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CASE REPORT

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Fetal hemochromatosis: rare case of hepatic and extrahepatic siderosis involving thyroid on fetal MRI

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Abstract

Background Neonatal hemochromatosis (NH) is a rare condition that is characterized by severe neonatal liver disease in association with hepatic and extrahepatic excess iron deposition (siderosis), while sparing the reticuloendothelial system. The most common cause of fetal liver injury leading to the NH phenotype (accounting for over 95% of cases) is gestational alloimmune liver disease. This condition is caused by the transfer of maternal IgG antibodies through the placenta, targeting a fetal hepatocyte antigen. Prenatal diagnosis, particularly the identification of iron overload involving both liver and thyroid, is of significant importance and can have a profound impact on patient care. To our knowledge, no case has been reported on prenatal diagnosis of iron overload involving both liver and thyroid.

Case presentation We present an exceptionally rare case of fetal hemochromatosis in a primigravida, a case that significantly contributes to our understanding of this condition. The diagnosis was made with the presence of hepatic and extrahepatic siderosis involving the thyroid using Ultrasonography (USG) and fetal Magnetic Resonance Imaging (MRI) findings. A 23-year-old primigravida was referred to our center in view of oligohydramnios, Intrauterine Growth Restriction (IUGR) and echogenic bowel at 29 weeks of gestation. USG and fetal MRI showed features of coarse liver echotexture and iron overload involving the liver and thyroid; this is the first case describing iron accumulation in the fetal thyroid gland diagnosed in utero.

Conclusion This case underscores the critical importance of performing MRI in suspected cases of fetal hemochromatosis for early diagnosis and intervention, emphasizing the potential to significantly improve patient outcomes.

Keywords Hemochromatosis, Iron overload, Liver, Thyroid, MRI, Tricho-hepato-enteric syndrome, Case report

Background

Neonatal hemochromatosis (NH) is a rare gestational disease characterized by severe prenatal liver injury associated with hepatic and extrahepatic iron overload that classically spares the reticuloendothelial system. By far, the most frequent cause of fetal liver injury leading to the NH phenotype (accounting for > 95% of cases) is a gestational alloimmune disorder called gestational alloimmune liver disease (GALD), which results from transplacental transfer of maternal IgG antibodies directed against a fetal hepatocyte antigen. MRI remains a valuable tool in the early prenatal diagnosis of iron overload in the liver and extrahepatic tissues. We present a rare case of fetal hemochromatosis, which was diagnosed with the presence of hepatic and extrahepatic siderosis involving the thyroid using USG and fetal MRI findings. This is the first case describing iron accumulation in the fetal thyroid gland diagnosed in utero.

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Case presentation

A 23-year-old primigravida with Rh-positive typing was referred to our center in view of oligohydramnios, IUGR and echogenic bowel at 29 weeks of gestation. Detailed USG showed fetal growth restriction, left axis deviation of the heart, and diffusely echogenic bowel walls. Follow-up USG at 32 weeks showed altered, coarse echotexture of the liver with a drop in growth velocity. Fetal MRI was done for further evaluation. It showed an enlarged liver with intense T2 hypointensity and loss of T1 hyperintense signal of the liver, splenomegaly, minimal ascites (shown in Fig. 1) and loss of T1 hyperintense signal of the thyroid (shown in Fig. 2). T2* images showed diffuse hypointensity in the liver which led to the suspicion of fetal hemochromatosis. Karyotyping was normal, TORCH and Parvovirus PCR were negative. Weekly follow-up for Doppler was done, and the baby was delivered at term by elective LSCS. The baby was admitted to NICU in view of Meconium Aspiration syndrome with tachypnea and Respiratory distress. The baby required non-invasive ventilation for 8 days; then the baby was gradually weaned to room air.

