Successful treatment of neonatal hemochromatosis with exchange transfusion and intravenous immunoglobulin in lower northern Thailand: Case report and review literature

Thitima Ngoenmak[1*], Julintorn Somran[2], Nongluk Oilmungmool[3]

[1] Department of Pediatrics, Faculty of Medicine, Naresuan University, Phitsanulok, 65000 Thailand

[2]Department of Pathology, Faculty of Medicine, Naresuan University, Phitsanulok, 65000Thailand

[3]Department of Radiology, Faculty of Medicine, Naresuan University, Phitsanulok, 65000Thailand

**Correspondent author: Thitiman@nu.ac.th. Thitima7@hotmail.com.*

Abstract

Background: Neonatal hemochromatosis is a rare disorder and clinically defined as severe neonatal hepatic disease in associated with extrahepatic siderosis. NH - GALD has a significant mortality and morbidity risk.

Case report: A 14-day old male neonate who is a second child in a Thai family and born to mother without a previous history of NH-GALD. He developed severe liver failure since birth.

Result: Diagnosis of NH-GALD is positive iron staining (Prussian blue) of minor salivary glands in lower lip biopsy and by magnetic resonance imaging (MRI). Additionally, serum ferritin level as well as alpha-fetoprotein is high and liver biopsy proves severe hepatocyte injury with iron overload. The patient successfully treated with combination of exchange transfusion, intravenous immunoglobulin, and chelation-antioxidant therapy.

Conclusion: The diagnosis of NH-GALD requires diagnosing extrahepatic siderosis by tissue analysis or MRI. Early treatment improves the outcome and decrease rate the liver transplantation

Keywords: Alloimmune, hemochromatosis, siderosis, liver failure, immunoglobulin

Introduction

Neonatal hemochromatosis (NH) is a rare clinical condition that cause severe liver injury with extrahepatic siderosis. Iron overload in hepatocytes and extrahepatic sites was previously described as an inborn error of iron metabolism. In present, it is discovered that the major etiology of NH is gestational alloimmune liver disease (GALD). Abnormal accumulation of iron is the consequence of fetal liver injury due to transplacental transfer of maternal IgG antibodies directed against a fetal hepatocyte antigen [1-3]. There are reported cases of GALD causing acute liver failure and fetal death without the neonatal hemochromatosis phenotype [4] and few NH cases are caused by non-GALD such as mitochondrial respiratory chain disorder [1,5]. Therefore, Neonatal hemochromatosis because of GALD (NH-GALD) is typically present with acute liver failure occurring shortly after birth. An elevation of ferritin and iron levels is not diagnostic. Iron overload in peripheral tissue and internal organs should be confirmed by special and standard techniques. Without specific treatment, the outcome of NH-GALD is poor and recurrence risk of further pregnancy is very high[1]. The postnatal treatment with exchange transfusion, intravenous

immunoglobulin (IVIG) has been successfully used, along with antioxidants, iron chelator without liver transplantation and for antenatal prevention, intravenous IgG during pregnancy has been proved[6-10]. Early diagnosis and treatment are critical. We report a case of neonatal liver failure (NLF) in a preterm infant who underwent extensive investigation and was diagnosed as neonatal hemochromatosis because of GALD (NH-GALD). Our patient was successfully treated with double exchange transfusion, intravenous immunoglobulin, and antioxidants.

Case report

A Thai male infant born by cesarean section, due to prolong PROM (96hr) with polyhydramnios at 34 weeks and 6 days of gestation with a birth weight of 2,600 grams. The first and fifth minute Apgar scores were 9 and 10, respectively. He was a second child of a 27-year-old healthy mother with a healthy first child. Parents were nonconsanguineous and denied any family history of neonatal death or chronic diseases. After birth, the infant presented jaundice and hepatosplenomegaly and laboratory results (Table 1) showed abnormal liver blood test and coagulopathy. He was referred to Naresuan University Hospital when he was fourteen-day-old. On admission in Naresuan University-NICU, he weighed 2,360 grams (10-25 th percentile). Physical examination revealed a jaundiced infant with hepatosplenomegaly. There were abnormal synthetic liver function (hypoalbuminemia and coagulopathy), mild rising of liver enzymes, mild anemia, mild thrombocytopenia and low level factor V,VII. His blood group was O, Rh+ and his mother was B, Rh+. Reticulocyte count and G6PD level were normal. TORCH titers were negative. The infant had abnormal iron profile, and high alpha Fetoprotein (Table 1).

