USZ Universitäts Spital Zürich

Gestational alloimmune liver disease (GALD) leading to fulminant coagulopathy in an extremely preterm infant

Dr. Sven-Eric Baller

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Introduction

GALD, which leads to neonatal hemochromatosis, is the most common cause of neonatal acute liver failure (NALF). In GALD, maternal IgG antibodies target fetal hepatocytes by binding to fetal liver antigens, activating the compliment cascade that leads to hepatocyte damage and severe liver failure. This condition can result in congenital cirrhosis, which may present with or without iron overload and siderosis.

Case

- Preterm boy 27 4/7 weeks of gestation presenting with hydrops fetalis and oligohydramnios at a routine pregnancy check-up
- Caesarean section due to pathologic cardiotocogram after one dose of antenatal steroids
- Intubated for respiratory distress syndrome and received surfactant
- Due to severe anemia with a hematocrit of 14%, packed red blood cells (pRBCs) were administered in the delivery room
- Global respiratory insufficiency, suprasystemic pulmonary hypertension and arterial hypotension → vasoactive drugs
- Significant coagulopathy → repeated transfusions of pRBCs and platelets, along with the administration of coagulation factors
- Bilateral intraventricular hemorrhage grade III and bilateral cerebellar hemispheric hemorrhage → posthemorrhagic hydrocephalus with herniation → compressing effect on the brain stem and the cranial spinal cord
- Redirection of care was performed on DOL 5
- At autopsy, the diagnosis of gestational alloimmune liver disease was made

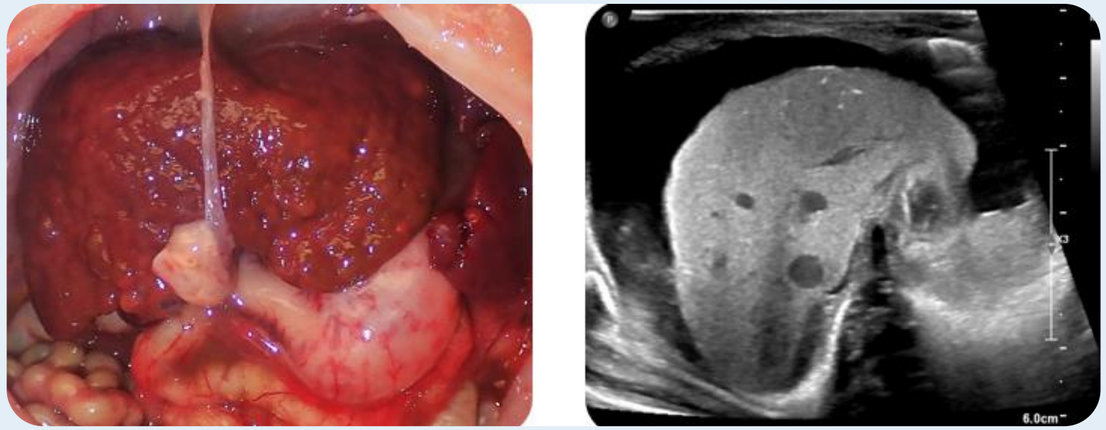

Figure 1: Left: Underweight liver (<5. percentile) with nodular alteration.
Right: Sonography of the liver showing an irregular surface and perihepatic accumulation of fluid.

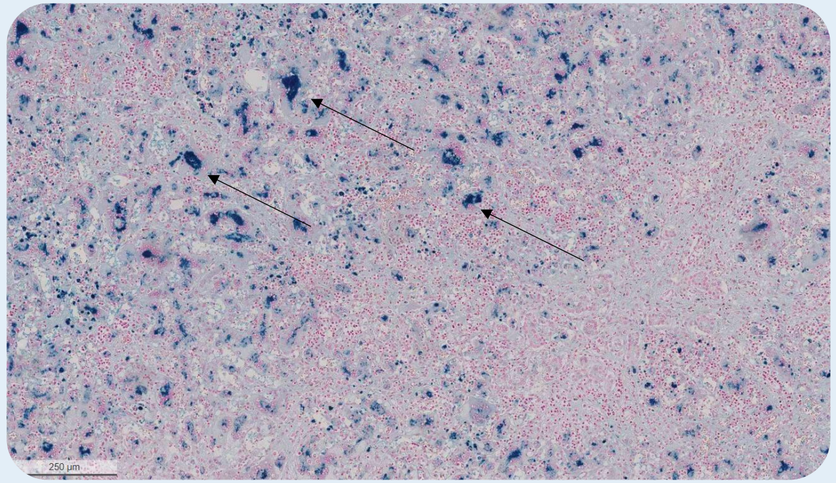

Figure 3: Prussian blue stained section of liver biopsy showing hemosiderosis marked by arrows.

