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Gestational Allo-Immune Liver Disease – Successfully Treated Leading to A Good Neonatal Outcome.

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ABSTRACT

Gestational alloimmune liver disease (GALD) is a rare liver disorder, yet one of the most important causes of neonatal hemochromatosis and fetal liver injury. It is an alloimmune reaction where maternal IgG antibodies attack the fetal hepatocytes leading to iron over load and liver failure in the baby. It has an incidence in the United States of 4 per 100,000 cases per live births[1].Considering the high recurrence rate in subsequent pregnancies, prompt diagnosis and treatment of GALD is important to ensure good outcome of present and future pregnancies. We describe a case of Gestational alloimmune liver disease, successfully treated with intravenous Immunoglobulin (IVIG)and went on to deliver a healthy term baby.

Keywords: Rare disorder, fetal liver failure, high recurrence, Intravenous Immunoglobulin

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INTRODUCTION

Neonatal hemochromatosis (NH) is a clinical condition in which severe liver disease in the newborn is accompanied by extrahepatic siderosis. Gestational alloimmune liver disease (GALD) has been established as the cause of fetal liver injury resulting in nearly all cases of NH [20]. IgG antibodies are directed against fetal hepatocytes. These antibodies bind to the liver antigen, activate terminal complement cascade and result in hepatocyte injury and death [20]. Recurrence is about 90% in consecutive pregnancies and can be prevented by IVIG treatment [23].

CASE PRESENTATION

Mother X was a 25-year-old, Gravida 3, Para 1+1. Healthy first baby delivered by caesarean section. Unfortunately, she lost her 2nd baby at 20 weeks gestation. Post-partum analysis showed possible neonatal haemochromatosis. Whole exome sequencing as a trio testing of DNA and compared to Mrs X. Detailed gene panel tests for iron storage disorders and sideroblastic anaemia and mitochondrial DNA analysis were carried out. No genetic causes were identified. Partner showed minor alteration in HFE gene but this particular one, not known to not cause haemochromatosis. Mrs X had both copies of H63D gene, this does not cause haemochromatosis. It was concluded that the likely cause was to be GALD.

GALD has a high recurrence rate – studies suggesting as high 90% [1]. In light of this, a multi-disciplinary team discussion was put in place when Mrs X conceived. Based on input from paediatric hepatologist, IVIG (Intravenous Immunoglobulin) was commenced from 16 weeks gestation onwards. Initially once every 2 weeks and then increased to every week. In view of the high-risk pregnancy, Mother X was closely monitored antenatally by our fetal medicine team which included regular growth scans and consultations.

During this monitoring period around 30 weeks gestation, Mother X's bloods showed a reduction in haemoglobin, ferritin and B12. This was initially treated with IV iron infusion and B12, due to suspicion of haemolytic anaemia; this was suspected given Mother X's ongoing IVIG therapy [25]. This was excluded by the hepatologists.

After treatment with IV iron infusion, her anaemia improved. IVIG infusions were continued meanwhile on labour ward with close monitoring. She had a healthy term baby by elective lower-segment caesarean section at 37 weeks.

DISCUSSION

Gestational alloimmune liver disease (GALD) is thought to be one of the most the most common cause of neonatal acute liver failure (NALF) associated with neonatal haemochromatosis (NH). GALD carries with it a high rate of both mortality and morbidity [2] and has proved to be diagnostically challenging to clinicians, given its rarity, our incomplete knowledge regarding its pathophysiology, the fact it can manifest at any point from 18 weeks of gestational age to 3 months of life [3] and its spectrum of presentation. Ultrasound features may include fetal growth restriction (33%) Oligohydramnios (13%) hydrops (13%) fetal anaemia, ascites, abnormal liver and spleen. Magnetic resonance Imaging can show extrahepatic hemosiderosis [24]

The pathophysiology of GALD is thought to be mediated by the transplacental active transport of maternal IgG antibodies targeted against foetal hepatocyte cell surface antigens [4]. This occurs in the 12th week of gestation [5]**.** The identity of this cell surface antigen, however, remains unknown; it has been posited that it could be a specific hepatic protein that is either only expressed by foetal hepatocytes or is downregulated in a mature liver [3]. Hepatocyte cell death is then thought to be mediated by a complement membrane attack complex known as C5b9 [6]. The endgame is reduced levels of hepcidin and transferrin, resulting in dysregulation of iron influx from the placenta, and inability of the liver to transfer iron intracellularly; thus, we see siderosis [1].

