CASE SERIES

Neonatal Acute Liver Failure

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Abstract

Acute liver failure is a rare event in the newborn period yet early recognition in the neonatal intensive care setting is essential for best outcome. Neonatal acute liver failure (NALF) is distinct from acute liver failure in older children and adults having different etiologies, presentation, and unique treatment interventions. There is a paucity of literature regarding NALF and several newly identified conditions merit discussion. Herein we report three cases of liver failure who were admitted to our neonatal intensive care unit and review the diagnostic approach and management of liver failure in this age group.

Keywords: Diagnosis, Enterovirus, Gestational alloimmune liver disease, Hemophagocytic lymphohistocytosis, Neonatal acute liver failure, Neonatal disease, Neonate.

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Introduction

Acute liver failure is a rare event in the newborn period yet early recognition in the neonatal intensive care setting is essential for best outcome. Neonatal acute liver failure is distinct from acute liver failure in older children and adults having different etiologies, presentation, and unique treatment interventions. There is a paucity of literature regarding NALF and several newly identified conditions merit discussion. Herein we report three cases of liver failure who were admitted to our neonatal intensive care unit and review the diagnostic approach and management of liver failure in this age group.

Case 1

A term female infant was born by spontaneous vaginal delivery to a healthy 33-year-old Caucasian gravida 2 para 1 mother in a community hospital. Mother's antenatal course was unremarkable with normal ultrasounds; GBS and GDM screening were negative, blood O positive, and protective serologies. She went into spontaneous labor with rupture of membranes one hour prior to delivery. The infant did not require any resuscitation; Apgar scores were 9 at 1 minute and 9 at 5 minutes. Infant's birth weight was 3480 gm (50–90th centile), length 50 cm (50–90th centile), and head circumference [34.5 cm (50th centile)]. Infant received IM Vitamin K at birth and was transferred to room in with her mother.

At 4 hours of age, the infant was noted to be pale, apneic, hypothermic (temperature of 35.9°C), and hypoglycemic (0.8 mmol/L). A D10W bolus (2 mL/kg) was given followed by maintenance IV D10 NS at 60 mL/kg/day. Blood culture was drawn and ampicillin and gentamicin were started. Hypoglycemia subsequently improved. Initial investigations were as follows: WBC 19.2×10^9/L ($9–30 \times 10^9$/L), neutrophils 15.4×10^9/L ($6–27 \times 10^9$/L), hemoglobin 188 gm/L (135–195 gm/L), hematocrit 0.52, platelets 136×10^9/L ($150–450 \times 10^9$/L), CRP <5 mg/L.

At 20 hours of age, she had hematemesis with hematochezia. Her vital signs remained stable. A nasogastric tube was inserted, and the infant was made NPO. An abdominal X-ray showed no signs of air fluid levels or obstruction or NEC. Her hemoglobin dropped to 105 gm/L with hematocrit 0.30. She was transfused with 20 mL/kg packed red blood cells, a second dose of vitamin K, and IV pantaprazole bolus was given, and she was transferred to our tertiary NICU.

On arrival, the infant was hemodynamically stable and in no respiratory distress; temperature 36.8°C, HR: 160 bpm, RR: 43 bpm, BP: 66/49 (55). She looked pale but well perfused, good air entry bilaterally, and no murmur. Her abdomen was soft, nontender, without hepatomegaly or splenomegaly. The rest of the physical examination was normal; there were no dysmorphic features or neurological findings. Laboratory results showed: WBC count 15.3×10^9/L ($9–30 \times 10^9$/L), neutrophils: 9.27×10^9/L ($6–27 \times 10^9$/L), hemoglobin 112 gm/L (135–195 gm/L), hematocrit: 0.32; platelets: 103×10^9/L ($150–450 \times 10^9$/L), INR 2.4 (N: 1.2–1.5), APTT 66 seconds (N: 28.0–40.0 seconds), PT 22.4 seconds (N: 9.6–11.8 seconds), fibrinogen <0.7μmol/L (N: 1.70–4.0 gm/L), ALT 40 U/L (6–50 U/L), AST 88 U/L (35–140 U/L), GGT 40 U/L (N: 34–263 U/L), unconjugated bilirubin 113 μmol/L, conjugated bilirubin <2 μmol/L (<5 μmol/L), ferritin 2770 μg/L (6–400 μg/L), serum albumin 18 gm/L (26–36 gm/L), alpha fetoprotein 340,000ng/ml (<20,000 μg/L), serum ammonia 18 μmol/L (<49 μmol/L), and triglycerides 0.94 mmol/L (<1.7 mmol/L). Newborn screen was negative for amino acid, fatty acid oxidation, organic acid disorders, hypothyroidism, hemoglobinopathies, galactosemia, and cystic fibrosis. Blood and urine cultures were negative. Serum HSV 1 and 2 and CMV PCR were negative. An echocardiogram showed normal anatomy and function and the ECG was normal. Abdominal ultrasound showed no focal abnormalities seen in the liver. Gall bladder, intra- and

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extrahepatic biliary ducts, pancreas, spleen, and kidneys were all unremarkable.

She received cryoprecipitate and fresh frozen plasma. Pantaprazole and IV vitamin K were continued. Acyclovir was added to the antibiotic therapy.

On day two of life, with a presumptive diagnosis of gestational alloimmune liver disease (GALD), she received intravenous immunoglobulin (IVIG) at 1 gm/kg and a double volume exchange transfusion, followed by a second dose of IVIG at 1 gm/kg. Magnetic resonance imaging of the abdomen [Fig. 1 (Image 1) and (Image 2)] was consistent with moderate-to-severe iron overload in the liver, mild pancreatic iron overload, and possible iron deposition in the choroid plexus within the brain. Buccal/salivary gland biopsy did not show evidence of iron deposition. Whole exome sequencing showed a heterozygous *de novo* variant of uncertain significance in KRT8, which puts her at risk for a KRT8 "keratin 8"-related liver disease.

