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Case Report

Neonatal Hemochromatosis with Acute Liver Failure

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Abstract

Gestational autoimmune liver disease (GALD) is now recognized as the major cause of neonatal hemochromatosis in almost all the cases. Cases of neonatal hemochromatosis due to gestational autoimmune liver disease can result in fetal demise, stillbirth or neonatal acute liver failure. Neonatal hemochromatosis due to GALD is not hereditary; rather it is congenital materno-fetal alloimmune disorder that results in fetal liver injury. This makes GALD a treatable and preventable disorder which underlines the importance of establishing a diagnosis early in order to provide the appropriate management.

Keywords: *GALD: Gestational Autoimmune Liver Disease; NH: Neonatal Hemochromatosis; IUGR: Intrauterine Growth Restriction; IVIG: Intravenous Immunoglobulin G*

Introduction

Neonatal liver failure due to GALD is a rare disorder which may present early in the neonatal period or later usually three months after birth. We present here a neonate who presented in the first two weeks of life with coagulopathy, hemochromatosis and acute hepatic failure with encephalopathy. Presence of perinatal IUGR and oligohydramnios are important markers that are found in the majority of these cases and help in alerting physician to the diagnosis. In contradistinction to untreatable hereditary causes of NH, GALD is a treatable and preventable cause of NH and liver failure. This mandates that the treating physician must have a high index of suspicion in cases with the described clinical presentation.

Clinical Presentation

A pregnancy which was complicated by intrauterine growth restriction (IUGR) and anhydramnios, resulted in preterm delivery at 33 weeks gestation of a very low birth weight female infant of 1280 grams. The baby had respiratory distress syndrome and went on to develop necrotizing enterocolitis from which she recovered without complications.

By the age of two weeks the infant developed significant conjugated hyperbilirubinemia with bleeding tendency, abnormal liver enzymes and hypoalbuminemia. Eventually the infant developed hepatic failure with encephalopathy shown by high ammonia level. Prothrombin time was prolonged at 28 sec and INR was 3.86. Further investigations revealed significantly elevated ferritin level suggesting presence of neonatal hemochromatosis (NH). Buccal biopsy for iron stain was negative. Whole exome sequence did not reveal any pathogenic variant.

The differential diagnosis of the case centred around conditions which could cause IUGR with coagulopathy and hepatic failure. A long list of diagnoses can be anticipated including intrauterine infections, metabolic disorders and NH. NH was confirmed by the presence of significant abnormalities in serum ferritin and transferrin.

NH can be caused by inherited and acquired hepatic disorders. Various investigations were carried out which ruled out intrauterine infections and metabolic and genetic hepatic disorders. Thus, the diagnosis of GALD was made by exclusion of these disorders. There is no specific serological confirmatory test for GALD and liver biopsy was not considered because of the unstable condition of the baby in addition to the presence of coagulopathy.

Investigations

Test	Result	Ref. Range
Serum iron	23.2 micromol/L	8.95 - 26.85
Ferritin	12492 ng/ml	30 - 400
Transferrin	1.03 mg/dl	204 - 360
Transferrin saturation	90%	20 - 50%
Total bilirubin	320 micromol/L	17 - 200
Direct bilirubin	290 micromol/L	< 17
Prothrombin time	28 sec	11 - 13.5
INR	3.86 sec	0.8 - 1.1
Ammonia	319 micromol/L	< 50
AST	70 units/L	10 - 40
ALT	68 units/L	7 - 56
Amino Acid Screen	Unremarkable	
Urine organic acids	Unremarkable	
Whole Exome Sequence	No pathogenic variant	

Table

Management of the case included repeated exchange transfusions, intravenous immunoglobulin G (IVIG), fresh frozen plasma, platelets transfusions and hemodynamic support. Eventually the infant expired in spite of significant improvements in ammonia and ferritin levels.

Discussion

For a long time, NH has been considered as a specific inherited disorder of iron metabolism. However, recent advances have shown that NH is not a disease. Rather it is a consequence of fetal liver injury.

The current definition of NH is that it is a clinical condition in which severe liver disease in the newborn is accompanied by extrahepatic siderosis in the distribution seen with hereditary hemochromatosis [1]. Although several disorders can result in NH, it is mostly seen in GALD.

NH caused by GALD is due to materno-fetal alloimmune disorder and siblings in the same family can be affected. Thus, NH resulting from GALD is not a genetic disorder because the recurrence pattern does not fit genetic inheritance, and multiple unaffected infants can occur in the family before an affected infant is delivered. Once one infant is affected, 90% of the subsequent infants would be affected.

NH in GALD affects maternal half siblings but not paternal half siblings. Female survivors of NH in GALD had unaffected infants. Hence it is congenital and familial but not hereditary [9].

Studies have shown that GALD is the cause of fetal liver injury in almost all cases of NH. The targeted antigen is a hepatocyte specific protein that is expressed either by the fetal hepatocyte or highly sequestrated in mature liver. When the antigen is expressed during fetal development, the mother may have lost tolerance to this self-antigen overtime in absence of central immune tolerance. Alternatively, if the antigen is sequestrated in the mature liver, the mother might have lost its recognition as self in the absence of central immune tolerance. When the mother is exposed to this hepatocyte specific antigen, an immune response is induced which targets the fetal hepatocyte. As a result, a specific IGG is passed to the fetus where it binds to the hepatocyte antigen. This reaction involves formation of a membrane attack complex (c5b-9) which produces the complement-mediated hepatocyte injury. This complement-mediated hepatocyte injury is the defining feature of GALD [2].

