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PEDIATRIC BODY MRI

Magnetic resonance imaging of neonatal hemochromatosis

Govind B. Chavhan[1,2] · Binita M. Kamath[3,4] · Iram Siddiqui[4,5] · Christopher Tomlinson[4,6]

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Abstract

Neonatal hemochromatosis is a rare condition that causes neonatal liver failure, frequently resulting in fetal loss or neonatal death. It is thought that most cases of neonatal hemochromatosis are caused by gestational alloimmune liver disease (GALD), with neonatal hemochromatosis being a phenotype of GALD rather than a disease process. Extrahepatic siderosis in the pancreas, myocardium, thyroid and minor salivary gland is a characteristic feature of neonatal hemochromatosis. There is also sparing of the reticuloendothelial system with no iron deposition in the spleen. Hepatic and extrahepatic siderosis seen in neonatal hemochromatosis is from iron dysregulation secondary to liver damage rather than iron deposition causing the liver damage. The presence of extrahepatic siderosis in the pancreas and thyroid is diagnostic of neonatal hemochromatosis and can be detected noninvasively by multi-echo gradient recalled echo (GRE) T2*-weighted sequence of MRI within hours of birth. This helps to expedite the treatment in the form of intravenous immunoglobulin and exchange transfusion, which improves the survival in these babies. The finding of hepatic siderosis is nonspecific and does not help in the diagnosis of neonatal hemochromatosis because it is seen with other causes of advanced liver disease.

Keywords Gestational alloimmune liver disease · Hemochromatosis · Iron · Liver · Magnetic resonance imaging · Neonates · Siderosis · T2 star

Introduction

Neonatal hemochromatosis is a rare condition characterized by severe liver disease in newborns in the form of cirrhosis present at birth and fulminant liver failure [1]. It is one of the common causes of neonatal liver failure [2–4]. Other causes of liver failure in neonates include ischemic insult, inborn errors of metabolism like galactosemia and tyrosinemia, infections, hemophagocytic lymphohistiocytosis and mitochondrial hepatopathy, among others [2–4]. Neonatal hemochromatosis frequently causes fetal loss or neonatal death in the first week after birth [5]. Most cases of neonatal hemochromatosis are now thought to be caused by gestational alloimmune liver disease (GALD). This understanding has led to effective methods of treatments and resultant improvement in survival — up to 80% with newer treatment regimens comprising exchange transfusion and intravenous immunoglobulin [1, 6]. Extrahepatic siderosis is the characteristic feature of neonatal hemochromatosis and its presence can be considered diagnostic of neonatal hemochromatosis in an infant with severe liver disease [1]. Various methods to detect presence of extrahepatic siderosis have been developed to establish the diagnosis, including detection by MRI [7, 8]. In this review, we discuss etiopathogenesis, clinical presentation, diagnostic work-up and role of MRI, and MRI technique in the evaluation of neonatal hemochromatosis.

Etiopathogenesis

The understanding of neonatal hemochromatosis has evolved over the last 3 decades. Prior to this, the diagnosis of neonatal hemochromatosis was almost exclusively made on autopsies

✉ Govind B. Chavhan
govind.chavhan@sickkids.ca

1 Department of Diagnostic Imaging, The Hospital for Sick Children, 555 University Ave., Toronto, ON M5G 1X8, Canada

2 Medical Imaging Department, University of Toronto, Toronto, ON, Canada

3 Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, Toronto, ON, Canada

4 Department of Pediatrics, University of Toronto, Toronto, ON, Canada

5 Department of Pediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, ON, Canada

6 Division of Neonatology, The Hospital for Sick Children, Toronto, ON, Canada

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[8, 9]. Autopsy studies established the extrahepatic iron deposition in cases with neonatal hemochromatosis in a variety of organs including the pancreas, myocardium, thyroid gland and salivary glands including minor salivary glands in the buccal mucosa, with sparing of the reticuloendothelial system including the spleen, lymph nodes and bone marrow [5, 10, 11]. Because this extrahepatic siderosis appeared in a similar distribution to that seen in hereditary hemochromatosis, it was previously thought to be part of this disorder. However, no genetic defect associated with neonatal hemochromatosis has been found, and clinical behavior of neonatal hemochromatosis is different from that of hereditary hemochromatosis. A study comparing hepatocyte injury and immunostaining for anti-human C5b-9 complex in 33 liver specimens of neonatal hemochromatosis with 37 cases of non-neonatal hemochromatosis neonatal liver disease shed some light on the potential cause of neonatal hemochromatosis [12]. C5b-9 is a terminal complement cascade neoantigen formed in the assembly of membrane attack complex that leads to cell injury. In this study, all neonatal hemochromatosis cases showed severe necrosis of hepatocytes and intense staining of surviving hepatocytes for C5b-9 complex compared to variable light staining in the non-neonatal hemochromatosis group. This finding of complement-mediated hepatic injury led authors to believe that neonatal hemochromatosis is caused by GALD [12].

