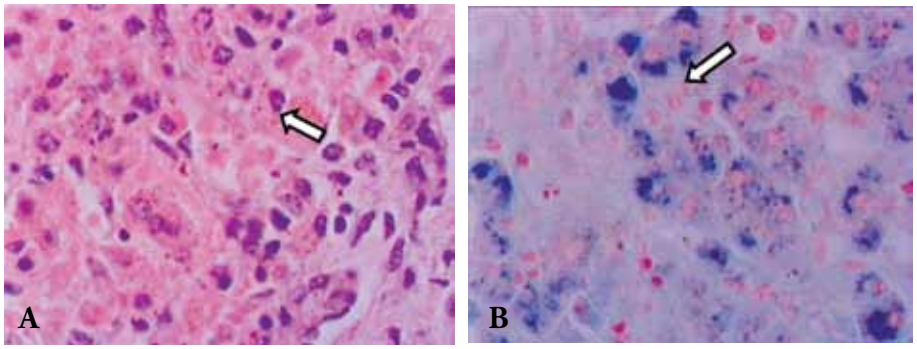

Figure 1 - Hematoxylin and eosin stain of patient one **A**) liver biopsy shows cholestasis and **B**) Prussian blue stain was positive for iron staining.

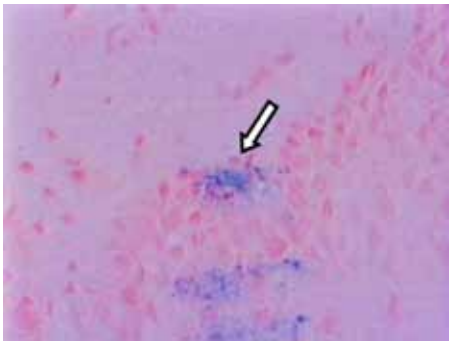

Figure 2 - Prussian blue stain of buccal biopsy of patient one tested positive for iron staining. Original magnification ×1,000.

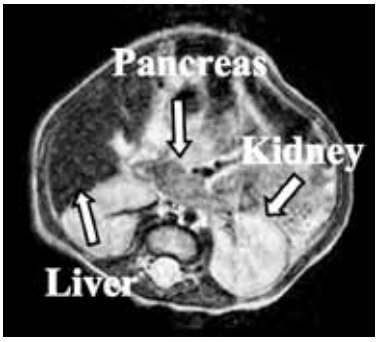

Figure 3 - Abdominal T2-weighed magnetic resonance imaging for patient 2 showed diffuse dark signal intensity of liver and pancreas indicating iron overload.

Discussion. Neonatal hemochromatosis is a rare syndrome presented as severe liver disease in the neonatal period.[2,3,9] The etiology of this disease is not fully understood.[5,9] It might be due to abnormal feto-placental iron handling, perinatal liver disease, a consequence of gestational alloimmune disease or familial.[2,4,6] Neonatal hemochromatosis showed no gender predilection.[3] However, this study had more in male patients than female. Other studies also found more male cases.[10-13] Equal gender distribution of cases were noted by some studies,[2,5,14] but no studies showed female predominance. This raised a question about the inheritance pattern of the disease and if it is sex linked. Consanguinity may play a role in the development of the disease. Two out of the 9 families (22.2%) in this study were consanguineous. Flynn et al[2] reported 8 patients of which 2 families were also related. Families of NH cases are at higher risk of having another affected newborn in subsequent pregnancies.[15] A woman might have unaffected infant before having the first child with NH, but after that the rate of recurrence is as high as 80%.[5] Nevertheless, some cases might pass undiagnosed, before the identification of the key case, as they were either still birth, abortion or mild form requiring no therapy. Bonilla et al,[16] reported 11 cases with NH, 2 of them were stillbirth. In this study, one family had a stillbirth and 2 siblings with elevated liver function tests. One of them died at the age of 2 months prior to the diagnosis of NH case (patient 3). In addition, a history of abortions was noted in 3 of the 9 families (33.3%). Most of NH affected live-born infants showed evidences of fetal insult (namely, intrauterine growth restriction, oligohydramnious).[17] The presence of oligohydramnious varies in those patients due to the variability in the severity of kidney insults. It ranges from mild defect to severe proximal tubular dysgenesis.[16] In this series, 2 infants (20%) were IUGR and one had oligohydramnious (10%). Similar percentage of IUGR was reported by Boyd et al study.[8] Heffron et al[18] reported IUGR in 11% and oligohydramnious in 33% of patients. Bonilla et al[16] reported oligohydramnious in 9 (81%) out of 11 patients. Premature birth among NH cases is common.[17] In this study, 6 patients (60%) were premature. This was similar to Rand et al study[19] were 10 out of 16 patients (62.5%) were premature. On the other hand, Flynn et al[2] reported 8 patients with NH, but only 3 of them (37.5%) were preterm.

Liver disease is commonly apparent within hours of birth, though in rare cases the liver disease can take a sub-acute way and manifests days to weeks after birth.[17] In this study, the median age at presentation was 16 days (range from birth to 90 days). The median age of presentation in other studies was less. It was 2 days in Grabhorn et al[20] study (range from birth to 21 days) and 4 days in Flynn et al[2] study (range from birth to 31 days). The difference in the age of presentation could be due to the variation of disease severity.