Non-hepatocyte liver cells and extrahepatic tissues are not affected by sensitization occurring to fetal antigen.

GALD is associated with marked loss of more than 90% of the hepatocytes whereas the surviving ones will show siderosis. Severe parenchymal fibrosis also occurs resulting in hepatic cirrhosis. In some babies GALD may produce acute liver injury leading to still birth or fetal demise [3,4]. However, GALD can cause liver disease with liver failure that is not accompanied by iron overload. This may explain the negative iron stain in the buccal biopsy and absence of extrahepatic siderosis.

Siderosis is seen in extrahepatic organs mainly in exocrine pancreas, thyroid, myocardium and salivary glands. However, it is not seen in the reticuloendothelial system [1].

GALD liver injury affecting fetuses and newborns disrupts the process of regulation of iron handling. Normally fetal iron transport is regulated by the placenta to ensure adequate iron supply for growth and oxygen-carrying capacity. The fetal liver will regulate and control iron by producing hepcidin which is a regulatory feedback molecule. In states of iron sufficiency, hepcidin suppresses the cell-surface expression of ferroportin which is a transmembrane iron transporter that transfers iron out of the cell. The hepcidin binding with ferroportin results in decreased iron influx. In GALD liver injury hepcidin production is markedly reduced resulting in less negative feedback on ferroportin which in turn will result in excess iron transport from the placenta to the liver. Also, transferrin gene expression is decreased resulting in reduced iron-binding capacity. The net-result is fetal iron overload and excess of circulating non-transferrin bound iron (NTBI) [5,6].

Clinically GALD can present from 18 weeks of gestation to three months after delivery. Although some babies may be asymptomatic, liver failure can present early after birth as seen in our case. Babies with antenatal history of IUGR, oligohydramnios and prematurity who develop features of liver disease should be investigated thoroughly for GALD and management started as early as possible. IUGR and oligohydramnios were the significant findings in 74 cases of NH with extrahepatic siderosis reported between 1993 and 2021. In addition to extrahepatic siderosis the presence of conjugated hyperbilirubinemia, alpha-fetoprotein above 100000 ng/ml, serum ferritin above 800 ng/ml with low transferrin and high iron saturation should suggest the diagnosis of NH due to GALD.

It has been suggested that immunohistochemical demonstration of c5b-9 in liver biopsy is diagnostic of GALD. However; a recent study by Collardeau-Frachon has shown that c5b-9 was expressed in GALD cases as well as non-GALD cases with iron overload. Non-GALD cases included cases of maternal erythrocytic alloimmunization, intrauterine infections, bile acid synthetic disorder and other metabolic liver disorders. It was also noted that some cases of GALD may not express c5b-9 [7]. Presence of extrahepatic siderosis in buccal biopsy may help in the confirmation of the diagnosis but if this is negative, then MRI is recommended. It is evident now that the diagnosis of GALD relies on the correlation of clinical, biological, radiological and pathological findings. Unfortunately, the diagnosis of GALD is often made at autopsy where extrahepatic siderosis is observed.

Management of babies with NH and GALD involves repeated exchange transfusions to remove the antibodies followed by administration of intravenous immunoglobulin G (IVIG) to block the antibody-induced complement activation [8]. Eventually liver transplant can be offered after the initial management. However, in severely affected babies the disease is usually fatal.

Prevention of GALD in future pregnancies is the best strategy in those families who had affected babies because the recurrence in any next pregnancy is more than 90%. Prevention has been achieved by administration of IVIG at 14 weeks gestation every two weeks until delivery of the baby. An excellent outcome has been reported after IVIG therapy with 99% of the newborn babies being normal [9,10].

Different mechanisms have been suggested for the role of IVIG in prevention of GALD. It is possible that IVIG works by dilution of maternal antibodies directed against hepatocyte antigen, blocking of placental receptors and reduction of placental transmission of maternal antibodies to the fetus and blocking of the Fc receptors on the macrophages in the fetal circulation thus limiting the destruction of fetal hepatocytes sensitized by maternal antibodies.

Because of the high recurrence of GALD in the subsequent offsprings, the family of our baby were counselled and were instructed to report early in the next pregnancy in order to establish the diagnosis and offer IVIG therapy during the pregnancy.

Conclusion

It is anticipated that more cases of GALD will be seen in practice. This entails presence of high degree of suspicion prenatally in pregnancies where the ultrasound at 18 weeks gestation is showing IUGR, oligohydramnios and nonimmune hydrops [11,12]. Recently magnetic resonance (MRI) has been employed in early pregnancies with previous GALD history to assess organ iron deposition specifically in extrahepatic siderosis. MRI can also be used to assess the response to IVIG in-utero treatment [12-14].

Consent

Written consent was obtained from parents for publication of this paper.

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Conflict of Interest

The authors declare that they have no conflict of interest with this publication.

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