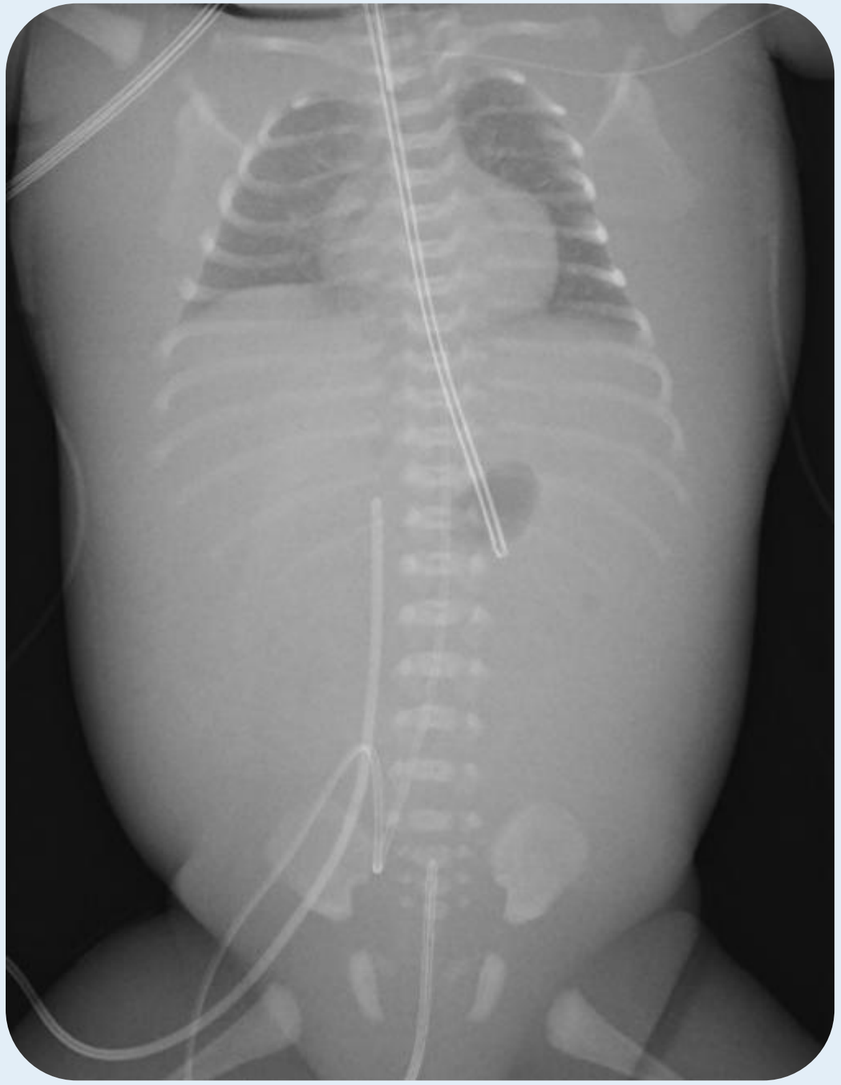

Figure 2: Chest and abdominal x-ray showing massive anasarca.

Discussion

GALD is a rare maternal-fetal alloimmune disorder (incidence of 4 per 100.000 live births in the US) that primarily affects the fetal liver and often leads to neonatal liver failure. The onset of damage typically occurs during the antenatal period, when the fetus is exposed to maternal IgG between the 17th and 22nd weeks of gestation. It causes a reduction in hepcidin production, leading to enhanced transport of placental iron to the liver, a decrease in transferrin production, and an increased uptake of iron by extrahepatic tissues (e.g. pancreas, salvary glands, thyroid and myocardium). GALD may manifest at any point between 18 weeks of gestation and up to three months after birth. Currently, no standard diagnostic test exists for GALD. Caution, particularly in cases with a maternal history of multiple fetal deaths or a sibling with neonatal liver failure. Prenatal diagnosis remains challenging, as ultrasound findings may be either absent or nonspecific. Typically, there is a history of intrauterine growth restriction, oligohydramnios, and prematurity.

