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ABCC8-Related Hyperinsulinemic Hypoglycemia With Neonatal Cholestasis: A Case Report

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ABSTRACT

Background: Neonatal cholestasis and familial hyperinsulinemic hypoglycemia (FHH) are rare but life-threatening illnesses that occur in newborns. While FHH is typified by hyperinsulinemia, often initiated by mutations of the ABCC8 gene, cholestasis involves defective bile drainage and jaundice. It is extremely rare for both diseases to coexist simultaneously, making diagnosis and treatment extremely challenging.

Case Report: A 2-month-old infant presented with recurrent hypoglycemia, dark-colored urine, and prolonged jaundice. The laboratory tests revealed direct hyperbilirubinemia, increased liver enzymes, and low glucose levels. A heterozygous mutation in the ABCC8 gene was identified through genetic testing. Upon initiation of diazoxide treatment, it failed. Octreotide and cornstarch supplementation were then introduced, which successfully maintained blood glucose levels. Fat-soluble vitamins and ursodeoxycholic acid were also administered as supportive management for cholestasis. Abdominal imaging ruled out biliary obstruction, while a urinary tract infection was diagnosed and treated. Despite continued cholestasis during follow-up, the patient showed improvement due to multidisciplinary care.

Conclusion: This case presents a unique and intricate of a newborn with concurrent neonatal cholestasis and familial hyperinsulinemic hypoglycemia due to an ABCC8 gene mutation. It's a delicate balance that needs close testing, and you need to monitor and treat both low blood sugars and jaundice early to prevent significant long-term problems. The child was then effectively treated with octreotide and corn starch for blood sugar management and supportive therapy for cholestasis, which led to better outcomes in difficult cases.

Keywords: *hypoglycemia, congenital hyperinsulinism, ABCC8 mutation, neonatal cholestasis, and familial hyperinsulinism.*

1. INTRODUCTION

Neonatal cholestasis is a clinical syndrome that occurs in about 1 out of 2,500 live births. It is a result of bile production or excretion dysfunction and usually presents in the initial weeks of life. The major presenting symptoms are jaundice lasting for more than 14 days, acholic stools, dark urine, and hepatomegaly[1].

Many things can cause neonatal cholestasis (biliary atresia, neonatal hepatitis, many metabolic disorders, infections, and genetic syndromes)[2,3]. A common, rare, and serious cause is Familial Hyperinsulinemic Hypoglycemia (FHH), which may be life-threatening. FHH occurs when there are recurrent bouts of hypoglycemia due to an abnormally regulated pancreas; essentially, the pancreas is not modulating the correct amount of insulin that needs to be secreted. FHH is often caused by mutations in the ABCC8 or KCNJ11 gene that encode for the subunits of ATP-sensitive potassium (KATP) channels[4]. When KATP channels are not functional, insulin can be produced and released without consideration of blood glucose levels, which leads to a persistent state of hypoglycemia. FHH can result in seizures, neurologic issues, and delays in development if not treated appropriately. Concurrent presentation of neonatal cholestasis and FHH in a single patient is extremely unusual and represents a subtle diagnostic and therapeutic dilemma. Overlapping signs like feeding difficulties, failure to gain weight, and somnolence may blur the diagnosis of such conditions. An organized, multidisciplinary treatment approach by neonatologists, endocrinologists, gastroenterologists, and geneticists is needed [2,5].

A similar case was of a female neonate who had recurrent jaundice and hypoglycemia. Genetic analysis revealed a heterozygous ABCC8 mutation, and the diagnosis of familial hyperinsulinemic hypoglycemia as well as neonatal cholestasis was made. This case emphasizes the need to investigate rare metabolic and genetic disorders in neonates with unusual presentations. Genetic evaluation should be done early, and intervention initiated promptly for better clinical outcomes.