Over the ensuing days, the thrombocytopenia, coagulopathy, and IV glucose requirement gradually improved and feeding was initiated without incident. At discharge on day 35 of life, she was exclusively breastfeeding and gaining weight. The hemoglobin was 130 gm/L (135–195 gm/L), platelet count 297×10^9/L ($150–450 \times 10^9$/L), INR 1.3 (N: 1.2–1.5), APTT 38 seconds (N: 28.0–40.0 seconds), PT 13.2 seconds, fibrinogen 1.4 μmol/L (N: 1.70–4.0 gm/L), albumin 31 gm/L (26–36 gm/L), ALT 38 U/L (6–50 U/L), AST 74 U/L (35–140 U/L), unconjugated bilirubin 57 μmol/L, and conjugated bilirubin 3 μmol/L (<5 μmol/L).

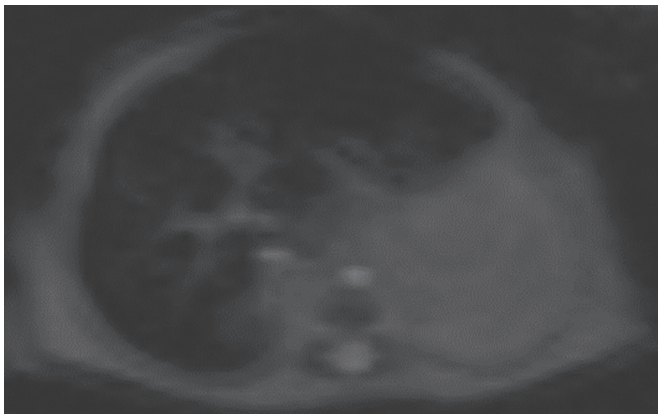


Fig. 1 (Image 1): Magnetic resonance imaging of the abdomen on day 3 of life shows moderate-to-severe iron load in the liver with mild pancreatic iron overload. Liver iron time to echo (TE) 2.4 ms. The TE is the time between the delivery of the radiofrequency pulse and the receipt of the echo signal

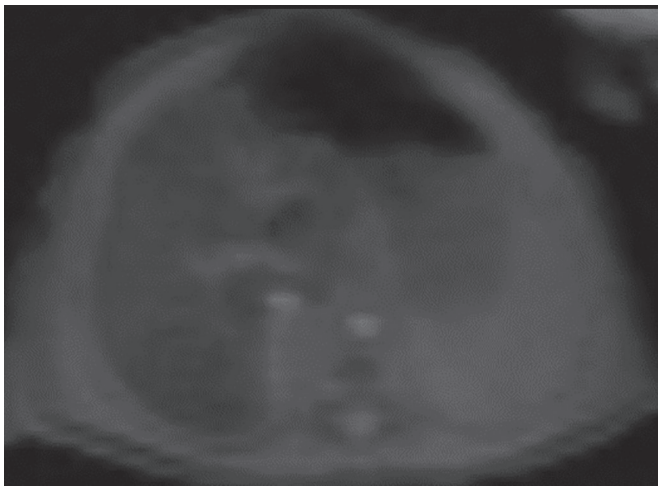


Fig. 1 (Image 2): Magnetic resonance imaging of the abdomen on day 3 of life shows moderate-to-severe iron load in the liver with mild pancreatic iron overload. Liver iron TE 12.27 ms