The baby had hepatosplenomegaly at admission associated with hypoglycemia, deranged liver function tests, thrombocytopenia, elevated ferritin and dysmorphic facies (retrognathia, macrostomia, low set posteriorly retracted ears). The baby was suspected to have neonatal hemochromatosis / GALD. MRI showed chronic

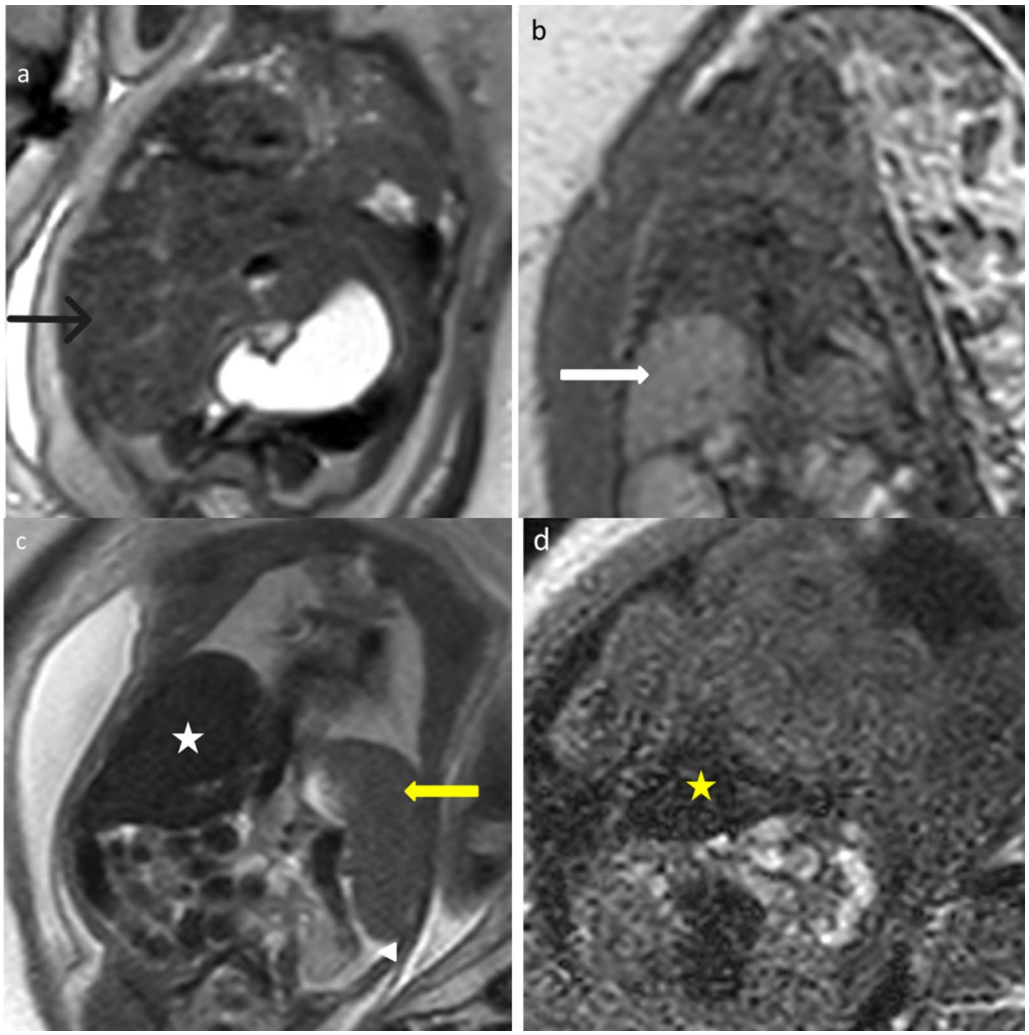

Fig. 1 (**a**,**b**) Normal T2 and T1 weighted coronal images of fetal MRI (1.5 T) at the level of thorax and abdomen in third trimester show normal T2 hypointense signal (white arrow) and normal T1 hyperintense signal of liver (black arrow). (**c**,**d**) T2 and T1 weighted coronal sections of fetal MRI (1.5 T) in our case show intense T2 hypointense (white star) and T1 hypointense signal of liver (yellow star), splenomegaly (yellow arrow) and mild ascites (arrowhead)

