The Effect of Prolonged Antenatal Intravenous Immunoglobulin Treatment in Preventing Gestational Alloimmune Liver Disease—A Case Series with Literature Review

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Abstract

Background Gestational alloimmune liver disease (GALD) is characterized by maternal IgG-directed fetal hepatocyte damage and can lead to severe liver failure and fetal or infant death. Moreover, GALD is associated with a near 90% risk of recurrence in subsequent pregnancies.

Case We present a case of a newborn patient delivered to a 32-year-old G2P1000 mother who received prolonged antenatal intravenous immunoglobulin (IVIG) treatment during the current pregnancy due to the neonatal death of the first child from GALD-related liver failure. Postnatal testing, including a liver magnetic resonance imaging (MRI) and buccal biopsy of this newborn, showed normal morphology of the liver without any abnormal iron deposition. Additional laboratory testing showed a lack of any liver injury.

Conclusion This case supports the use of antenatal IVIG immunotherapy to prevent the recurrence of GALD in subsequent pregnancies.

Keywords
- gestational alloimmune liver disease
- neonatal hemochromatosis
- antenatal IVIG
- recurrence
- fetal liver injury

Key Points

- GALD can lead to severe fetal liver injury.
- GALD is highly recurrent in subsequent pregnancies.
- Prophylactic IVIG may prevent GALD recurrence.

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Introduction

Gestational alloimmune liver disease (GALD) is a rare disease in which maternal antibodies are directed against fetal hepatocytes and lead to severe fetal liver injury.[1] The sequelae can be life-threatening, leading to late second-trimester fetal loss, third-trimester fetal loss, or neonatal liver failure presenting shortly after birth.[2] In the past, mortality was 80 to 90% in cases of GALD.[1] Treatment regimens have shifted over the last 10 to 20 years based on changing hypotheses of the pathogenesis of GALD, and intravenous immunoglobulin (IVIG) and plasma exchange transfusions have become the mainstays of treatment.[3] Since then, mortality rates associated with neonatal GALD have drastically decreased to less than 20%.[2]

More recently, it has been proposed that using IVIG antenatally in pregnant mothers who previously gave birth to an infant affected by GALD could improve infant outcomes in subsequent pregnancies.[2,4–6] Although randomized control trials for antenatal IVIG are unavailable given that there is not a current standard of treatment available, several prospective studies have shown significantly improved survival and health outcomes in children born to women treated with antenatal IVIG to prevent recurrence of GALD in subsequent pregnancies.[2,4–6] Most recently, a study using antenatal IVIG in 188 pregnancies resulted in the birth of 177 live infants with no evidence of clinical liver disease.[4] This is an especially important area of research, as recurrence rates of GALD in subsequent pregnancies are greater than 90%.[3] However, while the literature suggests that antenatal IVIG use can be beneficial in treating GALD, there are few studies available.

Here, we present the case of an infant who passed away several days after delivery due to complications secondary to GALD. We then present the case of a second infant delivered by the same mother who received prolonged antenatal IVIG infusions throughout the course of her pregnancy.

Case Presentation

Case 1

A term female infant was born to a 31-year-old G1P1000 mother at 38 weeks with severe respiratory distress requiring immediate intubation, ventilatory support, and neonatal intensive care admission with close cardiorespiratory monitoring. She was also noted to have significant pulmonary edema on day 1 of life (DOL 1). By DOL 3, she developed nuchal rigidity, repetitive head jerks to the left, and progressed to subclinical status epilepticus on DOL 4. She had cardiovascular compromise, could not be resuscitated, and was deceased.

On postmortem internal examination, the patient was noted to have 12 mL of ascites and a right pleural effusion containing 35 mL of sanguinous fluid. Her liver weighed 152.2 g (expected 78 g). She was diagnosed with neonatal hemochromatosis (NH) secondary to GALD via autopsy. Significant findings included diffuse steatosis and 3 to 4+ (out of 4+) panacinar iron deposition in the liver when evaluated with iron staining. Periportal fibrosis was seen upon evaluation with trichrome staining. Additional findings included regenerative hepatic tissue with non-confluent necrosis and periportal tract extramedullary hematopoiesis.