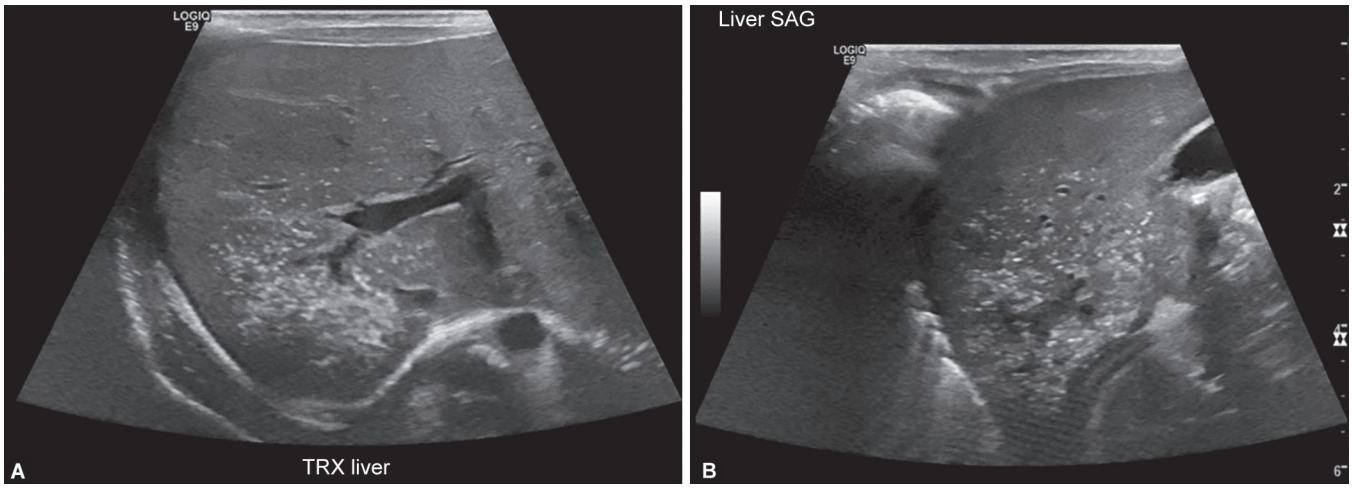
Case 2

A male infant was born at 38.5/7 weeks by repeated cesarean section to a 33-year-old G3T1A1 mother with a history of migraine. Mother was blood group O positive, serologies protective, GBS negative, and insulin-dependent GDM. Antenatal ultrasounds at 10- and 22-weeks GA were normal. Her pregnancy was complicated with a febrile illness in the third trimester. Meconium-stained amniotic fluid was noted at the time of delivery. Apgar's scores were 2, 5, and 7. Birth weight was 3450 gm (50th centile), length 55 cm (>97th centile), and head circumference 36.5 cm (90th centile). At 1 hour of life, hypoglycemia was noted (1.2 mmol/L) requiring increased rate of glucose delivery up to 18 mg/kg/minute glucose infusion rate via total parenteral nutrition to maintain normal blood glucose levels. Initial investigations showed: WBC: 10.9×10^9/L ($9–30 \times 10^9$/L), neutrophils 3.5×10^9/L ($6–27 \times 10^9$/L), hemoglobin 139 gm/L (135–195 gm/L), hematocrit 0.43, platelets 19×10^9/L ($150–450 \times 10^9$/L), unconjugated bilirubin 139 μmol/L. The infant was on mild respiratory distress requiring CPAP 5 cm H_2O FiO_2 21% with normal blood gases. The infant was transferred to our tertiary level NICU for further management.

At admission, the temperature was 37.6°C, HR 137 bpm, RR 59 bpm, BP 62/34 (mean 44). Infant was well perfused, with normal pulses and no murmurs, abdomen was soft, mildly distended with hepatomegaly at 4 cm below the right costal margin and the tip of the spleen was felt 1 cm below left coastal margin. Scattered petechiae were noted on his back and groin. He had no dysmorphic features or neurological signs. An echocardiogram was normal. Laboratory findings revealed WBC 11.2×10^9/L, platelets 18×10^9/L, and hemoglobin 164 gm/L. The INR was high at 3.8 (N: 1.2–1.5), APTT of 51 seconds (N: 28.0–40.0 seconds), PT of 34 seconds (N: 9.6–11.8 seconds), and low fibrinogen <0.7 μmol/L (N: 1.70–4.0 gm/L). He received fresh frozen plasma, cryoprecipitate, platelets, and vitamin K.

Liver function tests showed ALT 49 U/L (6–50 U/L), AST 187 U/L (35–140 U/L); LDH 5191 U/L (140–280 U/L) unconjugated bilirubin 169 μmol/L, conjugated bilirubin 44 μmol/L (<5 μmol/L), GGT 66 U/L (34–263 U/L), albumin 19 gm/L (26–36 gm/L), Ferritin 184 μg/L (6–400 μg/L); alpha fetoprotein 47,000 ng/mL (<20,000 μg/L), serum ammonia 42 μmol/L (<49 μmol/L). The newborn screen for amino acid, fatty acid oxidative, organic acid, thyroid, CAH, hemoglobinopathies, galactosemia, and cystic fibrosis was negative. TSH/FT4, ammonia, and acylcarnitine were normal, and blood, urine, and CSF cultures were negative.

An abdominal ultrasound (Fig. 2) showed abnormal liver parenchyma with multiple echogenic foci, most marked in the right lobe. Calcifications were noted, likely due to remote prenatal insult with small volume ascites. Viral studies for HSV, HIV, Parechovirus, and CMV were negative. Enterovirus by PCR amplification and nuclei acid testing (NAT) was positive in blood. Conjugated bilirubin peaked to 289 μmol/L (<5 μmol/L) on day 10 of life. Jaundice gene chip panels expressing trio whole exome sequencing and



Figs 2A and B: Abdominal ultrasonography on day 2 of life shows abnormal liver parenchyma with multiple echogenic foci mostly marked in the right lobe with calcifications also noted

mitochondrial gene sequencing were negative for pathogenic gene mutation.

He failed hearing test twice and ABR showed severe sensorineural hearing loss on the left. The baby received ursodiol, platelet transfusions, and general supportive measures. He was discharged home on day 45 of life on EBM with formula supplement and growing well.

Case 3

A term male infant was born via urgent C-section due to fetal bradycardia and reduced fetal movements to a healthy 33-year-old Caucasian gravida 2 para 1. Mother's antenatal course was unremarkable. She was blood group B positive with protective serologies; GDM and GBS screening were negative. An ultrasound at 38 weeks showed a fetus with IUGR, hepatosplenomegaly, mild ascites, hydroceles, and liver with starry sky appearance parenchyma with no evidence of anemia/hydrops by normal Doppler. Apgar scores were 8 and 9, birth weight 2600 gm (10th centile), length 50 cm (50th centile), head circumference 34 cm (50th centile). Infant received IM vitamin K in the delivery room and was transferred to the NICU for further evaluation. At admission he had temperature of 37°C, HR 126 bpm, and RR 45 breaths per minute, mean BP 38. He was hemodynamically stable without respiratory distress and no dysmorphic features, and normal neurological examination. Abdomen was soft and mildly distended, liver was palpated 4 cm below left coastal margin, and a tipped spleen. He was noted to have bilateral hydroceles. His first blood glucose was 2.3 mmol/L for which he received a D10W bolus (2 mL/kg).