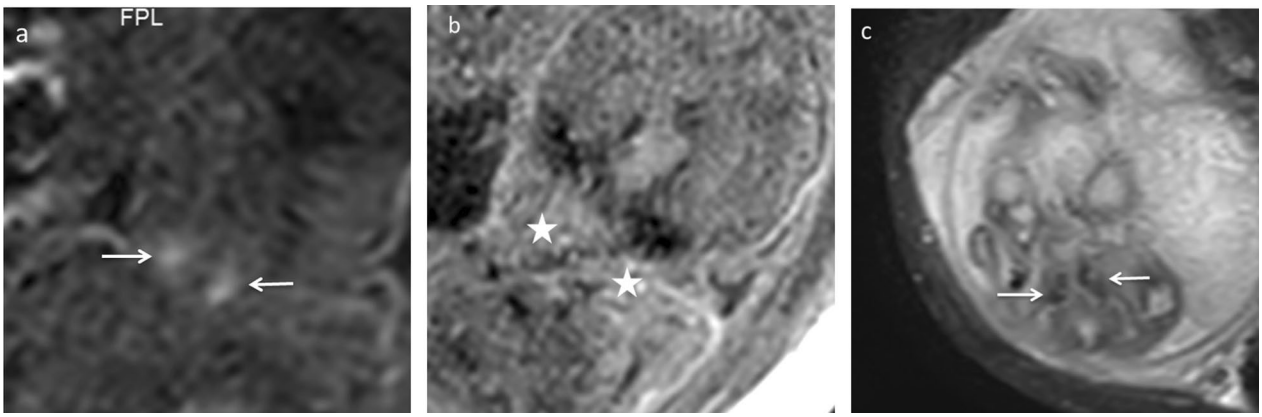

Fig. 2 (**a**) T1-weighted coronal image of fetal MRI (1.5 T) at the level of head and neck in a normal fetus shows normal T1 hyperintense signal in both lobes of thyroid gland (white arrows). (**b**) T1-weighted coronal image of our present case shows loss of normal hyperintensity in the region of thyroid gland (white stars). (**c**) T2* weighted coronal image of fetal MRI shows hypointense signal in the region of thyroid gland (white arrows)

parenchymal liver disease with moderate iron overload in liver (shown in Fig. 3a) and thyroid gland (shown in Fig. 3b). TORCH panel was negative. Urine reducing substances and urine succinyl acetone were done to rule out other causes of acute liver failure in neonates. Lip biopsy showed hemosiderin deposition within few of the acinar epithelial cells (shown in Fig. 4).

Clinical exome sequencing revealed compound heterozygous variants related to the SKIV2L gene, which is associated with Trichohepatoenteric syndrome. This syndrome is a rare genetic disorder characterized by growth failure, intractable diarrhea, woolly, brittle hair, immunodeficiency, liver failure and dyschromic skin spots. However, the child did not develop the typical phenotypic features of Trichohepatoenteric syndrome, leading us to consider GALD as the diagnosis of exclusion in this case.

Upon diagnosis, the baby was immediately started on liver protective measures, which included maintaining fluid and electrolyte balance. In addition, the baby received IVIg treatment for 2 days, followed by an exchange transfusion. This treatment regimen was aimed at reducing further damage to the liver. The baby showed gradual improvement in liver function tests and clinical symptoms and was eventually discharged. Unfortunately, the baby died at 2 months of age due to complications related to liver failure.

Discussion

This case underscores the critical importance of performing MRI in suspected cases of fetal hemochromatosis for early diagnosis and intervention, emphasizing the potential to significantly improve patient outcomes.

