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Evidence Based Case Report

Neonatal hemochromatosis attributed to gestational alloimmune liver disease treated with IVIG and exchange transfusion therapy: an evidence-based case report

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Neonatal hemochromatosis (NH) is a rare fatal liver disease accompanied by hepatic and extrahepatic iron overload.[1-3] Gestational alloimmune liver disease (GALD) is a materno-fetal alloimmune disorder and leading cause of NH.[2,4,5] This condition allows an interplay between the maternal adaptive immune system and the fetus, resulting in an allograft to the mother. The mother becomes sensitized to an alloantigen expressed by the fetus and forms specific reactive antibodies. Immunoglobulin G (IgG) is transported through the placenta and attacks the fetal hepatocytes, resulting in severe loss of hepatocytes and fetal iron overload.[3,6]

Liver transplantation has been the only definitive treatment for NH for many years, with a survival rate of ±35%. Conventional therapy containing antioxidants and chelation agents reportedly have very poor success, with survival rate of only 10-20%. A new treatment paradigm involving intravenous immunoglobulin (IVIG) and exchange transfusion (ET) therapy has shown significant success in survival rate in NH, decreasing the need for liver transplantation.[3,7,8]

Here we present a case of NH caused by GALD and treated successfully with a combination of IVIG therapy and ET. We also aimed to evaluate the efficacy of IVIG and ET therapy for NH. **[Paediatr Indones. 2021;61:350-5 ; DOI: 10.14238/pi61.6.2021.350-5].**

Keywords: *neonatal hemochromatosis; gestational alloimmune liver disease; intravenous immunoglobulin; exchange transfusion*

The Case

A male newborn infant of 33 weeks gestational age was born to a 29-year-old G1 mother suspected to have Parvovirus infection. The infant was delivered by emergency caesarean section due to severe oligohydramnion, preterm contraction, and fetal distress. He was not vigorous at birth, with APGAR scores of 1, 6, and 7, and required extensive resuscitation including endotracheal intubation. His birth weight was 2,000 g. The apnea was thought to be due to viral encephalopathy since the Thompson score was 6. Initial blood work showed elevated liver function tests: AST was 1031.10 U/L, ALT was 242.90 U/L, PT was 33.3 seconds, and APTT was 58.8 seconds. His serum ferritin level was 29,425 ng/mL. The NH attributed to GALD was suspected clinically due to prenatal history, severe clinical course, and poor liver function.

His breathing was supported by mechanical ventilation with volume guarantee mode. Hypoglycemia occurred and was corrected immediately after birth.

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Acyclovir combined with ampicillin sulbactam and gentamicin were given immediately after birth as a treatment and prophylaxis for infection. Surfactant and aminophylline were given to aid ventilation; fresh frozen plasma was also given. Intravenous immunoglobulin (IVIG) at a dose of 0.4 mg/kg/day was given immediately after birth. Exchange transfusion was done at the ages of 1, 3, 5, and 7 days, with 350 mL of whole blood each. After two days of IVIG infusion and four ETs, the infant's serum ferritin level gradually decreased by 45.26%, 91.02%, 96.07%, 95.99%, respectively, compared to the initial serum ferritin level.

Due to significant improvement in ventilation, the infant was extubated at the age of 4 days. The decrease of serum ferritin level was also enhanced by desferoxamine, acetylcysteine, and vitamin E given orally since day 8. Repeated tests showed improved liver function at 14 days of age (AST 16.2 U/L and ALT 8.9 U/L). Serum ferritin level also showed a notable decrease, reaching 552 ng/mL (98.12% decrease compared to the initial serum ferritin level) on day 18. The infant made significant progress in terms of nutrition and development without evidence of abnormal neurological findings. He was discharged at 26 days of life.

Clinical Question

Is IVIG combined with ET more effective than conventional therapy as the treatment for NH due to GALD?

Methods

A literature search to answer the clinical question was conducted on four electronic databases, namely *PubMed®*, *MedScape®*, *ScienceDirect®*, and *BMC®* from December 20, 2019 until January 1, 2020. The following Boolean combination of terms was inserted in the above-mentioned databases: ("neonatal hemochromatosis" OR "gestational alloimmune liver disease") AND ("intravenous immunoglobulin" OR "exchange transfusion"), including the synonyms and MeSH Terms. No date limits were inserted.