Initial investigations: CBC: WBC: 20.5 × 10^9/L (9–30 × 10^9/L), neutrophils 4.37 × 10^9/L (6–27 × 10^9/L), lymphocytes 10.72 × 10^9/L (2–11 × 10^9/L), platelets 9 × 10^9/L (150–450 × 10^9/L), hemoglobin 240 gm/L (135–195 gm/L), unconjugated Bilirubin 62 μmol/L, Conjugated bilirubin 9 μmol/L, ALT 27 U/L (6–50 μ/L), AST 33 μ/L (35–140 U/L), ALP 44 μ/L (110–300 μ/L), albumin 18 gm/L (26–36 gm/L), triglycerides 0.88 mmol/L (<1.7 mmol/L), ferritin 2100 μg/L (6–400 μg/L), alpha fetoprotein 510 μg/L (<20,000 μg/L), ammonia 19 μmol/L (<49 μmol/L). Coagulation studies: PT: 17.9 seconds (N: 9.6–11.8), INR 1.9 (N: 1.2–1.5), APTT 40 seconds (N: 28.0–40.0 seconds), fibrinogen 0.8 gm/L (N: 1.70–4.0 gm/L). He received a platelet transfusion and 1 mg/kg of IVIG. An abdominal ultrasound showed a liver with smooth margin and homogeneous echotexture and no focal parenchymal abnormalities. Free fluid noted which was anechoic and lacked septation. There was marked periportal echogenicity throughout the liver and especially along the right and left branch portal veins, gallbladder contained sludge-like material, normal pancreas, and spleen. TORCH screen and enterovirus PCR were negative. Metabolic workup for urine organic acids, plasma amino acids, mucopolysaccharides/creatinine ratio, oligosaccharides pattern, plasma, very long fatty acids profile which were all negative.

On day 5 of life, the infant had a rapid deterioration requiring intubation and maximal support to manage significant ascites due to profound liver failure: CBC: WBC: 7.3x10^9/L, neutrophils: 1.78x10^9/L, Hb: 131 gm/L, platelets 28x10^9/L, unconjugated bilirubin 75 μmol/L, conjugated bilirubin 25 μmol/L, albumin 15 gm/L, ALT 23 μ/L, AST 33 μ/L, ALP 114 μ/L, GGT 51 μ/L PT 18.5 seconds, INR 1.9, aPTT 66 seconds, fibrinogen 1 gm/L. He was started on triple antibiotics for possible spontaneous bacterial peritonitis. Double-exchange transfusion was performed followed by a second dose of IVIG for the suspicion of GALD. He had persistently low platelets requiring daily platelet transfusions and FFP and cryoprecipitate for management of a coagulopathy. He received daily vitamin K at 1 mg/kg. A peritoneal drain was inserted to drain the ascites. He received twice a day 25% albumin transfusions at 1 gm/kg and was started on spironolactone, furosemide, acetazolamide to manage the ascites and edema. A repeated abdominal ultrasound showed reversed (hepatofugal) flow in the main portal vein and left branch portal vein (Fig. 3). Increase in splenic size (Fig. 4) and irregular margins of the liver in keeping with the appearance of portal hypertension (Fig. 5). Thrombophilia DNA Factor V Leiden mutation and Prothrombin (Factor II) was done which was normal phenotype.

On day 13 of life, a bone marrow aspiration/biopsy showed presence of megakaryocytes, reversed myeloid: Erythroid ratio suggestive of erythroid hyperplasia. There was no evidence of hemophagocytosis—chromosomal microarray was normal and whole exome sequencing was negative for any genetic cause for HLH. On day 15 of life, the infant was transferred to another level 3 NICU for evaluation of liver transplant due to liver failure with portal hypertension. His ferritin, soluble IL, and CD136 levels were raised, and he was started on high-dose dexamethasone on day 21 of life. Due to suboptimal response to dexamethasone,