Table 1 Laboratory data and results

	Before admission**	14 day-olds	18 day-olds *#	22 day-olds #	33 day-old #	62 day-olds	92 day-olds	109 day-olds
Total Protein (g/dL)		4.0	3.9	4.5	5.3	5.4	4.6	
Albumin(g/dL)		2.4	2.8	3.1	3.1	4.0	3.3	
Globulin(g/dL)		1.6	1.1	1.4	2.2	1.4	1.3	
TB (<2 mg/dL)	25.3	18.23	5.11	10.99	18.71	9.09	2.44	
DB (<0.6 mg/dL)	13.3	11.35	4.13	8.2	13.86	7.18	2.11	
AST (25-75 U/L)	287	155	37	166	157	88	50	
ALT (13-45 U/L)	85	60	10	31	67	44	28	
ALP (150-420 U/L)	407	884	114	291	683	513	381	
PT	20.4	16	15.7	19.6	13.9	11.9	12.7	
PTT	87.3	59.6	40.5	73.9	47.7	39.2	39.10	
INR	1.94	1.4	1.38	1.72	1.23	1.05	1.12	
White blood cell count(cell/uL)		8,410	3,950		9,950	9,280	6,580	
Platelet (cell/uL)		221,000			384,000	388,000	284,000	
Hematocrit (%)		34.1			31.5	29.2	27.2	
Ferritin (ng/mL)		3,361		1,935				189.2
Serum iron (50–170 ug/ml)		98.6						
Transferrin Saturation (25-50%)		100						
Alpha Fetoprotein(ng/mL)		77,539						291.9
Factor V (70-130)		44						
Factor VII (60-140)		18						

(ALT = alanine aminotransferase; AST = aspartate aminotransferase; TB = total bilirubin; DB = directed bilirubin;
INR = international normalized ratio; PT = Prothrombin time; PTT = Partial thromboplastin time)

** After received intravenous vitamin K

* Double volume exchange transfusion

the day with or after Intravenous immunoglobulin treatment

The initial differential diagnosis includes infection, inborn error of metabolism, and metabolic liver disease. Serologic tests for Syphilis (VDRL), Cytomegalovirus (urine PCR), parvovirus B19 (IgG and IgM), Epstein-Bar virus (IgG and IgM), Herpes Simplex Virus 1 and 2 (IgG and IgM), Hepatitis B and C viruses (IgG and IgM) were negative. Eye examination was unremarkable. Film skull and long bone as well as ultrasound whole abdomen showed no abnormal features. Empirical antibiotic treatment (intravenous cefotaxime and ampicillin) started and infant formula was changed to lactose free, because of positive urine benedict test. Afterthat, blood test for metabolic comprehensive screening and urine organic acid were negative. In the age of 15-days-old, abnormal accumulation of iron in minor salivary gland from buccal mucosa punch biopsy was demonstrated by Prussian blue stain (Figure 1 and 2). Liver biopsy confirmed liver injury with giant-cell or pseudoglandular transformation, cholestasis, and moderate accumulation of hemosiderin pigment (Figure 3 and 4). MRI whole abdomen and thyroid were limited but showed diffused decrease T2-signal intensity of the liver with low signal intensity on the in-phase SPGR, suggestive of iron depositional disease or hemochromatosis. Small PDA was demonstrated by echocardiography and disappeared later before discharge. Based on clinical, biochemical, serological, histological, and imaging findings, the diagnosis of NH-GALD was considered. Therefore, A 14-day-olds infant received fresh frozen plasma before got double volume exchange transfusion and first-course intravenous immunoglobulin (IVIG) along with antioxidant cocktail (N-Acetyl cysteine, Vitamin E, Selenium) and iron chelation, except Prostaglandin E1 at 18-day-olds of age. Second and third course of IVIG were added at 22 and 29 day-olds of age. Our patient responses well with treatment and laboratory results gradually improved (Table 1). Recently, his growth and development proper for age and child at follow up.

