Case Report

Familial hypercholanemia Type 1 with associated glucose 6 phosphate dehydrogenase deficiency presenting with acute liver failure in the immediate newborn period

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ABSTRACT

Familial hypercholanemia, a very rare genetic disorder, is caused by defective bile acid transport. It can present with features of cholestasis, such as jaundice, pruritus, fat malabsorption, and fat-soluble vitamin deficiencies in early childhood. We report a case of familial hypercholanemia Type 1 presenting as acute liver failure in the immediate newborn period, from 0 h of life. This rare disorder was also incidentally found in association with G6PD deficiency, although there were no features of hemolysis in the infant. With this report, we hereby highlight the existence of this very rare genetic disorder in this part of India and that this disorder is an important differential diagnosis for acute liver failure in the immediate newborn period. Use of Ursodeoxycholic acid provided an excellent outcome in the baby till the follow-up period of 1 year.

Key words: Familial hypercholanemia, Neonatal acute liver failure, TJP2 mutation, Ursodeoxycholic acid

Familial hypercholanemia, also known as hereditary hypercholanemia, is a very rare genetic disorder that is inherited in an autosomal recessive manner [1]. The point prevalence of this disorder is estimated to be <1 per million worldwide [1]. It leads to impaired bile acid transport, which is characterized by elevated bile acid concentrations, itching, and fat malabsorption [2]. This leads to deficiencies of fat-soluble vitamins and overall poor growth of the child. Vitamin D deficiency results in rickets, and vitamin K deficiency presents as coagulopathy [3]. Defects in any one of the 7 genes have been implicated to cause familial hypercholanemia [4]. Older case reports and descriptions of this disorder have been made in children of old order Amish descent or Lancaster Amish [2,5], in whom two genotypes have been described: mutations in the *TJP2* and *BAAT* genes.

Hence, keeping in view the rarity of this disorder, we hereby describe a case of a newborn baby who presented with acute liver failure at birth, which was later diagnosed to be a case of familial hypercholanemia type 1 (FHC 1) with G6PD deficiency.

CASE REPORT

A 38-year-old multiparous lady, hailing from Yinkiong, Arunachal Pradesh, in a non-consanguineous marriage, at 38 weeks and 1 day of gestation, was diagnosed to have a fetus with moderate ascites and increased cerebral perfusion index (CPI) on routine the antenatal ultrasonography scan. The lady had no pre-pregnancy comorbidity or during the antenatal period. Membranes were intact. Due to increased CPI of the fetus, immediate termination of pregnancy was planned, and the baby was delivered by emergency lower segment cesarean section.

The baby was born limp and did not cry immediately after birth. Immediate resuscitation was performed according to the neonatal resuscitation program guidelines. The baby received positive pressure ventilation for 1 min; the Apgar scores were 6/10 and 8/10 at 1 min and 5 min, respectively. Baby required continuous positive airway pressure (CPAP) support. The birth weight was 3.9 kg. Detailed physical examination revealed no dysmorphic features. There was mild abdominal distension on physical examination, but no organomegaly.

Blood investigations revealed acute liver failure with a total bilirubin of 1.89 mg/dL, a serum glutamic-oxaloacetic transaminase level of 765 U/L, and a serum glutamic pyruvic transaminase level of 439.27 U/L. The total serum protein and albumin levels were normal. The trend of liver function test is depicted in Table 1. C-reactive protein level was very high (51.782 mg/dL). Erythrocyte sedimentation rate was normal. The coagulation

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Table 1: Trend of liver function test

Parameters	Day 1	Day 2	Day 5	Day 8	Day 15	1 month
Total bilirubin	1.89 mg/dL	11.26 mg/dL	8.11 mg/dL	4.21 mg/dL	3.80 mg/dL	1.48 mg/dL
Direct bilirubin	0.4 mg/dL	0.62 mg/dL	3.09 mg/dL	1.95 mg/dL	1.34 mg/dL	0.55 mg/dL
SGOT	765.1 U/L	562.66 U/L	69.57 U/L	67 U/L	38 U/L	56 U/L
SGPT	439.27 U/L	666.6 U/L	188.29 U/L	63 U/L	20 U/L	21 U/L
Alkaline phosphatase	191.78 U/L	266.77 U/L	245.71 U/L	211 U/L	162 U/L	270 U/L
Gamma-glutamyl transferase				>500 IU/L	>500 IU/L	456 U/L
Total protein	4.08 g/dL	5.15 g/dL	4.76 g/dL	4.4 g/dL	5.2 g/dL	5.9 g/dL
Albumin	3.07 g/dL	3.67 g/dL	3.21 g/dL	3.2 g/dL	3.2 g/dL	3.5 g/dL

SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase

profile was grossly deranged (Table 2). Complete blood count revealed thrombocytopenia (platelet count 1.01 lac/µL). Total leucocytes were 38,100/µL, which were predominantly lymphocytic. The kidney function test was normal. Workup for gestational alloimmune liver disease -hemochromatosis was normal. Whole exome sequencing was sent to Unigenome, Ahmedabad.