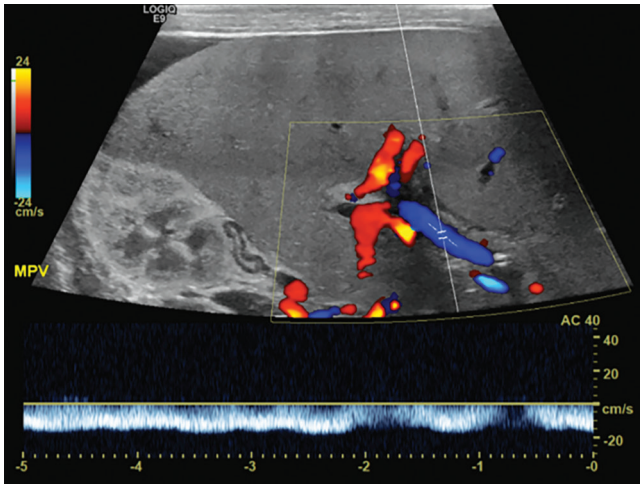


Fig. 3: Abdominal Doppler ultrasound showing reversed portal flow

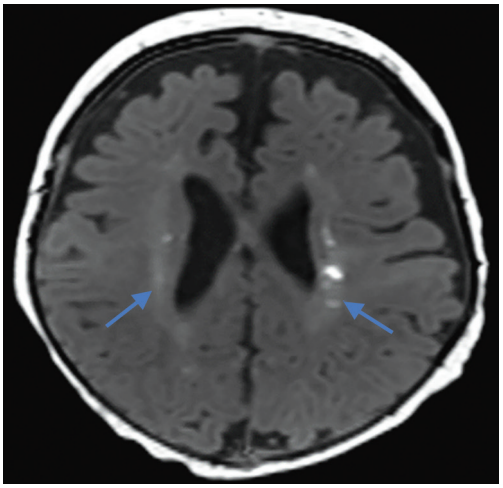


Fig. 6: Brain MRI showing bilateral white matter injury

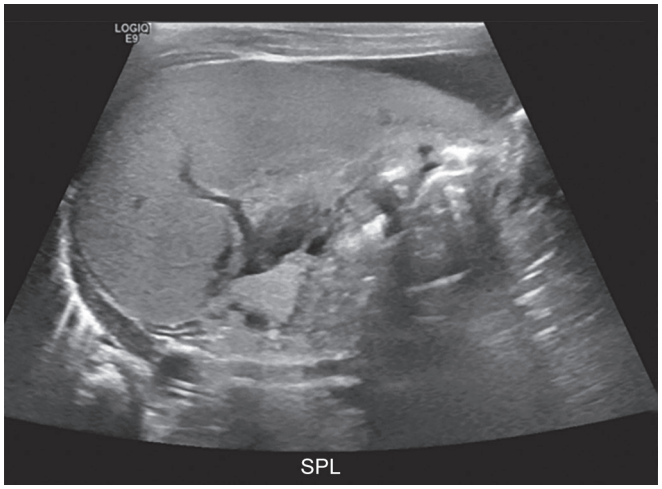


Fig. 4: Splenomegaly noted on the abdominal ultrasound

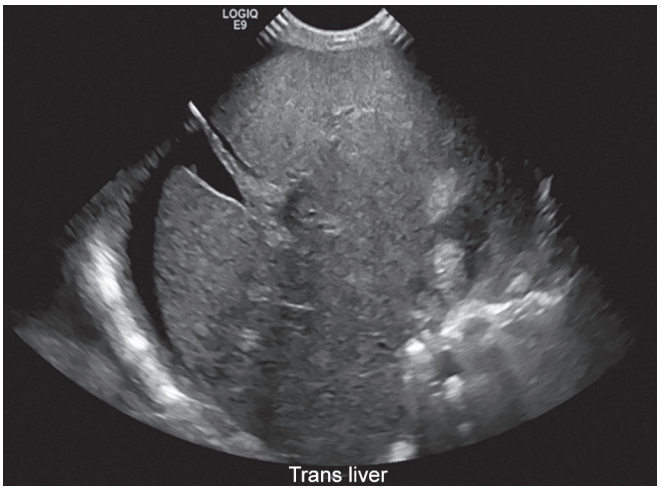


Fig. 5: Course liver with ascites noted on abdominal ultrasound

he was started on etoposide and fluconazole at 27 days of life for 8 weeks. A liver biopsy on day 30 of life did not show features of hepatitis. Instead, there was sinusoidal expansion with inspissated histiocytes more prominent in the periportal regions associated with up to 20% surrounding parenchymal loss. There was evidence of hemophagocytosis on both light and electron microscopy. The histological features were highly suggestive of a primary or secondary hemophagocytoic lymphohistiocytosis. There was no ultrastructural evidence supportive of mitochondrial disease or any abnormal storage material. On day 14 of life, he had a brain MRI which showed multifocal periventricular white matter signal abnormalities. A brain MRI on day 75 of life showed multiple T1 hyperintense subcentimeter foci throughout the periventricular white matter bilaterally. There was a focal abnormality in the posterolateral left thalamus (Fig. 6). The brain was otherwise structurally normal. This assessment showed evolution and progression of lesions in the right periventricular white matter which was suspected to be in keeping with CNS HLH. Based on the progression of these lesions, the decision was made to treat for HLH with CNS disease, which included intrathecal methotrexate and hydrocortisone. He continued with chemotherapy until he had received a successful bone marrow transplant at 4 months of age. He has done well post BMT with resolution of the liver disease and is growing well but with gross motor delay secondary to HLH.

Discussion

Neonatal acute liver failure is defined as the onset of clinical or biochemical features of liver injury in association with severe coagulopathy (INR >2.0) that persists despite the administration of vitamin K, within the first 12 weeks of life.[1] In contrast to acute liver failure in older adolescents and adults, hepatic encephalopathy is not an essential criterion to the diagnosis of liver failure in newborns. The etiologies for NALF include viral infection (15%),[2] metabolic/genetic disease primarily galactosemia, tyrosinemia, and mitochondrial depletion syndromes due to DGUOK (10%),[1,3–5] hematologic disorders (15%),[4,6] and ischemic injury due to poor perfusion with associated congenital heart disease (5%).[4] A newly characterized condition known as GALD, previously referred to as "neonatal hemochromatosis," is now recognized as the leading cause of NALF accounting for almost half of all cases in some centers. In contrast to adults with acute liver failure where acetaminophen is by far the most common cause, this drug toxicity is exceedingly rare in newborns. Whereas up to 50% acute liver failure in older

children and adolescents remain idiopathic, only 5% of neonatal cases are indeterminate.[1]

The typical presenting signs and symptoms of NALF include lethargy, fever, nausea/vomiting, jaundice, hepatomegaly, splenomegaly, and ascites. Neonatal acute liver failure should be considered in newborns with confirmed or presumed sepsis, and persistent coagulopathy despite vitamin K delivery in association with usually abnormal (but occasionally normal) liver function tests (LFTs): AST, ALT, GGT, ALP along with other features of hepatic dysfunction including conjugated hyperbilirubinemia, recurrent or persistent hypoglycemia, hyperammonemia, ascites, gastrointestinal bleeding, and renal dysfunction. Many of the known causes of NALF have disease-specific treatments that can improve outcome and survival. Yet the overall mortality of NALF is 25%.[1,2,4–8]

The immediate assessment for NALF includes a complete hematological profile (CBC, DAT, group, and cross match); coagulation profile; electrolytes, BUN, Cr, LFTs, glucose, blood gas, lactate, ammonia, serum amino acids, acylcarinitnes, cholesterol, triglycerides, alpha-fetoprotein, and ferritin; urine for glucose, ketones, reducing substances, organic acids including succinyl acetone; blood and urine cultures, viral screen and rapid request for your local newborn screening program results. The management of NALF requires the elimination of all feeds, effectively to remove lactose, fructose, and lipid from the diet until rare metabolic-induced NALF is excluded, and to deliver intravenous glucose to support glucose requirements. Given the association of NALF and sepsis, all cases should be promptly treated with antibiotics and acyclovir. Specific treatments for those metabolic diseases that may present as NALF include NTBC [2-(2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanedione] which is the mainstay treatment in tyrosinemia type I, carnitine, sodium benzoate, and hemofiltration.[9]