The searches were limited to randomized controlled trials (RCT), non-randomized controlled studies (NRS), cohort studies, systematic reviews, or meta-analyses. The RCTs were excluded if they had been reviewed in a systematic review and/or meta-analysis. Other inclusion criteria were full-text available in English, neonates (0 to 28-day-old), as well as diagnosed as neonatal hemochromatosis or gestational

Table 1. Clinical question formulation

Problem	Neonate with NH due to GALD
Intervention	IVIG combined with ET
Comparison	IVIG and/or conventional therapy only
Outcome	Treatment effectiveness
Type of Question	Therapeutic
Type of Study	Cross-sectional

NH=neonatal hemochromatosis; GALD=gestational alloimmune liver disease; IVIG=intravenous immunoglobulin; ET=exchange transfusion

Table 2. Description of study eligibility

Research question	To determine if immunomodulatory treatment including IVIG and ET can favourably affect survival in NH diagnosed postnatally
Study design	Non-randomized, controlled trial
Participants	16 subjects getting intervention (IVIG and IVIG and ET) 131 historical controls (chelation and antioxidant treatment)
Interventions	1. IVIG 2. IVIG and ET
Outcome measurement	Survival without OLT
Results	IVIG and ET therapy improved the outcome of NH associated acute liver failure
Length of follow up	Varied, up to more than 1 year
Lost to follow up	Not stated
Risk of bias	Majority of the subjects also received parts of conventional therapy combination

NH=neonatal hemochromatosis; IVIG=intravenous immunoglobulin; ET=exchange transfusion; OLT=orthotopic liver transplantation

alloimmune liver disease or gestational alloimmune liver failure. Exclusion criteria were irrelevant topic, antenatal intervention, and non-data based papers. The flow chart of the selection process and its result sare shown in **Figure 1**. The selected literature was appraised using tools from the *Centre of Evidence-based Medicine, University of Oxford*.[9] The criteria checked were validity, importance, and applicability.

Results

A total of 87 studies were retrieved after screening for possible relevant title/abstract and evaluated for potential inclusion. Seven studies remained after excluding irrelevant topics and duplicates related to the same title extracted from different databases. After reading full-text and excluding some studies, only one