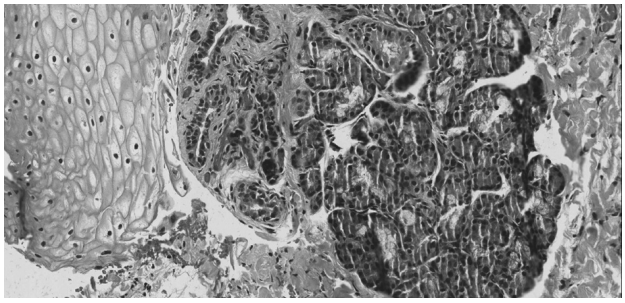

Figure 1 H&E stain: Normal-appearing minor salivary gland in lower lip biopsy

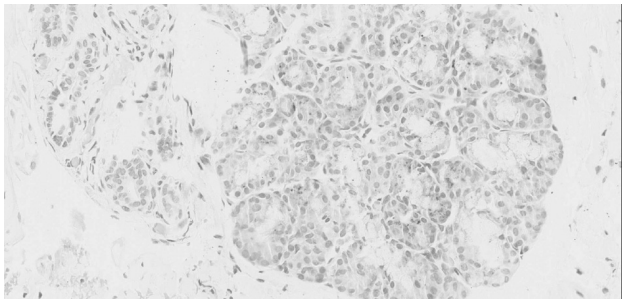

Figure 2 Prussian Blue stain: Accumulation of iron in minor salivary gland (Blue color)

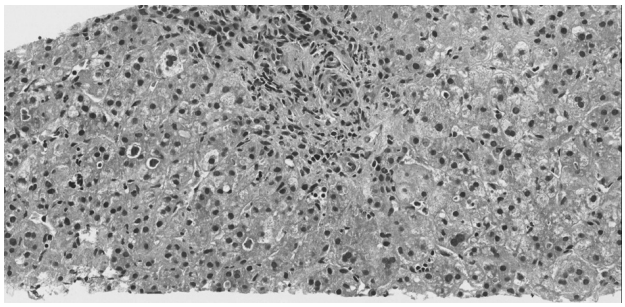

Figure 3 H&E stain: Neonatal hepatitis with giant cell and pseudoglandular transformation and canalicular cholestasis

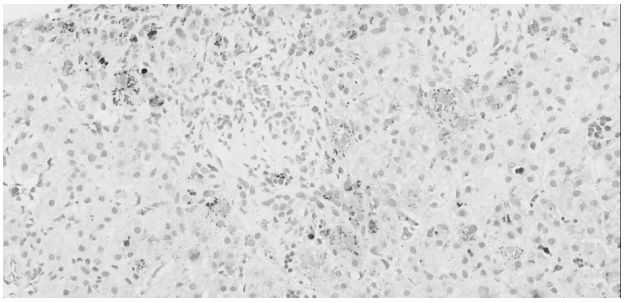

Figure 4 Prussian Blue stain: Accumulation of iron in hepatocytes (Blue color)

Discussion

Neonatal hemochromatosis, NH- GALD is the maternal IgG antibodies against the fetal-derived antigen transport across the placenta and cause complement-mediated fetal hepatocyte injury [1,2]. Iron overload in hepatic and extrahepatic tissue present afterward. The NH-GALD is include poor control of iron flux across the placenta and impairment of central repository and distribution apparatus for iron in the fetus[12]. Reduced synthesis of fetal hepcidin in the severely injured liver leads to impaired regulating of placental ferroportin function. Moreover, there are reported cases of non-GALD neonatal hemochromatosis [5,13]. We report a case of neonatal hemochromatosis due to gestational alloimmune liver disease, NH-GALD. Our case is a second boy of a healthy mother who has no evidence of GALD in the first child. Polyhydramnios presents and is one of antenatal signs of this disease that include intrauterine growth retardation, oligohydramnios, placental edema and sometime polyhydramnios [8,12,14,15]. The infant developed severe liver injury and hepatosplenomegaly at birth. Coagulopathy, thrombocytopenia, hypoalbuminemia, and transaminitis confirm severe hepatic injury and acute liver failure. The diagnosis of NLF can be defined based on the diagnostic criteria (pediatric ALF study group): 1.) hepatic-based coagulopathy (prothrombin time [PT] ≥ 15 s or international normalized ratio [INR] ≥ 1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy [HE] or PT ≥ 20 s or INR ≥ 2 regardless of clinical HE); 2.) biochemical evidence of acute liver injury; and 3.) no known evidence of chronic liver disease. Differential diagnosis of neonatal liver failure include viral infection, immune related disorder, metabolic diseases, hematologic diseases, and cardiovascular diseases[1]. NH-GALD should be suspected in all neonates with signs of severe liver disease or in unexplained cases of fetal demise in the late second or third trimester[4,8]. Even through, NH-GALD is one of the common causes of NLF, the others are more common and should be excluded. In our case, antenatal/ perinatal infection with syphilis infection, herpes viruses, adenovirus, parvovirus B19, and hepatitis B and C viruses and transplacental infection such as TORCH are excluded by many methods (Serology, PCR, culture, imaging, etc.) as well as metabolic disorders, hematologic disease (G6PD), and cardiovascular diseases (only small PDA found via echocardiography). In the literatures, the investigations which support the diagnosis of NH comprise 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 [11-13] 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). 80% of infants with NH-GALD have elevated serum AFP range 100,820 to 670,000 ng/mL and /or elevated serum ferritin range 1250 to 15,948 ng/mL[12]. 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[9,16]. The MRI can demonstrate iron overload in heart, pancreas, exocrine and endocrine organs, intestines, and gastric and salivary glands[17]. Because of immune mediated liver injury, liver biopsy reveals hepatocyte loss with giant cell or pseudoglandular transformation, diffuse fibrosis, and varying degrees of cholestasis with hemosiderin deposition[1,5] and the membrane attack complex, C5b9 expression in liver is demonstrated by immunohistochemical technique. Hepatic hemosiderosis is not specific,