2. CASE REPORT

A 2-month-old female infant was admitted to the hospital for persistent jaundice for 15 days. Her mother gave a history of concerning symptoms as poor weight gain, black coloured urine, and yellowish discolouration of eyes. She was born at a normal gestational age via C-section and was 2.5 kg birth weight. The infant was well and was breastfeeding with no issues after birth. There were no other symptoms (eg, pale stools, fever, seizures, vomiting), and there was no family history associated with consanguinity. The assessment and evaluation revealed two significant concurrent conditions: neonatal cholestasis and persistent hypoglycemia. Surprisingly, the infant had low blood glucose levels recurrently, and when IVDE and bolus glucose failed to reverse this, they suspected congenital hyperinsulinism. And started with diazoxide while awaiting genetic testing to confirm their diagnosis. When diazoxide was not sufficient in maintaining stable glucose levels, octreotide was added to help control the hypoglycemia. The infant's cholestasis was intended to be managed via four progressive measures: ursodeoxycholic acid (Ursodiol) to promote bile flow, supplementation of fat-soluble vitamins (A, K, and E), and the initiation of dietary care as a supportive treatment, like corn starch**.**

LAB INVESTIGATION

Parameter	Value	Normal Range
Hb	9.4 g/dL	10–14 g/dL
PCV	32%	30–47%
WBC	14,330 /cumm	5,000–15,000/cumm
Platelets	4,195,000 /cumm	150,000–450,000 /cumm
Bilirubin (T)	18.44 mg/dL	>18 mg/dL
Bilirubin (D)	12.23 mg/dL	< 2 mg/dL
AST	1027 IU/L	< 80 IU/L
ALT	218 IU/L	< 60 IU/L
GGT	64 IU/L	12–122 IU/L

ALP	936 IU/L	150–420 IU/L
Albumin	3.4 g/dL	3.5–5.5 g/dL
Globulin	0.9 g/dL	2.3–3.5 g/dL
Total Protein	4.3 g/dL	6–8.3 g/dL
AFP	37510	<10ng/ml
CPK	56.0 IU/L	20–200 IU/L
CRP	7.8 mg/L	<5 mg/L
Urea	6 mg/dL	7–20 mg/dL
Creatinine	0.19 mg/dL	0.2–0.4 mg/dL
Sodium	137 mEq/L	135–145 mEq/L
Potassium	5.1 mEq/L	3.5–5.5 mEq/L
PT	14.5 → 11.9 sec	12–15 sec,
INR	1.22	0.9–1.3
APTT	42.3 → 32.8 sec	30–45 sec
IgG	422.0 mg/dL	700-1600mg/dL
Glucose	78 mg/dL	70–140 mg/dL
CBG	83 mg/dL	70–140 mg/dL

DIAGNOSTIC INVESTIGATION

Investigation	**Findings**
USG Abdomen	GB wall edema present, but **no features of biliary obstruction** or **choledochal cyst**
Liver Size	6 cm (Normal)
Spleen	4.7 cm (Normal)
Pancreas	Normal
Portal Vein (PV)	4 × 2 mm
Common Bile Duct (CBD)	4 × 2 mm
Gall Bladder	Distended, wall minimally thickened
Echo (Cardiac)	Normal
Skin Examination	Hypopigmented lesions on face, neck, limbs
Genetic Test (Whole Exome Sequencing)	**ABCC8 Gene Mutation (Heterozygous)** – responsible for familial hyperinsulinemic hypoglycemia of infancy (Type II)
Liver Cytosolic Antibody (LCA)	Negative (0.06)
Serology	Anti-HAV Negative, Anti-HEV Negative
Urine Routine	Nitrite +ve, Bilirubin ++, Casts ++++, Bacteria +ve
Blood Culture	No Growth

FOLLOW UP AND OUTCOMES

The newborn was readmitted with elevated jaundice and hypoglycemic episodes. Since there was no response to the diazoxide, this was stopped, and the patient continued to be treated with octreotide and corn starch therapy for glucose management. The glucose levels in the infant stabilized between 60-70 mg/dL, and hypoglycemia episodes were minimal. Liver function tests remained elevated, although this was in relation to ongoing cholestasis, and there was no imaging obstruction. A urinary tract infection was diagnosed and treated. The infant was discharged with octreotide, ursodeoxycholic acid, multi-vitamins, and corn starch therapy. Comprehensive care follow-up was implemented at regular intervals to monitor glucose levels, liver function, and growth.