It is proposed that similar to other maternofetal alloimmune diseases, GALD is mediated by immunoglobulin G (IgG) that is produced when the maternal immune system does not recognize a fetal antigen as "self" [12]. These antibodies are directed against fetal hepatocytes but the specific antigen is not known at this stage. The IgG antibodies activate the complement cascade, resulting in hepatocyte necrosis and liver damage. The hepatic iron deposition and extrahepatic siderosis are thought to be secondary to dysregulation from liver damage rather than iron deposition causing the liver damage.

Neonatal hemochromatosis is considered a phenotype rather than a disease itself, while GALD is the typical underlying disease process causing fetal liver injury and the neonatal hemochromatosis phenotype [1]. Most cases of neonatal hemochromatosis are thought to be caused by GALD; however, neonatal hemochromatosis might be rarely caused by other diseases like tricho-hepato-enteric syndrome, mitochondrial deoxyribonucleic acid (DNA) depletion from deoxyguanosine kinase deficiency (*DGUOK* gene mutations), bile acid synthetic defect delta 4–3-oxosteroid 5 beta-reductase deficiency, GRACILE (growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis and early death) syndrome and some perinatal infections. Therefore, neonatal hemochromatosis and GALD should not be used synonymously.

In most neonatal hemochromatosis cases resulting from GALD, the liver injury occurs in the intrauterine period, hence liver damage is chronic, with the presence of advanced fibrosis or cirrhosis at birth. In some cases, the liver injury occurs acutely, hence fibrosis/cirrhosis and signs of portal hypertension are not seen. Moreover, in some of these cases, there might not even be hepatic and extrahepatic iron deposition at all. GALD causing liver failure without manifestations of neonatal hemochromatosis has been documented, albeit uncommonly [13, 14].

Clinical presentation

The clinical presentation of neonatal hemochromatosis depends on the time of liver injury. Most infants present within hours of birth because the injury has occurred during the intrauterine period. The timing of presentation varies from the antenatal period, as early as 18 weeks of gestation, to 3 months after the birth; liver failure is the presenting feature. Associated features at presentation include hemorrhage, jaundice, hypoglycemia, edema, ascites and oliguria [1]. Often these infants are premature and have a history of oligohydramnios and intrauterine growth retardation [15].

Diagnostic workup and role of magnetic resonance imaging

The diagnosis of neonatal hemochromatosis is difficult. However, making the diagnosis in an expedited fashion is important for emergently required therapy like intravenous immunoglobulin and exchange transfusion. Elevated serum ferritin level is a sensitive indicator of neonatal hemochromatosis but is not specific to liver failure caused by neonatal hemochromatosis. Buccal biopsy has been a staple diagnostic test for many years in the workup of neonatal hemochromatosis. Demonstration of siderosis in the minor salivary glands of buccal mucosa is considered diagnostic of neonatal hemochromatosis. However, in the setting of liver-failure-related coagulopathy, it can be a risky procedure. Also, it takes a few days to get the results, which could delay emergently required treatment. Alternatively, demonstration of positivity of C5b-9 complex on hepatocytes spared of necrosis on liver biopsy could be a way to make the diagnosis [16]. However, it is an invasive procedure and might not be possible in the setting of liver-failure-related coagulopathy. Also, its specificity is poor [17]. MRI is the quickest and least invasive method for demonstrating extrahepatic siderosis. It can be performed within hours of birth, expediting the management [7].

Treatment and prognosis

The prognosis of neonatal hemochromatosis is poor without treatment. Neonatal hemochromatosis is one of the common

indications for liver transplantation in infants <3 months of age. The survival used to be lower, in the range of 10–20% with the previous regimen of an antioxidant cocktail and iron chelators [1, 6]. However, the survival has improved up to 80% with a new treatment comprising exchange transfusion and intravenous immunoglobulin [6]. Neonatal hemochromatosis can recur in up to 90% of subsequent pregnancies [18]. Hence, the diagnosis of GALD is also important for the treatment of future pregnancies. Intravenous immunoglobulins given to at-risk mothers antenatally, starting at 14–18 weeks of gestation, have been shown to prevent development of neonatal hemochromatosis [19, 20].