Conclusion

- Consider GALD for all cases of NALF, especially in preterm infants and firstborns presenting with oligohydramnios and intrauterine growth restriction
- Main differential diagnosis of NALF are viral infection, hemophagocytotic lymphohistiocytosis, metabolic diseases (e.g. Galactosemia, Tyrosinemia Typ 1 and mitochondrial hepatopathy) and ischemic injury.
- It is important to identify infants with GALD as early as possible, as treatment options (e.g. double volume exchange transfusion) are available and effective for subsequent pregnancies (e.g. IVIG) to prevent recurrence of GALD

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Sven-Eric Baller[1], Huy Leng Khov Eberhard[2], Beate Grass[1]
[1]Department of Neonatology, University Hospital Zurich, Switzerland; [2]Institute of Pathology and Molecular Pathology, University Hospital Zurich, Switzerland

References

Taylor SA, Whitington PF. Neonatal acute liver failure. Liver Transpl. 2016 May;22(5):677-85.

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Differential diagnosis of NALF

TABLE 1. Presenting Clinical Findings in NALF Based on Etiology

	GALD-NH	Viral Infection	HLH	Mitochondrial Hepatopathy
Age at presentation	Usually at birth and almost always < 3 days	Typically 5-14 days	Variable, sometimes at birth	Variable, often first weeks to months of life
Premature birth	Most (70%-90%)	Usual population incidence	Uncommon	Uncommon
History of maternal sibling death	Common	Almost never	Uncommon	25% risk in full siblings
Oligohydramnios	Most (70%-90%)	Rare	Rare	Uncommon (polyhydramnios seen)
Intrauterine growth restriction	Most (70%-90%)	Rare	Rare	Possible (20%-30%)
Multiorgan involvement	Renal tubular dysplasia	Common in HSV especially brain	Bone marrow	Central nervous system and heart
Ascites	Common (40%-60%)	Rare	Uncommon	Uncommon
Patent ductus venosus	Most (70%-90%)	Never	Never	Never
Hepatomegaly	Uncommon (10%-20%)	Common	Common	Common
Splenomegaly	Uncommon (10%-20%)	Common though often mild	Common	Uncommon
Hypoglycemia	Usual	Common	Common	Usual
Coagulopathy	Profound (INR, 4-10)	Moderate to profound	Moderate to profound	Moderate to profound
Metabolic acidosis	No	No	No	Yes
Cholestasis	Not at birth; increasing afterward	Minimal at presentation	Moderate to severe	Moderate
ALT	Typically low or normal and almost always < 100 IU/L	Typically high and often > 1000 IU/L	Typically high and often > 1000 IU/L	Typically high and often 100-500 IU/L
Ferritin	Almost always > 800 ng/mL and < 7000	Often very high (>20,000 ng/mL)	Very high (>20,000 ng/mL)	Variable elevation
Alpha-fetoprotein	Almost always high (> 80,000 ng/mL in term neonate); typically > 300,000 ng/mL	Almost always normal (< 80,000 ng/mL in term neonate)	Almost always normal (< 80,000 ng/mL in term neonate)	Variable elevation
Lactate:pyruvate molar ratio and ketone body ratios	Normal	Normal	Normal	Abnormal

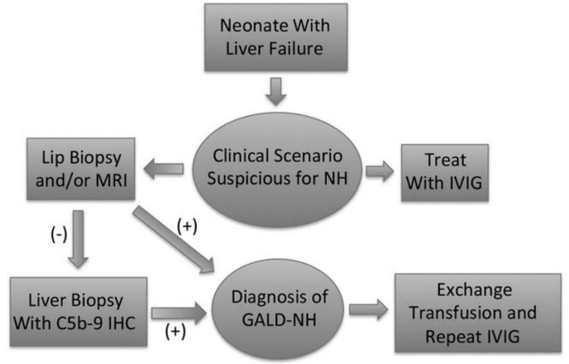

FIG. 1. Diagnostic and treatment algorithm for GALD-NH in NALF. Treatment with IVIG should be initiated upon clinical suspicion of GALD-NH while further diagnostic workup is ongoing. Liver biopsy staining with C5b-9 remains a research tool but has proven useful in diagnosis of GALD. Upon confirmation of GALD-NH, treatment with exchange transfusion and repeat IVIG should be performed.

Clinical presentation in NALF:

- Lethargy (49%)
- Fever (20%)
- Nausea/vomiting (20%)
- Hepathomegaly (71%)
- Splenomegaly (41%)
- Ascites (39%)
- Peripheral edema (38%)

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