Gestational Alloimmune Liver Disease

Gestational alloimmune liver disease is the most common cause of NALF.[4,6] This disease was first described in 1961 as "neonatal hemochromatosis" (NH) with fewer than 100 cases reported over the next 45 years.[10] "Neonatal hemochromatosis" was the term ascribed to newborns with liver and multiorgan failure who were frequently diagnosed as having sepsis with associated edema with or without ascites, oliguria, and evidence of advanced end-stage liver disease and cirrhosis with portal hypertension that was already present at birth. Typically, LFTs, in particular AST and ALT, were disproportionally low or normal for the degree of liver injury and hepatic dysfunction. Other notable features were the marked coagulopathy (INR >2) with unusually elevated alpha-feto protein and extremely high serum ferritin levels (>800 ng/mL). It was this latter finding in association with the autopsy findings of extrahepatic siderosis that led to the nosology of "neonatal hemochromatosis." Despite the historical treatment of NH with antioxidant cocktail, the mortality rate was upward of 80–90%.[10]

In a careful review of NH cases, an unusual familial pattern of disease penetration was identified that mimicked fetal hydrops rhesus factor incompatibility disease.[11] This led to the more recent characterization of the condition called as GALD. Gestational alloimmune liver disease is now recognized to result from maternal production of immunoglobulin (IgG) against a putative 32 kd fetal liver antigen that remains elusive. In utero, after a first "sensitizing" pregnancy, maternal IgG crosses the placenta to bind with the fetal hepatocyte antigen, causing activation of the compliment cascade that results in the production of membrane attack complex (MAC) with consequent liver cell injury and dysfunction.[7] This hepatic injury involves decreased production of hepcidin and increased transport of placental iron, decreased transferrin production, and increased iron uptake into the liver and extrahepatic tissues.[8] The tissues most affected with siderosis are pancreatic acinar cells, myocardium, thyroid follicular epithelium, adrenal cortex and mucosal glands of oronasopharynx, and respiratory tree. Often a buccal mucosal biopsy is obtained to demonstrate the extrahepatic siderosis. Imaging with T2-weighted MRI can also show evidence of extrahepatic tissue iron overload. Notably, reticuloendothelial cells including Kupffer cells and those in the spleen do not accumulate iron as would be expected in secondary hemochromatosis from multiple blood transfusion.[5] Moreover, the pathogenesis of "NH" or GALD is distinct from adult hemochromatosis which is a genetic disease caused by mutation in the HFE gene.[12]

There is mounting evidence to suggest that the alloimmune injury in GALD begins in midgestation.[8] Ongoing injury to developing hepatocytes during the second half of gestation results in proliferation of progenitor liver cells with production of alpha fetoprotein and extensive parenchymal fibrosis.[13] That there is a fetal onset liver failure which is further evidenced by the associated GALD features of IUGR, decreased fetal movement in the second, and early third trimester of gestation and at birth, the newborn is usually small for gestation age, sick with features of cirrhosis.

The hallmark features for GALD supported the diagnosis in Case 1. The relatively normal liver function tests with signs of hepatic dysfunction (persistent high INR not corrected by vitamin K), elevated ferritin, and high alpha fetoprotein along with the T2-weighted MR evidencing extrahepatic siderosis were in keeping with this newborn having GALD.

Whole exome sequencing found a heterozygous *de novo* variant of uncertain significance in KRT8. KRT8 is a type II keratin that is present in the liver, pancreas, and intestine that is important for the maintenance of the cellular scaffolding and cellular trafficking. KRT8 variants have been associated with liver fibrosis and cirrhosis in patients with cryptogenic and noncryptogenic liver disease. Importantly case 1 did not exhibit neurological disease including nystagmus which can be associated with genetic mitochondrial disorders and mutations in the DGUOK gene, which can be confused with GALD diagnosis.[14]

Gestational alloimmune liver disease is now recognized as a preventable disease. Treatment of future pregnancies with the administration of weekly high-dose IVIG to the mother starting as early as 14 weeks of gestation can abrogate the development of in utero liver injury and GALD. In a recent report of the world experience antenatal administration of IVIG led to significantly increased healthy offspring (94%) compared with untreated gestations (30%).[15] For the untreated GALD cases that present to the NICU, prompt treatment early in the postnatal period with IVIG and double volume exchange transfusion can attenuate the disease progression and improve survival.[16]

Enterovirus

Enteroviruses, which include the echoviruses, coxsackie A and B viruses, are among the most common viruses causing disease in humans.[17] In contrast to older children and adults for which the hepatotropic viruses A, and rarely B, and EBV are leading causes of acute liver failure; in neonates herpes virus and enteroviruses are the major infectious etiologies for NALF and they are associated with significant morbidity and mortality. Early initiation of intravenous

acyclovir, even before a firm diagnosis is recommended, offers best outcome for newborn herpes disease.[18] Enterovirus infections can be acquired antenatally, intrapartum, and postnatally. In antenatal transmission neutralizing immunoglobulin M (IgM) antibodies can be detected on the first day of life.[19] Studies have reported isolation of enterovirus from amniotic fluid and umbilical cord blood.[20–22] Other modes of transmission include intrapartum exposure to maternal blood, genital secretions, and stool, as well as postnatal exposure to oropharyngeal secretions from the mother and other individuals who have close contact with the baby.[20,23,24] We believe in our case two that the enterovirus infection was acquired antenatally because the infant was presented with acute liver failure at birth.