Magnetic resonance imaging procedures

Preparation and transport of baby

Magnetic resonance imaging in babies suspected of having neonatal hemochromatosis does not need any special preparation. However, because these infants are often unstable, they might require a dedicated neonatal intensive care unit (NICU) transport team to ensure safety during the MR and to provide sedation as needed. This should be facilitated by close communication between radiology and NICU teams.

Equipment and radiofrequency coils

A 1.5-tesla (T) scanner is preferred for neonatal hemochromatosis evaluation. The 3-T scanner might cause artifactual degradation of upper abdominal images because of its increased susceptibility, making visualization of the pancreas difficult. Coverage includes neck for the thyroid assessment, separately, and upper abdomen up to the lower pole of the kidneys. Neonatal abdominal coils work well if available. A head coil is a good option that can cover the neck and abdomen of a neonate. Occasionally, we use a large flex surface coil to cover the neck and abdomen.

Protocol

Our protocol is summarized in Table 1. It is important to keep the slices thin (<4 mm) so that the pancreas and thyroid can be visualized in at least in 2–3 slices. Even though MRI is primarily performed for the assessment of neonatal hemochromatosis, a complete examination without injection of contrast medium is performed to help with diagnosis and management of neonatal liver failure. The routine sequences help to assess liver parenchyma for any changes in cirrhosis, gross vascular assessment on balanced steady-state free precession (SSFP), signs of portal hypertension, gross biliary assessment and any potential focal abnormality like lesions or infarctions.

Technical challenges and solutions

In general, the overall signal and signal-to-noise ratio is low in babies because of small body size. The smallest radiofrequency coil that can cover the region of interest, like phased-array or surface coils, is essential for obtaining a good signal-to-noise ratio. The main purpose of MR imaging in these cases is to detect the presence of extrahepatic siderosis in the pancreas and thyroid. It is difficult to depict these organs because of their size in neonates. The GRE T2* sequence is artifact-prone and particularly the small pancreas and thyroid can get obscured by susceptibility artifacts of adjacent bowel and trachea, respectively. Gaseous distension of the stomach is a common cause of obscuration of the pancreas, especially on later echo images. This can be mitigated by injecting 5–10 cc

Table 1 Neonatal hemochromatosis protocol

Sequence	Plane	TR/TE (ms)	Flip angle	Matrix, slice thickness	NSA	ETL	Pixel bandwidth (Hz)	Time[a]
Multi-echo T2* GRE thyroid	Axial	700/2.5–30.6 (11 echoes)	60°	195×105, 3 mm	4	11	375	2 min
Multi-echo T2* GRE upper abdomen	Axial	600/2.5–30.6 (11 echoes)	60°	195×105, 3 mm	4	11	375	2 min
STIR	Cor	2,100/54	150°	300×196, 3 mm	4	9	260	3 min
T2 FSE fat-saturated	Axial	3,900/100	160°	320×240, 3 mm	2	19	195	3 min
Balanced SSFP	Axial	5/2.5	70°	256×208, 3 mm	4	1	490	3 min
T1-W in- and out-phase	Axial	178/4.6 and 2.3	75°	256×134, 3 mm	4	2	415	40 s
Diffusion (b values 50, 400, 800 s/mm^2)	Axial	7,600/137	90°	192×126, 4 mm	4	95	1,630	4 min

Cor coronal, *ETL* echo train length, *FSE* fast spin echo, *GRE* gradient echo, *min* minutes, *NSA* number of signal averages, *s* seconds, *SL* slice thickness, *SSFP* steady-state free precession (TruFISP [true fast imaging with steady state precession]/bTFE [balanced turbo field echo]/FIESTA fast imaging employing steadystate acquisition]), *STIR* short tau inversion recovery, *TE* echo time, *TR* repetition time

[a] Approximate time

of normal saline through an in situ nasogastric tube in consultation with the NICU transport team. The multi-echo T2* sequence should be acquired first in case the baby wakes and the exam cannot be completed.