however the more characteristic of NH-GALD is extrahepatic hemosiderosis. Demonstration of iron accumulation in others tissue with reticuloendothelial sparing is important. Many evidences in our case support the diagnosis of NH-GALD that includes abnormal iron profiles (high ferritin, high serum iron, and high transferrin saturation), iron overload in liver with giant cell hepatitis, abnormal accumulation of iron in minor salivary glands from buccal mucosa punch biopsy (extrahepatic hemosiderosis). Our case is abnormal findings in MRI only liver that showed diffuse decrease T2-signal intensity and low signal intensity on the in -phase SPGR. It is not confirmed supportive diagnosis NH. Because MRI whole abdomen, heart and thyroid were limited. Normally, MRI should be demonstrated decrease T2 signal or siderosis in hepatic and extrahepatic tissue, most commonly the pancreas, heart, and adrenal glands. The immunohistochemical study for C5b9 is not available in our laboratory, nevertheless C5b9 expression in liver is not specific for this disease in recent study[18]. Usually literatures demonstrated on immunostaining for the C5b-9 complex. This test can be used to distinguish NH-GALD from NH associated with other causes [19,20]. Currently, the treatment of NH-GALD recommendations for medical treatment though liver transplantation can be considered. The combination of double volume exchange transfusion and intravenous immunoglobulin G (IVIG) is accepted to improve outcome and reduce the requirement of liver transplantation in many studies [3,7,10,21,22]. By the concept of alloimmune disease, exchange transfusion initially removes possible maternal antibodies against neonatal antigen and intravenous immunoglobulin G blocks antibody action and interferes with complement activation. However, numbers of volume exchange transfusion and numbers of IVIG course as well as its dose are variable. Some studies successfully treat with double volume exchange transfusion [10,23,24] or two exchange transfusion [22], and a reported case requires four exchange transfusions [21]. The course numbers and dose of IVIG seem to be adjusted base on the patient clinical data. Two or three courses of IVIG might be required in some cases. In each course, the dose of IVIG is 1 g/kg or higher (such as 2g/kg). Close monitoring of IVIG side effects including fever, hypotension, hypoglycemia and necrotizing enterocolitis is recommended [7]. The benefits of antioxidant cocktail and iron chelation are controversial in the past [22,25,26]. Later, up to 80% survival rate of severe NH treated by exclusive chelation-antioxidant therapy present in a literature [27] but this literature [19] was reported these 100 infants had a 13% survival rate. Our case received double volume exchange transfusion and three courses of IVIG (1g/kg) that is similar to one successful literature [10]. Additionally, antioxidant cocktail and iron chelation, except Prostaglandin E1 are added. The infant responses well with a combination of exchange transfusion, IVIG treatment, and short duration of chelation-antioxidant therapy.

Conclusion

NH-GALD is a serious condition. Without proper management and adequate treatment, the outcome of this disease is very poor. Recurrence of disease is high, estimated at 90% in subsequent pregnancy [3,28] and can be prevented by maternal gestational therapy with intravenous IgG [2,6,15]. Systematic approach of NH-GALD are essential for neonate who develop acute liver failure at or shortly after birth. Early postnatal treatment is required for the good outcome and antenatal management reduces the recurrent rate in subsequent pregnancy.