Newborn enterovirus infection may present with a wide spectrum of clinical manifestations and with a varying degree of severity. A maternal history of recent respiratory disease or diarrhea raises suspicion. In neonates, symptoms may range from nonspecific febrile illness to fatal multisystem disease, frequently referred to as "neonatal enterovirus sepsis" or "enteroviral sepsis syndrome." The most common presenting features include fever, irritability, poor feeding, and lethargy.[20,25–27] A nonspecific macular or maculo-papular rash is observed in many cases during the illness.[25,26] Patients may develop respiratory symptoms, including nasal discharge, cough, apnea, tachypnea, recessions, grunting, and nasal flaring. Gastrointestinal symptoms such as vomiting, abdominal distension, and diarrhea are less common, reported in 20% of cases.[26] Other potential manifestations include pancreatitis, adrenal hemorrhage, and necrotizing enterocolitis.[20] Approximately half of the neonates with enterovirus infection have evidence of acute hepatitis evidenced by a marked rise in ALT, often 10 times the upper limit of normal. This is an important distinguishing feature from GALD where the ALT is low or normal and there is advanced end-stage cirrhotic liver disease. The hepatic inflammation may progress to acute liver failure evidenced by marked coagulopathy not correctable with vitamin K.[26,27] Jaundice with conjugated hyperbilirubinemia may develop during the illness and hepatomegaly may be detected in 20%.[20,25] Splenomegaly is a relatively uncommon feature.[26] Central nervous system disease may manifest as meningitis or encephalitis. Some neonates develop cardiac complication including myocarditis, cardiac arrhythmias, cardiomegaly, poor ventricular function, systemic hypotension, congestive heart failure, pulmonary edema, and myocardial ischemia. Many of these neurologic or cardiac features may also present in genetic mitochondrial disease.[20,26–29]

The diagnosis of an enteroviral infection can be by PCR from blood, CSF, and stool. Though case two had an atypical presentation of enterovirus NALF (normal AST/ALT), PCR and NAT for enterovirus were positive, establishing the diagnosis.

Treatment of neonatal enterovirus infection is supportive and expectant care. Although there is no FDA-approved therapy for enteroviral infection, there is some experience for using IVIG albeit its effectiveness is controversial.[28,30–32] There have also been reports and clinical trials on the use of pleconaril though it is not available for systemic administration. In a RCT of neonates with suspected enetrovirus disease assigned to seven days of pleconaril or placebo, there was more rapid viral clearance and lower mortality among pleconaril-treated infants (23 vs 44% with placebo).[33] Other clinical trials with pleconaril included two combined studies of approximately 200 patients with enterovirus meningitis who were randomly assigned to pleconaril or placebo, patients who received pleconaril had shorter clinical course with modest benefit.[34]

Hemophagocytosis Lymphohistiocytosis (HLH)

The first report of familial HLH (F-HLH) in 1952 described two siblings who developed fever and hepatosplenomegaly at 9 weeks of age.[35] Subsequently, familial clusters of children with similar phenotypes were observed, as sporadic cases of a similar syndrome were seen in the context of severe infection, rheumatologic disorders, or malignancy.[36–40] In 1999, defects of PRF1 (encoding perforin) were discovered as the first inherited gene defect underlying F-HLH.[41] Before this discovery, a committee from the Histiocyte Society developed consensus enrollment criteria for the HLH-94 study to capture the HLH disease phenotype: Fever, splenomegaly, cytopenias, increased triglycerides/decreased fibrinogen, and hemophagocytosis.[42] Enrollment criteria for the subsequent HLH2004 trial were revised to incorporate ongoing discovery of the genetic basis of F-HLH and development of specialized immune studies.[43] Over the last decade, this criterion has become an effective criterion for defining/diagnosing HLH, though their sensitivity and specificity remain unknown.

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation. It most frequently affects infants from birth to 18 months of age, with highest incidence reported in those <3 months,[44] but it is also observed in children and adults of all ages. Hemophagocytic lymphohistiocytosis can occur as a familial or sporadic disorder, and it can be triggered by a variety of events that disrupt immune homeostasis. Infection is a common trigger both in those with a genetic predisposition and in sporadic cases. It is critical to make an early diagnosis and start treatment, but the greatest barrier to a successful outcome is often a delay in diagnosis due to the rarity of this syndrome, variable clinical presentation, and lack of specificity of the clinical and laboratory findings.

The diagnosis of HLH is often challenging because it mimics severe sepsis and there are several biochemical features that overlap with other diseases causing NALF, in particular GALD and tyrosinemia. While clinical and laboratory criteria for the diagnosis of HLH have been established, HLH therapy is often initiated in suspected patients who deteriorate despite supportive care, regardless of whether they fulfill stringent criteria.[45,46] The diagnostic criteria derived from a 2004 HLH study trial are as follows:

Five of the following eight findings: Fever ≥38.5°C, splenomegaly; pancytopenia, with at least two of the following: hemoglobin <9 gm/dL (for infants <4 weeks, hemoglobin <10 gm/dL); platelets <100,000/μL; absolute neutrophil count <1000/μL, hypertriglyceridemia (fasting triglycerides >265 mg/dL), and/or hypofibrinogenemia (fibrinogen <150 mg/dL); hemophagocytosis in bone marrow, spleen, lymph node, or liver; low or absent NK cell activity; ferritin >500 ng/mL, elevated soluble CD25 [soluble IL-2 receptor alpha (sIL-2R)].