There was a history of a previous male sibling death at 9 months of age, 6 years ago, with clinical features suggestive of cholestasis. Review of his reports suggested a cholestatic liver disease for which a liver biopsy was performed, which was unremarkable. Workup for extrahepatic biliary atresia was negative. The workup for progressive familial intrahepatic cholestasis (PFIC) and tyrosinemia was non-confirmatory. A genetic study was not performed. The infant sibling died of liver failure. There are 3 surviving well siblings (Fig. 1).

Feeding was initiated at day 2 of life, which was tolerated well. The baby was weaned off CPAP support by day 3 of life. The baby remained euglycemic throughout. Ursodeoxycholic acid (UDCA) was started. The baby was discharged on day 11 of life on full breastfeeds and UDCA supplementation.

Whole exome sequencing revealed a heterozygous nonsense variant c.1252G>T; p.Glu418 in the *TJP2* gene on chromosomal position chr9:69227806:G>T, which was consistent with a diagnosis of FHC 1 (Table 3). Incidentally, a heterozygous missense variant was also detected in the glucose-6-phosphate dehydrogenase (*G6PD*) gene. A confirmatory G6PD level revealed a level of 1.31 U/g of hemoglobin, which was low and confirmed G6PD deficiency. No feature of hemolysis was found, though, during the hospital stay, as well as during the follow-up. Review of LFT and coagulogram at 1 month of life was normal. Review of clinical profile, including growth and development at 3 months, 6 months, 9 months, and 1 year of life, remained unremarkable. Liver function remained normal.

DISCUSSION

The *TJP2* gene was first discovered and described in 1994 by Duclos *et al*. [6]. It is located at chromosome 9q21.11 and has a total of 140,901 base pairs comprising 23 exons (NM_004817.3). The product of the *TJP2* gene is the tight junction protein 2, also called zona occludens 2 (ZO-2), which belongs to the membrane-associated guanylate cyclase family and is involved in the connection between epithelial cells and endothelial cells [7]. The TJP2 protein not only binds to the C-terminus of various transmembrane binding proteins but also interacts with multiple nuclear proteins, and participates in the regulation of gene expression and cell proliferation [8,9]. It is a ubiquitous tight junction scaffold protein present in the liver [7]. Tight junctions are intercellular barriers that control paracellular solute diffusion across cell layers and separate bile from plasma in the liver [10].

Table 2: Trend of coagulation profile

Parameters	Day 1	Day 3	Day 8	Day 15
Prothrombin time	42 s	55.9 s	15.5 s	13.8 s
International normalized ratio	3.81	5.2	1.27	1.12
Activated partial thromboplastin time	143.1 s	29.7 s	35.4 s	38.3 s

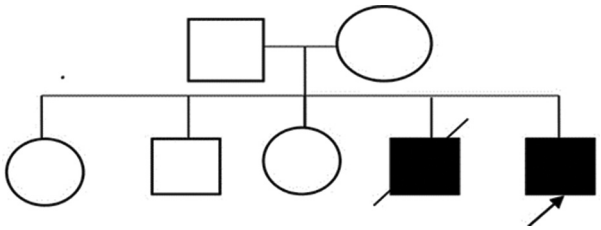

Figure 1: Pedigree of the family. The fifth-order child is our index case

There are seven genes associated with familial hypercholanemia, namely, *BAAT*, *EPHX1*, *SLC10A1*, *TJP2*, *WDR83 OS*, *WDR83*, and *LDLR* [4]. There are three types of familial hypercholanemia, types 1–3 [4]. FHC 1 is caused by a mutation in the *TJP2* gene, which encodes the tight junction protein ZO-2, which is located on the long arm of chromosome 9, or from homozygosity of the *BAAT* gene [2]. The *TJP2* gene is affiliated with positive regulation of blood-brain barrier permeability, regulation of membrane permeability, guanosine diphosphate metabolic process, protein localization to cell-cell junction, and guanosine monophosphate kinase activity [11]. Carlton *et al*. inferred that mutations in TJP2 and BAAT resulted in diffusion of most of the bile acids into the plasma from the hepatocytes, with very little bile acid entering the bile, which leads to high serum bile acid concentrations and low biliary