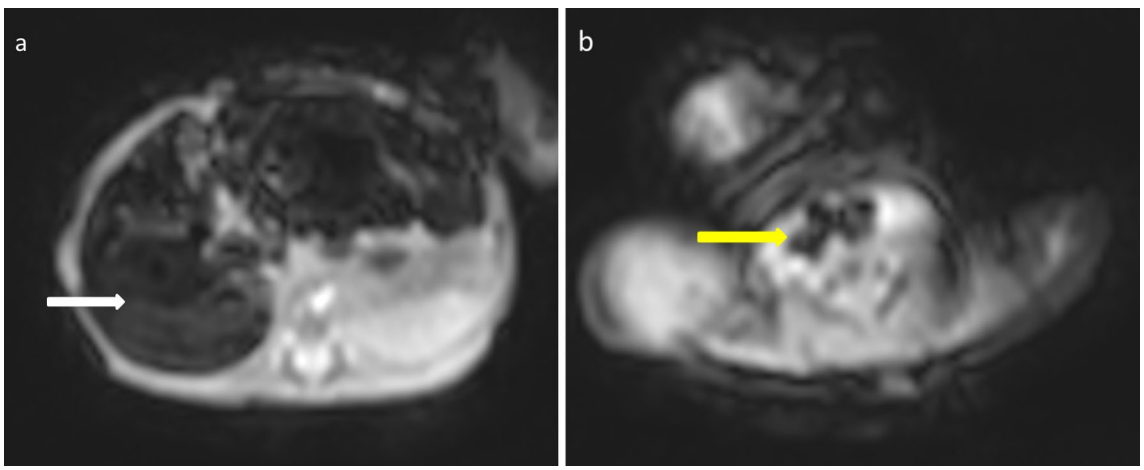

Fig. 3 (**a**,**b**) T2* weighted axial postnatal MRI images show hypointense signal of liver (white arrow) and thyroid (yellow arrow)

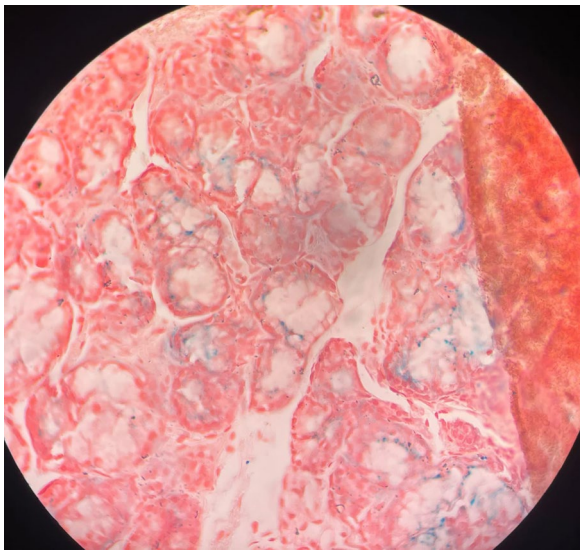

Fig. 4 Lip biopsy specimen showing hemosiderin deposition within few of the acinar epithelial cells stained blue with Perls stain

GALD is a condition characterized by the immune mediated fetal liver injury during pregnancy. This can lead to liver failure in utero, which is the most common cause of neonatal acute liver failure (NALF) [1]. GALD occurs when the mother's IgG antibodies cross the placenta and target an unknown antigen on the fetal liver [2, 3].

Fetal hepatocytes become targets of these antibodies and the attack of membrane complexes, leading to disruption of iron homeostasis and subsequent deposition in extrahepatic tissues, typically starting with hepatic siderosis sparing the Kupffer cells, ultimately resulting in severe fetal liver damage and cirrhosis [4, 5].

The fetal hepcidin pathway regulates the fetal iron stores [1]. Maternal antibodies damaging the fetal liver can decrease hepcidin levels, leading to an accumulation of iron in the liver [2]. To differentiate the NH-GALD phenotype from other causes of neonatal hemochromatosis, a comprehensive assessment is necessary. Specific investigations to rule out alternative etiologies with a similar clinical presentation have been described [6]. These other causes, which make up approximately 2% of NH cases, primarily involve fetal liver injury disrupting placental iron flux regulation [1].

Early indicators of GALD often include IUGR which can be detected in the early mid-trimester scan [7]. Because FGR can stem from various causes, such as uteroplacental insufficiency, genetic factors, and infections, an accurate diagnosis of FGR associated with the NH phenotype requires careful consideration.