Case 2

A term female child was born to the same mother as Case 1, 32-year-old G2P1000, via scheduled c-section at 37 weeks. During her antenatal visits, she was advised to receive weekly infusions of 77 g IVIG, which were started at 14 weeks gestation. She received her last dose approximately 2 weeks prior to delivery. After birth, the patient had a normal physical exam with no evidence of acute liver failure, such as ascites or jaundice. Her laboratory studies showed normal albumin, normal liver profile, and glucose levels (►**Table 1**). Her coagulation profile was slightly elevated but normal for age as per newborn hematological laboratory values (►**Table 1**).

Alpha-fetoprotein levels were 82,100 ng/mL at birth and 58,092 ng/mL on DOL 1, slightly elevated but not within the ranges characteristically seen in GALD (►**Table 1**). Ferritin levels were also slightly elevated, a nonspecific finding consistent with hepatocellular injury (►**Table 1**). One dose of 3.2 g IVIG was administered on DOL 1, lowering the alpha-fetoprotein level on DOL 2 and increasing fibrinogen levels on DOL 2 to 4 (►**Table 1**).

Magnetic resonance imaging (MRI) demonstrated normal size and morphology of the liver, with normal parenchymal signal. No abnormal hepatic signal dropout was observed on in-phase and out-of-phase T1 GRE imaging (►**Fig. 1**). T2 MRI relaxometry of the liver showed that the hepatic iron concentration was predicted to be 0.7 mg/g, which is within normal limits. A buccal biopsy was also performed to rule out NH, and no iron deposition was found when evaluated with Prussian blue staining. MR hemoflash of the brain showed no signs of iron deposition within the brain parenchyma (►**Fig. 2**). However, the abnormal signal was identified in the right transverse sinus, right sigmoid sinus, and right internal jugular vein, and MR venography of the brain demonstrated loss of flow-related enhancement in this distribution, compatible with dural venous sinus thrombosis, for which enoxaparin was initiated (►**Fig. 3**). On DOL 9, the patient was discharged home on enoxaparin therapy for 30 days, with subsequent resolution of the thrombus. The patient was followed by the neonatal development follow-up team and pediatric hematology team after discharge. At the time of the submission, the patient was noted to be growing and developing appropriately for age.

Discussion

GALD is a disease characterized by fetal liver injury.[1,7] Sensitization to fetal liver antigens leads to the production of maternal IgG antibodies, which cross the placenta and act against fetal hepatocytes through complement-mediated damage.[3] The subacute form of GALD is most common, where hepatocyte injury in utero causes the infant to present with liver failure at birth.[8]

Hallmarks of GALD include severe liver injury and extrahepatic siderosis.[9] Extrahepatic siderosis is often used to

Table 1 Laboratory values on days 1 to 4 of life

Laboratory test	Day 1	Day 2	Day 3	Day 4
Liver profile				
Total bilirubin (2–6 mg/dL)	2.5	5.3	7.8	10.7
Direct bilirubin (<0.2 mg/dL)	<0.2	<0.2		
Alkaline phosphatase (110–300)	122	110		
ALT (6–50 U/L)	8	11		
AST (35–140 U/L)	29	34		
Albumin (2.9–5.5 g/dL)	3.4	3.1		2.9
Coagulation studies				
PTT (28.7–53.7 seconds)	69.3	71.9	60.6	54.9
PT (12.9–16.9 seconds)	16.0	17.3	16.5	12.9
INR (1.0–1.4)	1.4	1.6	1.5	1.2
Fibrinogen (135–283 mg/dL)	186	208	257	318
Other studies				
Alpha-Fetoprotein (<86,000 ng/mL)	82,100	58,092		
Ferritin (36–391 ng/mL)	418			
Glucose (30–80 mg/dL)	61	90	82	83