Table 3: Interpretation of next-generation sequencing of the patient showing a mutation in exon 8, with diagnosis of disease as familial hypercholanemia 1, involving TJP-2 protein

Gene (transcript)	Location	DNA/Protein change	Zygosity	Inheritance	Classification	Associated diseases/OMIM
TJP2(+) NM_004817.4	Exon 8	c.1252G>T p.Glu418	Heterozygous	Autosomal recessive	Likely pathogenic	Hypercholanemia familial 1 (#607748)

and intestinal concentrations [2]. This leads to features similar to cholestasis. It leads to severe chronic pruritis, fat malabsorption due to low intestinal bile acid levels, which manifests as failure to thrive, potentially life-threatening Vitamin-K dependent coagulopathy and rickets, and hearing loss [2,4]. Whole exome sequencing of our index case revealed a heterozygous nonsense variant c.1252G>T; p.Glu418 in the *TJP2* gene on chromosomal position chr9:69227806:G>T. This variant is noted to have a known total depth of ×127. It is located in exon 8 of the transcript NM_004817.4, and it leads to truncation at codon 418. FHC 2 is caused by a mutation in the *SLC10A1* gene on chromosome 14q24, and FH Type 3 is caused by a mutation in the *BAAT* gene on chromosome 9q31 [4].

Another genetic disease entity caused by TJP2 mutation is PFIC Type 4 (PFIC 4), which is caused by a homozygous or compound heterozygous mutation in the *TJP2* gene (phenotype MIM 615878) on chromosome 9q21.11 (MIM 607709), just like FHC 1, which is also due to a mutation in the *TJP2* gene (phenotype MIM 607748) on chromosome 9q21.11. PFIC 4 leads to rapidly progressive, early onset, severe liver disease [12] and predisposes to hepatocellular carcinoma in infancy and early childhood [13]. Children with PFIC 4 require a liver transplant in early childhood [12,13]. Meanwhile, FHC 1 leads to milder liver disease, probably because the inheritance in FHC is oligogenic. It requires concomitant mutation in a second locus, such as BAAT or a third locus postulated to be associated with FHC, according to Carlton *et al*. [2]. Our case was heterozygous for the TJP2 mutation, but a second causative gene was not identified besides the G6PD mutation.

Management of familial hypercholanemia 1 is by the use of UDCA, which can improve symptoms of cholestasis, prevent fat malabsorption, and improve fat-soluble vitamin absorption [2]. The baby in our report was born with clinical and laboratory features of acute liver failure, which improved drastically with ursodiol. Liver failure in the newborn period due to FHC1 has never been described before this.

Use of UDCA in our index case provided an excellent outcome within a week of its institution. These children need to be followed up regularly, and monitoring of diet, bone density, and coagulation profile should be done [2]. Due to the non-availability of sufficient data from older individuals, estimation of long-term prognosis remains unclear. However, it is assumed that the prognosis is probably excellent [4]. Some children become asymptomatic by the first decade of life, but certain children remain symptomatic. Our index case had normal growth and development, and did not develop any features of cholestasis till 1 year of follow-up. The clinical outcome up to the 1st year of life was excellent. All developmental milestones were achieved on time.

With our case report, we also postulate the possibility of the role of mutation in the *G6PD* gene in the modification of the penetrance of heterozygous *TJP2* gene, since the previous affected sibling was also a boy. This will be the first reported case if an association is hence proved by further analysis in an advanced research facility.

CONCLUSION

FHC 1 is a very rare genetic disorder transmitted in an autosomal recessive manner. A very high index of suspicion is to be kept for this disorder, especially when there is a previous history of a possibly affected sibling. It can present with liver failure in the intrauterine period and lead to fetal distress. In the immediate newborn period, supportive management while awaiting reports is crucial. Ursodiol is the drug of choice for this disorder, and the prognosis remains excellent if timely management of acute crises and use of UDCA is done. The possibility of the role of the *G6PD* gene in modifying the penetrance of the heterozygous *TJP*2 gene needs further probing.

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