Given that liver biopsy is impractical during the intrauterine period, prenatal diagnosis relies on MRI findings. GALD may induce non-immune hydrops due to hypoproteinemia [8]. Suspicion of NH arises in fetuses presenting with hydrops, anemia, and hepatomegaly, warranting fetal MRI examination.

The quantification of organ iron accumulation using T1 or T2* relaxometry can be adapted for pediatric use. However, there is a lack of normative data regarding iron quantification in various neonatal tissues [2, 9]. Fetal MRI in cases of GALD could potentially assess responses to in utero treatment [10]. Qualitative assessment of signal intensity on various MRI sequences such as T2, T2*, T1, and gradient recalled echo (GRE) sequences may be employed. While fetal organ iron deposition can be detected by MRI, it may not always be present at the time of examination [10]. Conversely, liver siderosis may be absent due to the destruction of targeted hepatocytes, and the presence of extrahepatic siderosis potentially aids diagnosis in such cases [4, 7]. The first case of intrauterine hemochromatosis was studied by Marti-Bonmati et al. in 1993 using a T2* sequence, revealing markedly low hepatic parenchymal signal intensity compared to fetal and maternal fat tissue [11]. Currently, fast, single-shot T2-weighted sequences are the primary tool in fetal MRI, which can initially raise suspicion of liver iron deposition. Organ iron load quantification can be achieved through MRI T2* relaxometry techniques, as demonstrated by Schoennagel et al. [12]. A retrospective multicentric study from France observed that iron storage in fetuses was more common in the thyroid than in the pancreas [13]. The detection of extrahepatic siderosis can be done non-invasively using multi-echo gradient recalled echo T2*-weighted MRI sequences shortly after birth [2, 9]. Postmortem MRI can be valuable in confirming neonatal hemochromatosis, especially in cases where traditional autopsy methods are not feasible due to parental preferences, and can provide justification for further investigations such as guided liver biopsy [14]. In our case, the genotype–phenotype correlation of tricho-hepato-enteric syndrome could not be established; further studies are required to establish a correlation.

Presently, IVIG treatment has significantly altered the outlook for affected women, enabling them to carry a healthy child following an NH pregnancy [15].] This treatment has altered disease progression, leading to the absence of ultrasound manifestations and an improved life expectancy compared to untreated pregnancies [10]. Nonetheless, IVIG therapy is costly, may face availability constraints in certain regions, and can pose severe adverse effects [15].

Prenatal findings of NH are frequently nonspecific. MRI should be considered in specific cases involving

unexplained fetal growth restriction (FGR), oligohydramnios, hydrops, enlarged fetal liver, and the presence of ascites or fetal anemia. Typically, MRI is recommended after ruling out more common conditions. MRI can identify hepatic and extrahepatic siderosis, confirming NH. In cases where parents decline fetal autopsy, postmortem MRI should be available for unexplained fetal and newborn deaths with liver failure, as it can readily detect liver siderosis and guide further investigations. Further studies are warranted to identify underlying genetic causes of fetal liver injury and to establish genotype–phenotype correlation.

Abbreviations

NH	Neonatal hemochromatosis
GALD	Gestational alloimmune liver disease
USG	Ultrasonography
MRI	Magnetic resonance imaging
NICU	Neonatal intensive care unit
IUGR	Intra uterine growth restriction
TORCH	Toxoplasmosis rubella cytomegalovirus herpes
PCR	Polymerase chain reaction
LFT	Liver function test
NALF	Neonatal acute liver failure
FGR	Fetal growth restriction
GRE	Gradient recalled echo
IVIG	Intravenous immunoglobulin

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RK and SN contributed to conceptualization, investigation, validation, writing—original draft, review and editing. SR and DM doen validation and writing—review and editing.

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Availability of data and materials
All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
Study approval statement: Ethics approval was not required as decided by the ethics committee of KMCH. Consent to participate statement: Written informed consent was not required as decided by the ethics committee of KMCH.

Consent for publication
Written informed consent was obtained from the parents for publication of the details of their medical case and any accompanying images.

Competing interests
The authors declare that they have no competing interests.

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