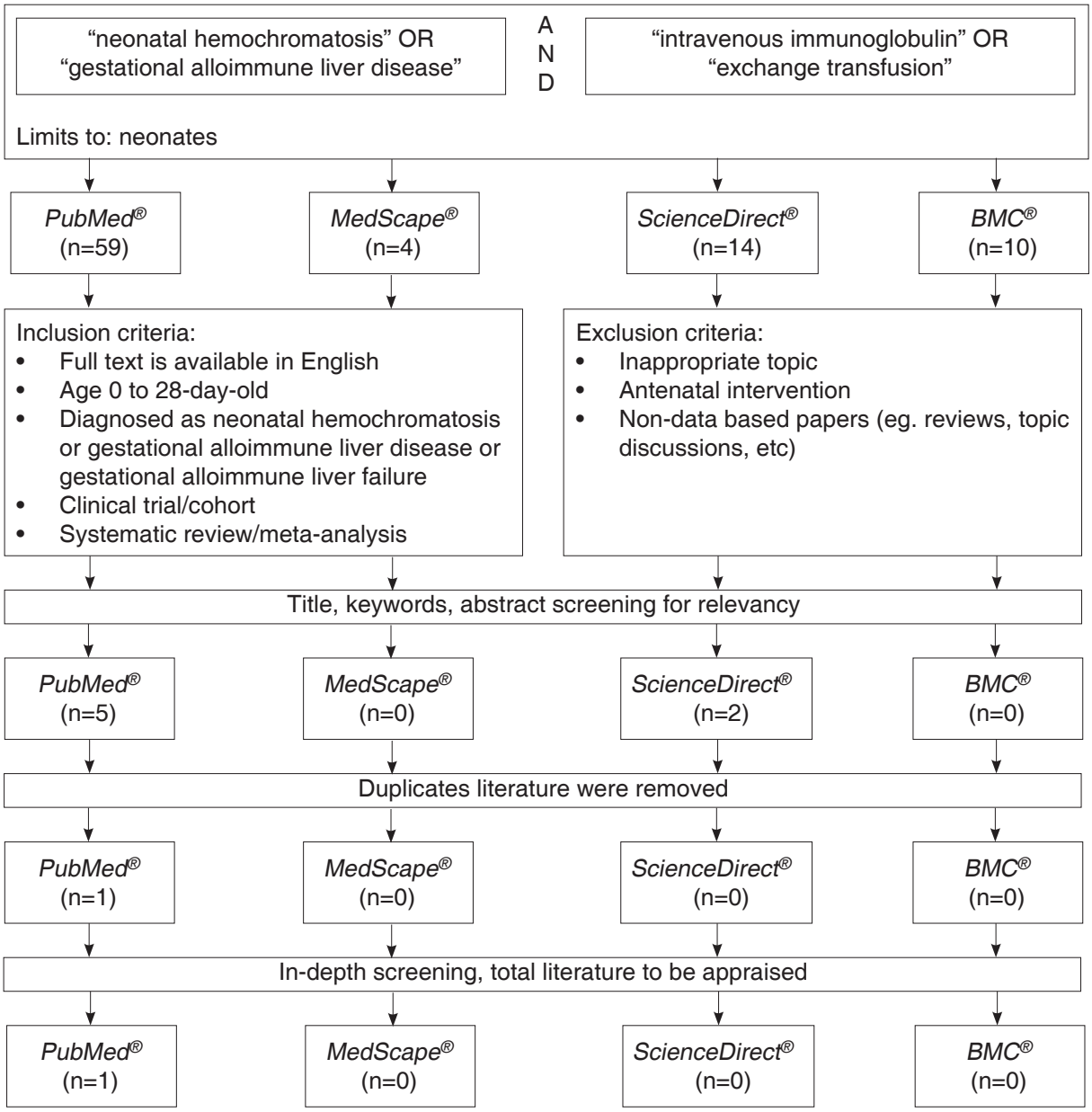

Figure 1. Study selection flow chart

study was included to be reviewed. No systematic review, meta-analysis or randomized controlled trial (RCT) was identified.

The single non-randomized clinical study appraised was by Rand *et al.*[14] in *PubMed®*. This journal was appraised using the tool from the Centre of Evidence-based Medicine, University of Oxford.[9] Subjects in the study were obtained from various centers. The 16 subjects were enrolled between 2004 and 2008 in 7 institutions in the United States and 1 each in The Netherlands and Australia. The baseline characteristics of the subjects were considered similar in terms of the degree of coagulopathy. The study groups received equal treatment according to the existing recommendations. The recommended volume of ET was twice the calculated blood volume of the subject. The recommended dose of IVIG was 1 g per kg body weight. All patients included in the study were accounted. Blinding or masking in the treatment of subjects was not clearly stated in this study. Results were presented as a comparison of survival outcome without liver transplantation. Seventy five percent of subjects had good outcome, defined as survival without liver transplantation, whereas good outcome was achieved in only 17% of historical control patients ($P<0.001$). Student T-test, ANOVA, and Fisher's exact test revealed P values of less than 0.001.

They compared newborns with liver failure due to NH treated with high-dose IVIG in combination with ET (IVIG and ET), and historical controls treated conventionally with a combination of chelating agents (deferoxamine) and antioxidants (vitamin E, N-acetylcysteine, selenium, and PGE-1). Seventy-five percent of the subjects had good outcome, which was defined as survival without orthotopic liver transplantation (OLT). On the other hand, good outcome was achieved in only 17% of control patients ($P<0.001$) who received antioxidant-chelation therapy, which the authors concluded might not be affected by the conventional therapy. Patients who received IVIG and ET therapy had significantly improved outcome compared to those who underwent conventional therapy.

The above study described and non-randomized their treatment (IVIG and ET and historical controls). They did not randomize their trial because of the difficulty to do so in severe NH. However, they did compare all 16 subjects getting intervention (IVIG *vs.* IVIG and ET) with 131 historical controls receiving conventional treatment (chelating agents and antioxidants). Characteristics of participants were significantly different between groups. Some participants were followed for more than one year, analyzed in the groups to which they belonged, and were treated similarly.

Although the study showed significant results, one of the shortcomings was that it did not include confidence intervals in the result. Albeit Rand *et al.*[14] did not explicitly state the cause of NH in their subjects, but since most cases of NH are attributed to GALD and the rest of characteristics in our patient was similar to the subjects in their study, the treatment carried out in this study was possible in the hospital setting where our patient was treated. The potential benefits of treatment outweigh the potential side risks in our patient.

Discussion

Neonatal hemochromatosis is a clinical syndrome in which liver disease in the newborn is accompanied by siderosis of hepatic and extrahepatic tissues in the pattern seen in hereditary hemochromatosis.[1,5,8] Studies suggested a genetic prevalence of 0.03-0.038 or a heterozygosity prevalence of 6-7%.[10] Gestational alloimmune liver disease is a materno-fetal alloimmune disorder directed at the fetal liver, often producing neonatal liver failure. The most common presentation is NH. The demonstration of deposition of complement component C5b-9 complex (membrane attack complex) in most hepatocytes in neonates with NH provided evidence for the alloimmune mechanism of the fetal liver injury.[4,5,11] The mechanism of iron overload in GALD relates to markedly depressed hepatic expression of hepcidin (HAMP) in the damaged fetal liver, which leads to dysregulation of placental iron flux. The occurrence of NH has 3 modes of transmission: infection, an unknown "maternal factor," or autosomal recessive inheritance.[4,5]