Conflicts of interest

All authors have none to declare.

Acknowledgments

The authors would like to thank teams at Naresuan university hospital including nurses for nursing care and scientists in the diagnostic pathology unit for rapid tissue and special stain preparation.

References

1. Russo P, Ruchelli ED, Piccoli DA. Pathology of Pediatric Gastrointestinal and Liver Disease. 2nd ed: Springer, Berlin, Heidelberg; 2014.
2. Feldman AG, Whitington PF. Neonatal hemochromatosis. Journal of clinical and experimental hepatology. 2013;3:313-20.
3. Lopriore E, Mearin ML, Oepkes D, Devlieger R, Whitington PF. Neonatal hemochromatosis: management, outcome, and prevention. Prenatal diagnosis. 2013;33:1221-5.
4. H, Malladi P. Gestational alloimmune liver disease in cases of fetal death. The Journal of pediatrics. 2011;159:612-6.
5. Heissat S, Collardeau-Frachon S, Baruteau J, et al. Neonatal hemochromatosis: diagnostic work-up based on a series of 56 cases of fetal death and neonatal liver failure. The Journal of pediatrics. 2015;166:66-73.
6. Whitington PF, Hibbard JU. High-dose immunoglobulin during pregnancy for recurrent neonatal haemochromatosis. Lancet (London, England). 2004;364:1690-8.
7. Rand EB, Karpen SJ, Kelly S, et al. Treatment of neonatal hemochromatosis with exchange transfusion and intravenous immunoglobulin. The Journal of pediatrics. 2009;155:566-71.
8. Annagur A, Altunhan H, Yuksekkaya HA, Ors R. Therapeutic management of neonatal hemochromatosis: report of four cases and literature review. Human & experimental toxicology. 2011;30:1728-34.
9. Flynn DM, Mohan N, McKiernan P, et al. Progress in treatment and outcome for children with neonatal haemochromatosis. Archives of disease in childhood Fetal and neonatal edition. 2003;88:F124-7.
10. Jimenez-Rivera C, Gupta A, Feberova J, de Nanassy JA, Boland MP. Successful treatment of neonatal hemochromatosis as gestational alloimmune liver disease with intravenous immunoglobulin. Journal of neonatal-perinatal medicine. 2014;7:301-4.
11. Whitington PF. Fetal and infantile hemochromatosis. Hepatology (Baltimore, Md). 2006;43:654-60.
12. Whitington PF. Neonatal hemochromatosis: a congenital alloimmune hepatitis. Seminars in liver disease. 2007;27:243-50.
13. Neil E, Cortez J, Joshi A, et al. Hepatic failure, neonatal hemochromatosis and porto-pulmonary hypertension in a newborn with trisomy 21--a case report. Italian journal of pediatrics. 2010;36:38.
14. Knisely AS, Mieli-Vergani G, Whitington PF. Neonatal hemochromatosis. Gastroenterology clinics of North America. 2003;32:877-89, vi-vii.
15. Pearson L, Bissinger R, Romero KR. Neonatal hemochromatosis: a case report. Advances in neonatal care : official journal of the National Association of Neonatal Nurses. 2009;9:72-6.
16. Lee WS, McKiernan PJ, Kelly DA. Serum ferritin level in neonatal fulminant liver failure. Archives of disease in childhood Fetal and neonatal edition. 2001;85:F226.
17. Whitington PF, Kelly S, Ekong UD. Neonatal hemochromatosis: fetal liver disease leading to liver failure in the fetus and newborn. Pediatric transplantation. 2005;9:640-5.
18. Dubruc E, Nadaud B, Ruchelli E, et al. Relevance of C5b9 immunostaining in the diagnosis of neonatal hemochromatosis. Pediatric research. 2017;81:712-21.
19. Taylor SA, Kelly S, Alonso EM, Whitington PF. The effects of gestational alloimmune liver disease on fetal and infant morbidity and mortality. J Pediatr 2018;196:123-8.
20. Chu A, Beritto T D, Kesavan K, Hageman J R and Azzam R. Neonatal hemochromatosis: Evaluation of the neonate with hepatic failure. Neoreviews 2016; 17:e154-60.
21. Nair J, Kumar VHS. Liver Failure and Conjugated Hyperbilirubinemia in a Preterm Neonate: Role of Early IVIG and Exchange Transfusion. AJP reports. 2018;8:e95-e8.