Interpretation

Even though GRE T2* sequence can be used for iron quantification, no algorithm or software is available for quantification specific to the neonatal age group. Moreover, no normative data on iron quantity in various tissues of neonates are available. Hence, current MR evaluation for neonatal hemochromatosis is purely qualitative. Qualitative assessment can be graded as mild, moderate and severe degrees of iron deposition based on the echo on which organs start showing darkening/signal drop [7]. The darkening of the parenchyma on first echo (echo time [TE] 2.5 ms) itself is graded as severe, on second echo (5.3 ms) as moderate, and on sixth echo (16.6 ms) as a mild degree of iron deposition [7]. Most cases of neonatal hemochromatosis show at least a moderate degree of iron deposition in the pancreas [7]. The darkening seen only on the last 2–3 echoes should be interpreted cautiously because it could be artifactual.

An autopsy study has demonstrated that extrahepatic siderosis in neonatal hemochromatosis is more frequent in the thyroid gland than the pancreas [11]. The presence of at least a mild degree of iron deposition in the pancreas and thyroid establishes the diagnosis of neonatal hemochromatosis in a baby with liver failure (Figs. 1 and 2). This needs to be correlated with the absence or minimal degree of splenic siderosis because the reticuloendothelial system is typically spared in GALD [7, 10]. The presence and severity of hepatic siderosis does not help in differentiating neonatal hemochromatosis from other causes of liver failure. Some degree of hepatic siderosis can be seen in liver failure of any cause [7]. Moreover, some degree of hepatic siderosis has been shown to be physiological in the third trimester and the neonatal period [8, 9].

Depending on the time of hepatic injury, the liver morphological findings and presence of portal hypertension vary. The imaging findings of cirrhotic/atrophic liver with portal hypertension are seen in the majority of cases of neonatal hemochromatosis [7]. The presence of patent ductus venosus has been described with neonatal hemochromatosis. However, this is a nonspecific finding reflecting increased intrahepatic resistance to blood flow and can be seen with any cause of liver scarring or fulminant hepatitis as a shunt mechanism to relieve portal circulation pressure [21].

Future avenues

Future avenues for MR imaging of neonatal hemochromatosis could include improved sequences with better depiction of the small pancreas and thyroid in neonates. GRE T2* sequence could become more robust to movements like breathing and other involuntary movements. This improved sequence could then be applied in fetal imaging so that the diagnosis could be

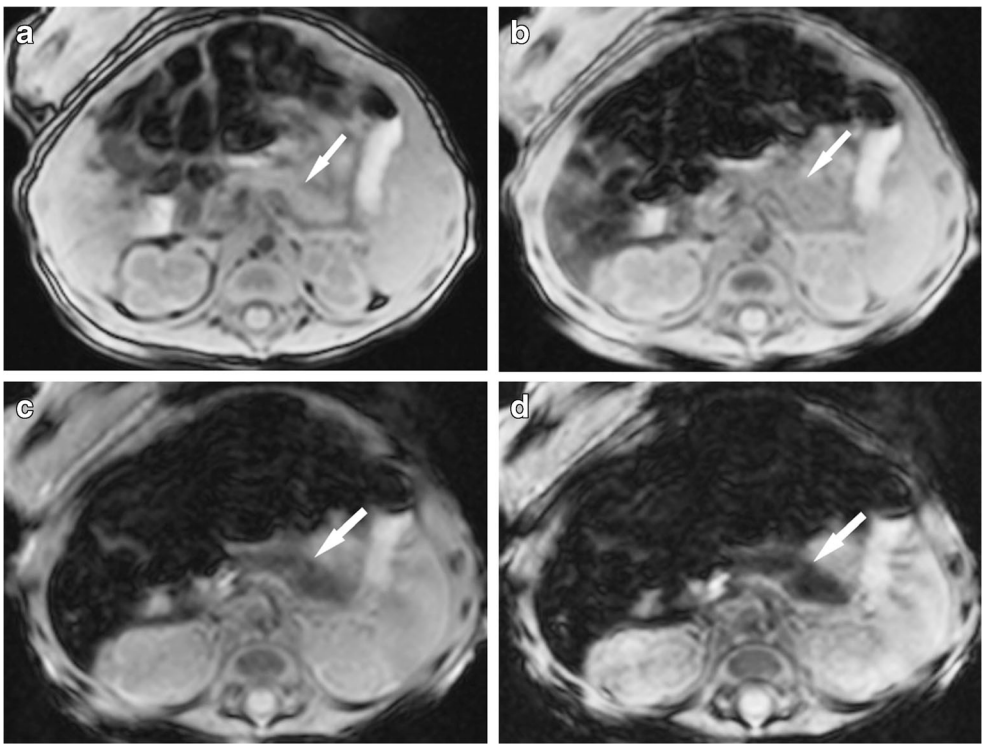

Fig. 1 Neonatal hemochromatosis in 7-day-old girl. **a**–**d** Select images from axial T2* sequence with progressive echo times (**a**, 2.5 ms; **b**, 8.1 ms; **c**, 19.4 ms; **d**, 27.8 ms) demonstrate progressive decrease in pancreas signal (*arrows*). There is also a similar or larger degree of hepatic parenchymal signal decrease. Note sparing of the splenic parenchyma