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

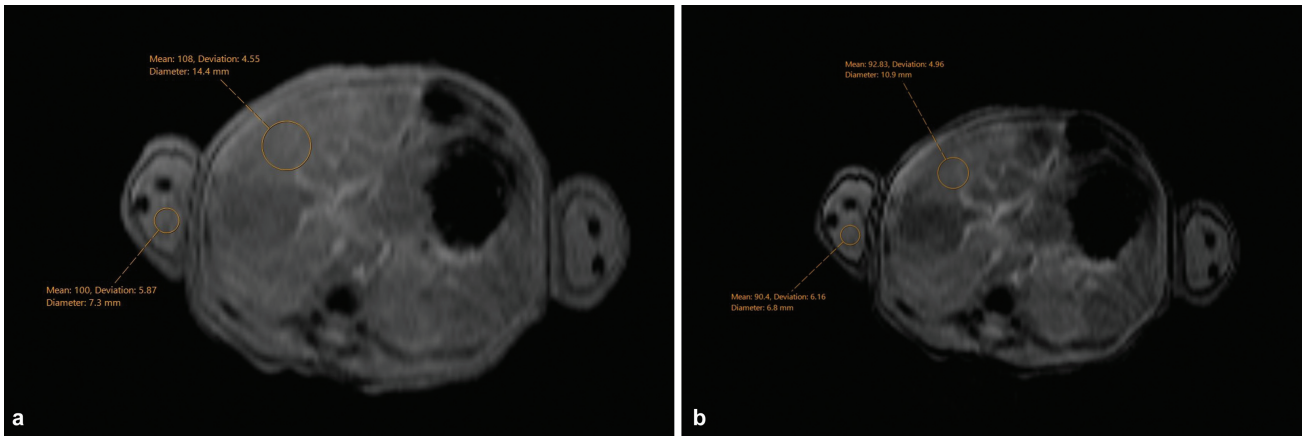

Fig. 1 (**a**) In-phase and (**b**) out-of-phase T1 GRE imaging showing no abnormal hepatic signal dropout.

diagnose cases of GALD and can be seen in the salivary glands, heart, pancreas, and/or thyroid; it can be identified with MRI and/or iron staining of biopsied tissue.[3,7] For MRI, decreased T2 signal intensity suggests iron overload.[1] For tissue biopsy, samples are usually taken from the salivary glands, and siderosis is identified using iron staining.[10] In the setting of severe liver injury, a positive finding of either tissue biopsy or MRI documenting extrahepatic siderosis is

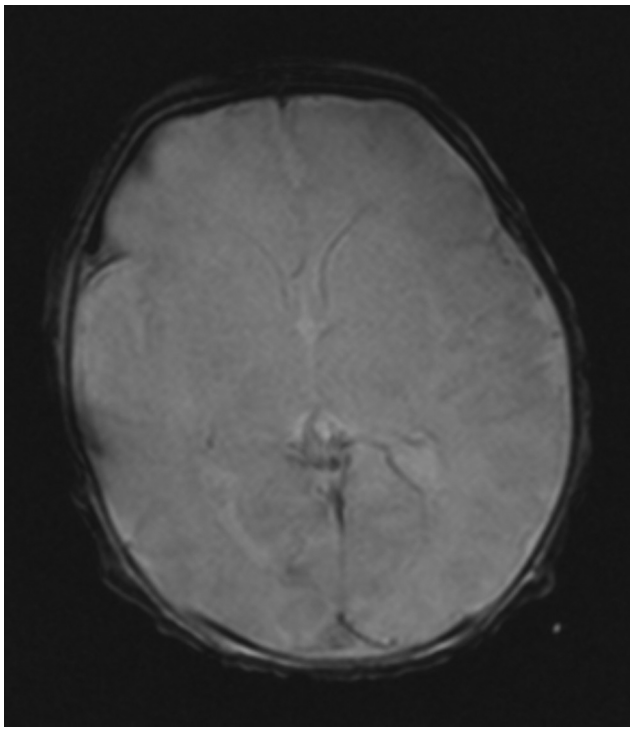

Fig. 2 MR brain T2 gradient echo sequence demonstrating no evidence of iron deposition.

adequate for the diagnosis of GALD.[3] Other significant findings that are associated with GALD, although not diagnostic, include hypoglycemia, coagulopathy, edema, hypoalbuminemia, and hyperbilirubinemia.[7,11] Alpha-fetoprotein levels are abnormally high and range from 100,000 to 600,000 ng/mL and aminotransferases are often normal or low, suggestive of a poor switch from fetal to neonatal metabolism.[7] Regarding liver changes, liver injury due to GALD typically leads to elevated ferritin and iron saturation levels, and decreased transferrin levels due to iron overload and poor liver function.[1]