3. DISCUSSION

Neonatal cholestasis is a serious condition of conjugated hyperbilirubinemia occurring in infants of less than three months of age. According to pediatric guidelines (NASPGHAN, ESPGHAN, and Indian Academy of Pediatrics), any newborn with jaundice persisting more than 14 days should be worked up for cholestasis. In this case, a female neonate brought to the attention at 15 days of life with progressive jaundice, yellowish discoloration of the sclera, and high colored urine has been appropriately investigated. Laboratory studies confirmed cholestasis with a direct bilirubin of 12.23 mg/dL and a total bilirubin of 18.44 mg/dL, which was greater than the diagnostic cutoff of >20% conjugated bilirubin. History in the infant was notable for familial hyperinsulinemic hypoglycemia that was diagnosed at birth after multiple episodes of hypoglycemia. Genetic analysis demonstrated a heterozygous ABCC8 mutation, an established etiology of congenital hyperinsulinism secondary to KATP channel dysfunction. According to pediatric endocrine standards, diazoxide is the initial treatment for hyperinsulinemic hypoglycemia; however, the patient did not respond to diazoxide and was treated with octreotide and corn starch supplementation, maintaining glucose levels at 60–70 mg/dL.

Additional assessment of cholestasis involved abdominal ultrasonography, which revealed no signs of biliary atresia or choledochal cyst, decreasing the chance of surgical cholestasis. The lack of pale stools and USG results decreased the likelihood of biliary atresia, but may warrant a HIDA scan in follow-up if cholestasis continues. The infant also had a urinary tract infection, supported by urine nitrite positivity, bacteriuria, and bilirubin in urine, that could have added to hepatic stress. The management was by guidelines such as initiation of ursodeoxycholic acid (UDCA), supplementation with fat-soluble vitamins (A, D, E, K), and antibiotic treatment of the infection. While TORCH screening and metabolic workup for galactosemia and tyrosinemia are included in standard recommendations, only incomplete infectious screening was done in this case, which can be supplemented in future follow-up. The association of familial hyperinsulinism, parenteral nutrition-associated cholestasis, and infection probably played a part in the liver dysfunction.

Rabbone et al. (2017)[6] provided a strong case study on the complexity of managing insulin-dependent conditions in newborns. Their study concluded that hypoinsulinemic, or dysregulated, insulin secretion syndromes, particularly with genetic mutations involving ABCC8, were cumbersome to manage therapeutically. The authors emphasize a need for tailored therapies, including diazoxide, octreotide, and nutritional changes to achieve euglycemia. Consider as an example, our case of octreotide and cornstarch supplementation after treatment with diazoxide failed.

The case highlights the necessity of early identification and in-depth evaluation in neonatal cholestasis, in addition to individualized management of hyperinsulinemic hypoglycemia, according to pediatric guideline-based protocols in an effort to maximize outcomes.

4. CONCLUSION

This report emphasizes the unusual combination of familial hyperinsulinemic hypoglycemia secondary to ABCC8 mutation with neonatal cholestasis, necessitating meticulous diagnostic work-up and multidisciplinary treatment. Prompt recognition of enduring hypoglycemia and jaundice, in addition to evidence-based therapy, is crucial to avoid long-term sequelae. The effective maintenance of blood glucose with octreotide and corn starch supplementation, coupled with supportive management for cholestasis, reaffirms the value of customized treatment in intricate neonatal presentations.

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