The goal of therapy for patients with HLH is to suppress life-threatening inflammation by destroying immune cells. Induction therapy based on the HLH-94 protocol consists of a series of weekly treatments with dexamethasone and etoposide (VP-16). Intrathecal methotrexate and hydrocortisone are given to those with central nervous system disease. After induction, patients who are recovering are weaned off therapy, while those who are not improving are continued on therapy as a bridge to allogeneic hematopoietic cell transplantation (HCT). Hematopoietic cell transplantation will be required in those with an HLH gene mutation, central nervous system disease, or disease relapse (Table 1).[47]

Table 1: Summary on causes of NALF: incidence, mechanism, clinical features, diagnosis, and management

	Gestational alloimmune liver disease (GALD)	*Hemophagocytic lymphohistiocytosis (HLH)*	*Mitochondrial diseases*	*Metabolic*	*Ischemic injury*
Incidence	60–70% of NALF	3–10% of NALF	2–12% of NALF	Rare	4% of NALF
Mechanism	Is a result of maternal alloimmune injury caused by transplacental passage of specific reactive maternal immunoglobulin G (IgG) The maternal alloantibody activates fetal complement cascade to produce a membrane attack complex and fetal liver injury	Syndrome of excessive immune activation. May be primary (gene mutations affecting the cytotoxic function of NK cells and T cells, in particular perforin) or secondary to viral infection	Broad classification of gene-based diseases includes: 1. Respiratory chain defects, e.g., BCS1L mutation (GRACILE syndrome); 2. Errors in fatty acid oxidation, e.g., carnitine palmitoyltransferase II (CPTII) deficiency and 3. Mitochondrial DNA depletion syndromes e.g., deoxyguanosine kinase (DGUOK) deficiency, MPV17 mutations	Three autosomal recessive inherited diseases have the potential for producing NALF: 1. Hereditary tyrosinemia type I, 2. Galactosemia and 3. Hereditary fructose intolerance	Decreased blood flow to the liver can result in increased transaminase levels and coagulopathy
Clinical features	IUGR Hypoglycemia Coagulopathy Hypoalbuminemia Ascites Hyperbilirubinemia both unconjugated and conjugated Normal or minimally abnormal AST, ALT	Fever, hepatosplenomegaly Normal or abnormal LFTs	Hypotonia Seizures Failure to thrive Poor suck Hypoglycemia	Jaundice, hepatomegaly, ascites, failure to thrive, hypoglycemia, coagulopathy **Tyrosinemia type I** Acute gastrointestinal bleeding **Galactosemia:** *Escherichia coli* sepsis, Cataracts **HFI:** Postprandial hypoglycemia Lactic acidosis, renal failure, seizures, coma	Risk factors for hypoxic liver injury include: Perinatal asphyxia, hypovolemic or cardiogenic shock, and right-sided heart failure
Diagnosis/lab findings	T2 weighted MRI: Extrahepatic or extrareticuloendothelial iron overload in pancreatic acinar cells, myocardium, thyroid follicular epithelium, adrenal cortex and mucosal glands; High levels of ferritin (>800 ng/mL and <7000 ng/mL) High alpha-feto protein levels >300,000 ng/mL Salivary gland biopsy confirming siderosis	Pancytopenia; Hypertriglyceridemia and/or hypofibrinogenemia; Elevated ferritin >20,000 ng/mL low/absent NK cell activity; elevated soluble CD25 (soluble interleukin 2 receptor); and evidence of hemophagocytosis in bone marrow, ascites, spleen, lymph node, or liver	Metabolic distress, such as hypoketotic hypoglycemia with lactic acidosis—which may worsen with glucose provision. ALT-typically high and often 100–500 IU/L INR-moderate/significant increase	**Tyrosinemia type I** increased levels of succinylacetone in the urine. **Galactosemia:** Newborn screening test Urine for reducing substances (positive if baby has been fed for 24–48 hours) **HFI:** Molecular testing of the ALDOB gene	Significant increase in transaminases (1,000–6,000 IU/L) INR—moderate/significant increase Hypoglycemia-variable Ferritin level—variable depending on the underlying cause

Management	IV immunoglobulins (IVIG) Exchange transfusion with repeated dose of IVIG. Supportive care	Chemotherapy HCT	Depends on the specific mitochondrial diagnosis	**Tyrosinemia:** Dietary restriction of tyrosine and phenylalanine as well as use of 2 (2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTSB) **Galactosemia:** Elimination of lactose and galactose from the diet **HFI:** Strict avoidance of fructose-containing and sucrose-containing food and products such as sorbitol	Supportive care Severe, non-responsive cases investigate for other causes of NALF Consider Liver transplant

Learning Points

What We Learnt from these Three Cases of NALF

- High index of suspicion for liver failure even in newborns with sepsis.
- Start empiric antibiotics and acyclovir therapy until HSV is excluded.
- History (especially maternal pregnancy history and consanguinity) and physical examination. Initiate diagnostic evaluation immediately, including cultures and viral PCRs (especially for HSV and enterovirus), obtain CBC, liver transaminases, INR, ferritin, alpha-fetoprotein, lactate levels, urinary succinyl acetone, and urinalysis as a minimum to focus on the differential diagnosis since most causes of NALF can be differentiated into four categories based on tests (GALD, viral infections, metabolic disorders, HLH, and ischemic injury).
- Provide supportive care to all neonates while determining underlying cause for NALF, maintain euglycemia, provide adequate nutrition (only glucose).
- Coagulation studies should be performed in all infants with biochemical evidence of abnormal liver function tests (ALT, AST, GGT, ALP).
- Medical management of GALD includes intravenous immunoglobulin (1 gm/kg) and double volume exchange transfusion, which can lead to favorable outcome.
- Liver transplant may be considered in neonates not responding to supportive care or specific therapy. Early consultation with a liver transplant center is encouraged.
- Mothers of infants with GALD should be referred for specialist assessment prior to a next pregnancy. Management with IVIG starting at gestational week 14 should be initiated.
- In case of enterovirus causing NALF, therapy is usually supportive care; however IVIG can be considered.
- Making an early diagnosis and initiation of appropriate HLH treatment with the view toward bone marrow transplant is critical for best outcome.

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