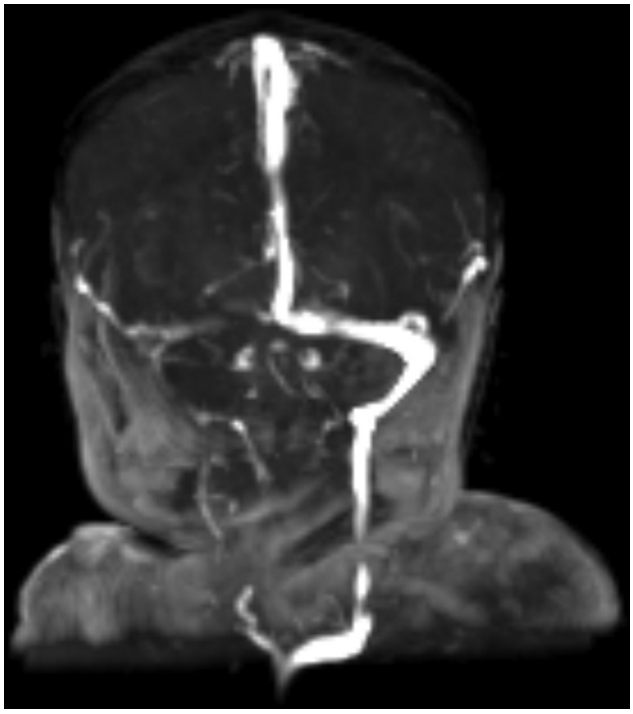

Fig. 3 MR venography of the brain demonstrating loss of flow-related signal in the right transverse sinus, sigmoid sinus, and internal jugular vein, compatible with dural venous sinus thrombosis.

While extrahepatic siderosis is often used to diagnose GALD, it is important to note that extrahepatic tissue siderosis is technically a diagnostic criterion for NH and not for GALD itself. NH is a phenotypic presentation noted in many cases of GALD, and it is characterized by liver disease and extrahepatic siderosis.[1] Extrahepatic siderosis is often used to diagnose GALD because over 98% of cases of NH are attributed to GALD.[1,7] However, because NH is not always seen in cases of GALD, the absence of extrahepatic siderosis should not rule out a diagnosis of GALD.[1] In cases where GALD is suspected but extrahepatic siderosis is not found, C5b-9 staining of a liver biopsy can be performed for a definitive diagnosis.[1,3]

Given its severe presentation, antenatal treatment of GALD is critical to prevent infant demise. The treatment of NH has evolved greatly over time. Until the late 20th century, the most common etiology of NH was thought to be oxidative injury.[12] Therefore, treatment was an "antioxidant cocktail" that included selenium, prostaglandin E1, vitamin E, N-acetylcysteine, and an iron chelator like desferrioxamine.[12] Historically, this treatment has been associated with poor survival rates that were as low as 10%.[1]

However, once researchers discovered that the overwhelming majority of NH cases were associated with GALD, management became centered around IVIG therapy.[1] Even more recently, antenatal IVIG treatment has been introduced as a preventative therapy useful in patients with previous pregnancies complicated by GALD.[9] It is thought to help flush alloantibodies, prevent complement binding activation, and diminish maternal production of reactive antibodies.[3,6] Antenatal IVIG treatment has significantly improved survival rates of GALD.[2,4–6]

There are a limited number of reports on GALD in the current literature, and most available reports discuss the treatment of infants born with GALD. However, this case study uniquely documents the effects of maternal IVIG treatment to prevent GALD prenatally in a subsequent pregnancy. These results, along with limited available research, suggest that antenatal treatment with IVIG can significantly improve infant outcomes.

Conclusion

This case report exemplifies the effect of antenatal IVIG infusions in subsequent pregnancies for women with a history of GALD in prior children, an occurrence that is not well-documented in scientific literature. This effect is protective based on the lack of liver injury noted in this patient, supporting the use of immunotherapy during pregnancy to prevent the recurrence of alloimmune injury.

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Conflict of Interest
None declared.

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