Routine scans and antenatal appointments can play an important role in detecting GALD. The manifestations of GALD antenatally include tailing growth/intra-uterine growth restriction, hydrops, oligohydramnios, placental oedema [1]. The mother may have a history of miscarriage or premature birth, and in the case of the hyperacute process, possibly stillbirth or foetal demise [2].

In the post-natal period, newborn will likely develop symptoms of acute liver failure within the first few hours of life [2]. Therefore, as a clinician, one must assess for signs and symptoms of liver failure. These include hepatomegaly, lethargy, splenomegaly, ascites, peripheral oedema, fever and nausea/vomiting [7]. With these features, a neonate may present appearing septic; thus, illustrating the challenge facing clinicians in diagnosing GALD as the cause of what to some may appear to be non-specific signs.

A wide range of biochemical derangements can be noted on laboratory findings. Rapid loss of hepatic function can manifest with a prolonged prothrombin time of > 20s and an elevated INR of ≥ 2 that is not responsive to administration of parenteral vitamin K. The Paediatric Acute Liver Failure Study Group include this as a diagnostic criterion for NALF [8]. Full blood count can reveal anaemia, thrombocytopaenia and hyperleukocytosis. Liver function tests may display mild transaminitis, but it is important to bear in mind that there may be an absence of transaminitis [6]. In addition, one may observe hypalbuminaemia and hyperbilirubinemia. Serum ferritin will be markedly elevated, and alpha-fetoprotein raised.

As part of the work up, it is vital to exclude infective causes. Herpes-simplex virus (HSV) is the second most common cause of NALF, but one should also exclude enterovirus and cytomegalovirus [7]. Blood and CSF should be taken for culture. Other infective causes to be considered include TORCH, listeria, parvovirus and hepatitis B and C. Further tests should be run to exclude metabolic, endocrine, and autoimmune causes of ALF.

Biopsies may be taken of the lower lip mucosa – which may reveal stainable extrahepatic deposits of iron – and of the liver – which can show an inflamed, fibrotic liver with deposits of the aforementioned C5b9 attack complexes [1]. A less invasive modality of investigation is MRI, which can be used to assess hepatic iron overload and extrahepatic siderosis [9].

The mainstay of treatment in GALD is intravenous immunoglobulin. Of particular interest is the risk of haemolytic reaction with IVIG treatment. This was first described in the late 1980s and gained traction moving into the next decade [10-12], the incidence of haemolytic reaction increased with use of higher doses of IVIG, and risk factors for haemolytic reaction include patient blood group being A or AB and IVIG products containing higher titres of anti-A and anti-AB isoagglutinin [13]. A recent systematic review by Cuesta et al. reported an incidence of haemolysis secondary to IVIG administration to range from 0% to up to 19% in observational studies and up to 21% in clinical trials [14]. Multiple studies have reported favourable outcomes with IVIG administration during pregnancy for mothers who have either had previous children affected by NH [15] or were considered to be high risk NH pregnancies [16]. The use of double exchange transfusion reaction preceding administration of IVIG has also been reported to improve outcomes for infants affected by GALD [17-19].

The recurrence rate of GALD in subsequent pregnancies is high; greater than 90% [20]. This stresses the importance of early recognition that a pregnancy may be affected by GALD; prompt antenatal identification and management of high-risk pregnancies can lead to substantially better outcomes of pregnancy [21, 22].

CONCLUSION

GALD is a rare disorder with a high rate of recurrence. Early diagnosis is crucial as it is fatal. IVIG has shown a good outcome in our case report. This novel treatment, a multi-disciplinary approach involving a team of obstetrician specialised in Fetal medicine, paediatrics, hepatology and genetics has ensured a good neonatal outcome. We conclude that early diagnosis and prompt treatment in tertiary care is the key to ensure a healthy new born

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