Neonatal hemochromatosis starts in utero when maternal IgG is passed to the fetus between the 17th and 22nd week of gestation.[12,13] This period has been suggested as the time of liver injury onset in NH-affected fetuses.[12] The typical clinical picture of NH due to GALD, although not specific, includes edema, ascites, little or no hepatomegaly, and severe

coagulopathy contrasting with a moderate rise in liver function markers. Signs of liver cirrhosis, such as atrophic heterogeneous or multinodular liver seen on ultrasound, can be findings that suggest NH related to GALD. However, these signs are also seen in mitochondrial respiratory chain disorder (MRCD). Increased neonatal serum ferritin level has been considered to be a biological marker of NH. There is no gold diagnostic tool for GALD yet. But some suggested to use immunohistochemistry for C5b-9 of a liver biopsy or T2 weighted MRI to show iron-laden tissues.[8] Nevertheless, hyperferritinemia is non-specific and most likely the hallmark of hepatocellular injury, regardless of the etiology. Massive hepatic necrosis, systemic inflammation, or decreased hepatic ferritin clearance may lead to hyperferritinemia.[12] Currently, the nature of maternal alloantibodies has not been identified, and no serologic test is available for the diagnosis of NH due to GALD. The diagnosis could be suggested by maternal gestational history of consecutive pregnancies resulting in fetal death or neonatal liver failure (NLF), clinical course, imaging study, and/or histopathologic findings. Immunohistochemistry demonstrating activated complement at hepatocytes (IDACH) in damaged liver is the best method to prove GALD.[12]

A cocktail containing both antioxidants and chelating agents has been used as conventional therapy to treat NH, but with poor survival rates of 10 to 20%.[8] A suggested cocktail includes N-acetylcysteine 200 mg/kg/day per oral three times a day for 17-21 doses, alpha-TPGS 25 IU/kg/day per oral twice a day for 6 weeks, deferoxamine 30 mg/kg/day intravenously over 8 hours until serum ferritin level decreases to less than 500 mcg/L, selenium 3 mcg/kg/day as continuous infusion for the length of hospitalization, and prostaglandin E1 0.4 mcg/kg/hour intravenously increased to 0.6 mcg/kg/hour over 3-4 hours.[10] Neonatal hemochromatosis is a frequent indication for liver transplantation in the first 3 months of life. When performed for NH, liver transplants are frequently complicated by prematurity, small size for gestational age and multi-organ failure. The overall survival of infants receiving a liver transplant for the indication of NH is ±35%.8 A high suspicion of GALD-induced NH in the affected neonate should prompt the use of ET and IVIG therapy, which may be life-saving. Exchange transfusion with IVIG at birth lessens the severity of the illness in affected neonates and improves outcomes.[12] The IVIG and ET therapeutic strategy seeks to limit any ongoing liver injury mediated by maternally derived IgG. Exchange transfusion is intended to remove maternal alloantibody remaining in the neonate's circulation. High-dose IVIG has many beneficial effects in IgG mediated injury.[14]

Rand *et al.*[14] analyzed a combination of double-volume ET to remove existing reactive antibodies and administration of high-dose IVIG (1 g/kg) to block antibody action (i.e., interfere with complement activation). Their experience with this approach in 16 infants with severe NH showed notable improvement in survival compared with 131 historical controls (published results with the antioxidants/chelation agents). Twelve subjects (75%) had good outcome, defined as survival without OLT, whereas good outcome was achieved in only 17% (23/131) of historical control patients ($P<0.001$). Four subjects died, two without and two after liver transplants. The authors concluded that IVIG and ET therapy might improve the outcomes of NH and should be considered as early as possible for the treatment.

Our patient underwent combination therapy of IVIG and ET starting from day 1, and continued on consecutive days with conventional therapy consisting antioxidants and chelating agents. Our patient's liver function tests showed improving results indicating a good response to the treatment. Our patient's clinical course demonstrated that the combination of IVIG and ET could be a promising treatment for GALD-induced NH, similar to that of Rand *et al.*[14]

Due to the lack of robust studies, there is insufficient evidence to warrant the advocacy of IVIG in combination with ET as a therapeutic approach to improve neonates with NH as GALD when compared to conventional medical therapy (chelating agents and antioxidants). Further RCTs will be needed to address the role of IVIG and/or ET in NH due to GALD.

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