22. Timpani G, Foti F, Nicolo A, Nicotina PA, Nicastro E, Iorio R. Is exchange transfusion a possible treatment for neonatal hemochromatosis? Journal of hepatology. 2007;47:732-5.
23. Babor F, Hadzik B, Stannigel H, Mayatepek E, Hoehn T. Successful management of neonatal hemochromatosis by exchange transfusion and immunoglobulin: a case report. Journal of perinatology : official journal of the California Perinatal Association. 2013;33:83-5.
24. Machtei A, Klinger G, Shapiro R, Konen O, Sirota L. Clinical and Imaging Resolution of Neonatal Hemochromatosis following Treatment. Case reports in critical care. 2014;2014:650916.
25. Sigurdsson L, Reyes J, Kocoshis SA, Hansen TW, Rosh J, Knisely AS. Neonatal hemochromatosis: outcomes of pharmacologic and surgical therapies. Journal of pediatric gastroenterology and nutrition. 1998;26:85-9.
26. Murray KF, Kowdley KV. Neonatal hemochromatosis. Pediatrics. 2001;108:960-4.
27. Grabhorn E, Richter A, Burdelski M, Rogiers X, Ganschow R. Neonatal hemochromatosis: long-term experience with favorable outcome. Pediatrics. 2006;118:2060-5.
28. Whitington PF, Kelly S. Outcome of pregnancies at risk for neonatal hemochromatosis is improved by treatment with high-dose intravenous immunoglobulin. Pediatrics. 2008;121:e1615-21.

รายงานผู้ป่วยและทบทวนวรรณกรรม การรักษา Neonatal Hemochromatosis ด้วยการเปลี่ยนถ่ายเลือดและการให้ Immunoglobulin

ธิติมา เงินมาก[1], จุลินทร สำราญ[2], นงลักษณ์ อ้อยมั่งมูล[3]

บทคัดย่อ

บทนำ: โรค Neonatal hemochromatosis เป็นโรคที่พบไม่บ่อย ซึ่งผู้ป่วยจะมีอาการตับวายที่รุนแรงตั้งแต่ทารก โดยโรคนี้จะเกี่ยวกับการสะสมธาตุเหล็กที่นอกตับปริมาณมาก และ Neonatal hemochromatosis จะพบแบบ GALD ได้บ่อยกว่าแบบอื่น ซึ่งจะทำให้พบอัตราการตายที่สูง ในผู้ป่วยเด็กชายรายนี้ มีอาการตับวายเฉียบพลันตั้งแต่เกิด เป็นบุตรคนที่สอง ประวัติในครอบครัวไม่เคยมีประวัติเป็นโรคตับหรือโรคนี้มาก่อน ส่วนการวินิจฉัยโรคนั้นสามารถตรวจทางพยาธิวิทยาซึ่งมีการย้อมชิ้นเนื้อ Prussian blue บริเวณเยื่อบุริมฝีปากล่าง ต่อมน้ำลาย จะพบลักษณะมีธาตุเหล็กสะสมอยู่ และนอกจากนี้ได้ตรวจคลื่นแม่เหล็กไฟฟ้าก็จะพบลักษณะ T2 signal ลดลง ส่วนระดับ ferritin ในเลือด และระดับ Alpha fetoprotein จะพบมีค่าสูง ในแง่ของการรักษาในผู้ป่วยเด็กรายนี้ได้ทำการเปลี่ยนถ่ายเลือด ให้อิมมูนโนโกลบูลิน และ anti-oxidant ต่อมาอาการของผู้ป่วยดีขึ้น

สรุป: การวินิจฉัยและรักษาอย่างรวดเร็วจะทำให้ลดการปลูกถ่ายตับในเด็กได้

คำสำคัญ: Alloimmune, hemochromatosis, siderosis, ตับวาย, อิมมูนโนโกลบูลิน

[1]*ภาควิชากุมารเวชศาสตร์*

[2]*ภาควิชาพยาธิวิทยา*

[3]*ภาควิชารังสีวิทยาคณะแพทยศาสตร์ มหาวิทยาลัยนเรศวร ต. ท่าโพธิ์ อ. เมือง จ. พิษณุโลก 65000*