Neonatal hemochromatosis is a diagnosis of exclusion. It is diagnosed after the exclusion of other causes of hepatic failure, which could sometimes result in delayed diagnosis.[11] Ekong et al[5] recommended measuring serum ferritin and AFP as they are the most sensitive tests for detecting NH. In this study, all patients had raised serum ferritin level and serum transferrin saturation level (median 2422 μg/l and 86%, respectively). This was similar to Grabhorn et al[20] study where all of his patients had elevated serum ferritin level, but their levels of ferritin and levels of transferrin saturation were higher (median 4179μg/l and 99% respectively). Serum alpha-fetoprotein levels were very high in all tested patients and this supports a case report carried out by Pearson et al[11] in which the serum alpha fetoprotein levels was very high. The median prothrombin time (PT) was 17.5 seconds (range 11-60 seconds) which was considered low in comparison to Flynn et al[2] and Rand et al[19] studies, which was 40 seconds and 41 seconds, respectively. This might be explained by the presence of mildly affected patients in this study. Most of the pathological descriptions of NH were obtained from autopsy specimens of stillbirths and newborns.[6] In this study, NH was confirmed by hepatic histology (liver biopsy in one and postmortem autopsies in 2). No fibrosis was found in the liver biopsy, while both autopsies showed mild focal to prominent fibrosis. Biopsies were not taken from other patients either due to the parental refusal or their critical conditions. Ekong et al[17] reported 2 infants with advanced portal fibrosis and focal formation of regenerative nodules in liver biopsies. Grabhorn et al[20] reported 16 patients, significant hepatocytes siderosis was seen in the liver biopsies of 14. The labial salivary gland biopsy has been recognized as a useful means of establishing a diagnosis of NH. These biopsies were recommended as a diagnostic addition as hemosiderin accumulates in acinar epithelial cells.[14] In this study, buccal biopsies were performed in 8 patients, but only one stained positive for iron. Although the benefits of labial biopsy make it attractive as routine work-up for NH, the procedure is not without drawbacks. The quantity of hemosiderin in the acinar epithelial cells of minor salivary glands is often minimal especially in the early stage of the disease leading to false negative results. Having said that,negative staining for hemosiderin does

not necessarily exclude the diagnosis of NH.[14] Abdomen MRI scan is a helpful tool in the diagnosis of NH. In this study, 8 patients underwent abdominal MRI which revealed iron overload. In 3 patients, the pancreas was also involved. In other studies, hepatic iron overload was seen only in 4 patients out of 16 and in 2 out of 6 patients,[10] which raised the issue of MRI sensitivity.

Neonatal hemochromatosis carries a high mortality despite medical therapy.[2] On 1993-1994, anti-oxidant cocktail therapy was established as a supportive treatment.[2] Studies have shown varied success with cocktail therapies, and more than few combinations and dosages have been described in the literature.[11] In this study, the overall survival rate was 80%. Grabhorn et al[20] reported 68.7% survival rate without the need of liver transplantation. Early diagnosis and treatment have improved outcomes for infants with NH.[11] However, the cocktail therapy may pose potential risks such as PGE1 might lead to persistent ductus arteriosus while desferrioxamine, being a side rophore, may predispose infants to infections.[21] Exchange transfusion (ET) was used before as a non-specific supportive care for patients with NH.[9] In this study, patient 9 underwent ET for indirect hyperbilirubinemia prior to the diagnosis and he survived with residual hepatosplenomegaly. Escolano-Margarit et al[13] reported a case of confirmed NH that underwent ET at an early stage of the illness and subsequently presented with a complete cure. Rand et al[19] reported 16 newborn infants treated with high-dose IVIG, in combination with ET in 13 (ET/IVIG), and compare the outcome with historical controls treated conventionally. They concluded that immune therapy with ET/IVIG appears to improve the outcome and reduce the need for liver transplantation in infants with NH.

Maternal IVIG has been reported to be a successful way of fetal therapy to prevent the fatal course of NH and was associated with better survival rate.[15,22,23] Neonatal hemochromatosis carries a variable prognosis. Many patients die of hepatic failure or require liver transplant, whereas others survive without any specific treatment.[12] In this study, one patient developed hepatopulmonary syndrome, another had chronic liver disease and awaiting for liver transplant, one patient showed spontaneous improvements without medications. Inui et al[12] reported one case who survived without use of any specific therapy such as an antioxidant and chelator regimen or liver transplant.

This study was limited by the small sample size, which can be justified by the rarity of the disease. A further limitation is that, it is a retrospective study which misses some of the related data. Further multicenter studies of NH are required to increase our understanding of the etiologies and pathogenesis of this fatal disease and to develop its preventive and therapeutic choices.

In conclusion, NH is a rare liver disease of newborns with a spectrum of clinical severity. An elevated serum ferritin and AFP levels will help to confirm the diagnosis. This study showed male preference of the disease and good outcome for treatment with antioxidant therapy. We recommend starting antioxidant therapy for any newborn with acute liver failure suspected to have NH until other causes hepatic failure were excluded. Further studies of NH are indicated to improve our understanding of this fatal disease.

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