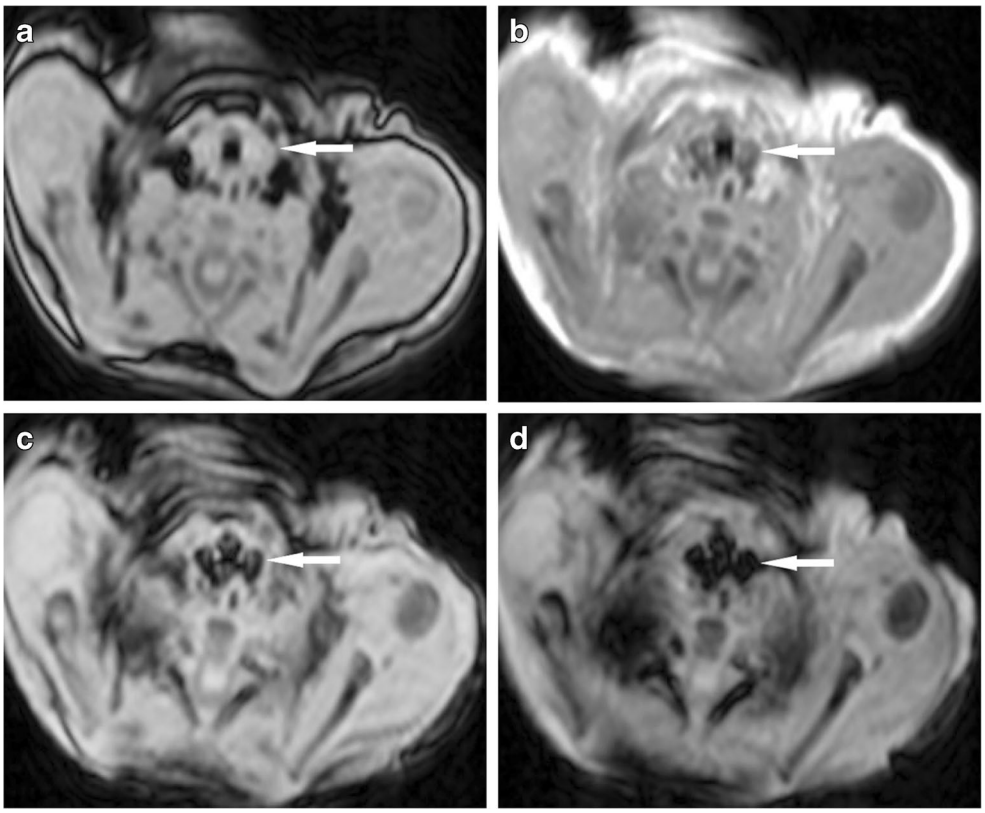

Fig. 2 Neonatal hemochromatosis in the same baby as in Fig. 1. **a–d** Select images from axial T2* sequence with progressive echo time (**a**, 2.5 ms; **b**, 5.3 ms; **c**, 10.9 ms; **d**, 19.4 ms) demonstrate progressive lowering of thyroid parenchyma signal (*arrows*)

made prior to birth. There are limited data on iron quantification in neonatal organs [22]. With improved technology, quantification of iron deposition in neonatal organs could be possible. This would make the MRI a more objective method for diagnosing neonatal hemochromatosis and might even be used for follow-up to assess response to therapy.

Summary

Neonatal hemochromatosis is a rare condition causing neonatal liver failure and often leads to fetal loss or neonatal death. Extrahepatic siderosis in the pancreas, myocardium, thyroid and minor salivary gland is a characteristic feature of neonatal hemochromatosis. There is sparing of the reticuloendothelial system, with no iron deposition in the spleen. The presence of extrahepatic siderosis in the pancreas and thyroid can be detected noninvasively by MRI within hours of birth. This helps to initiate treatments that improve survival in these babies. The presence of hepatic siderosis is nonspecific and does not help in diagnosing neonatal hemochromatosis because it is seen with any causes of liver failure.

Declarations

Conflicts of interest None

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