Case Report

Bile acid synthesis defect (5B-reductase deficiency) a rare cause of cholestasis in an infant

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Abstract

Bile acid synthesis disorders (BASD) are rare inborn errors of metabolism and its presentation includes- neonatal cholestasis, neurologic disease or deficiency of fat-soluble-vitamins. [1]The trait features of these diseases are failure to produce normal bile acids, which leads to accumulation of unusual bile acids and bile acid intermediaries in liver and blood. Pathophysiological manifestations are due to deficiency of bile acids in gastrointestinal tract and accumulation of bile acid intermediates. Delay in initiating treatment can result in progressive chronic liver disease and liver failure. Bile acid therapy can lead to remarkable clinical response, if disorder is recognized earlier and liver transplant can be averted. Here we present an infant with cholestatic jaundice with chronic liver disease and subdural hematoma who was diagnosed to have 5 beta reductase deficiency.

Keywords: Bileacidsynthesis defect, 5B-reductasedeficiency, Cholestasis, Bile acids, Cholic acid and chenodeoxycholic acid

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Introduction

Bile acid synthesis disorders (BASD) is a rare cause of cholestatic jaundice in infants. It leads to rapidly progressive chronic liver disease and complications which can be prevented by early initiation of treatment with bile acids. In our case, infant presented with cholestatic jaundice with intracranial bleed [1]. Due to high degree of suspicion his genetic test was done which showed 5β-reductase deficiency.

Case report

This is a case of child born as term male without any impediment and required no hospitalization or treatment. At 6 weeks of life, he was admitted with complaints of yellowish discoloration of sclera since birth, refusal to feeding and increased sleepiness since last 6 and 3 days respectively.

There was no history of diarrhea, vomiting, clay colored stool or melena. On examination child was drowsy, had deep icterus, pallor, bulging anterior font anelle and had no ecchymotic patches over body. He had hepatomegaly of 5 cm with liver span of 9 cm and splenomegaly of 4 cm along the long axis. Clinical diagnosis of acute onset jaundice with encephalopathy was made. His laboratory examination showed elevated bilirubin (12.4 mg/dl (normal–1 mg/dl), with direct bilirubin of 7.5 mg/dl (normal-0.3 mg/dl), ALT- 1176 IU/L (normal- 5-15 IU/L),AST- 1312 IU/L (normal-5-40 IU/L), ALP- 882 IU/L (normal- 245-770 IU/L), GGTP was 50 IU/L, INR was normal, Hb- 9.4 gm/dl (normal-11-18 g/dl), TLC- 12000/cumm (normal-4000-11000/cumm), Plt- 2.2 lac/cumm (normal- 1.2-5.0 lac/cumm). Over next 1 month bilirubin peaked to 15.3 mg/dl (direct bilirubin- 7.9 mg/dl), ALP peaked to 2142 over next 2 months from admission, however his transaminase levels settled (ALT- 125 and AST- 185). His ALT and AST became near normal (37 and 47 IU/ml) but, his bilirubin (6.1 mg/dl/ direct 5.2 mg/dl) on follow-up. His test for viral hepatitis, TORCH screening was negative. Table 1 outlines summary of laboratory investigations. Abdominal ultrasound showed a normal

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gall bladder, with no choledochal cyst with hepatosplenomegaly. Slit-lamp examination showed no KF ring in eyes, chest radiograph and echocardiogram were normal. His computed tomography (CT) scan of brain was done in view of drowsiness and bulging anterior fontanelle, which revealed Fronto-parieto-temporal-occipital hematoma.

Hematoma was managed conservatively. Patient underwent liver biopsy (figure 1) which showed features of cholestatic liver disease with dense periportal fibrosis and early cirrhosis. His Hepatobiliary scintigraphy was normal.

After ruling-out infective, autoimmune and hematological causes for jaundice workup for metabolic and genetic causes were initiated.

Tandem mass spectrometry of urine, urinary amino acids and serum amino acids were normal. Due to high clinical suspicion his genetic study was done, which revealed, a homozygous single base pair deletion in exon 6 of the ***AKR1D1*** gene suggesting congenital defect in bile acid synthesis with delta (4)- 3 –oxosteroid 5-beta – reductase deficiency.

He was managed with UDCA (ursodeoxycholic acid) dose of 20mg/kg/day initially and later with cholic acid (20mg/kg/day), fat soluble vitamins supplement as follows- vitamin A (10000IU/day), vitamin D (2000IU/day), vitamin E/tocopherol (100IU/kg/day), vitamin K/phytonadione (5mg /day).

Patient responded to treatment and his hematoma resolved. His jaundice improved however he continued to have mild hyperbilirubinemia with mild cholestasis.

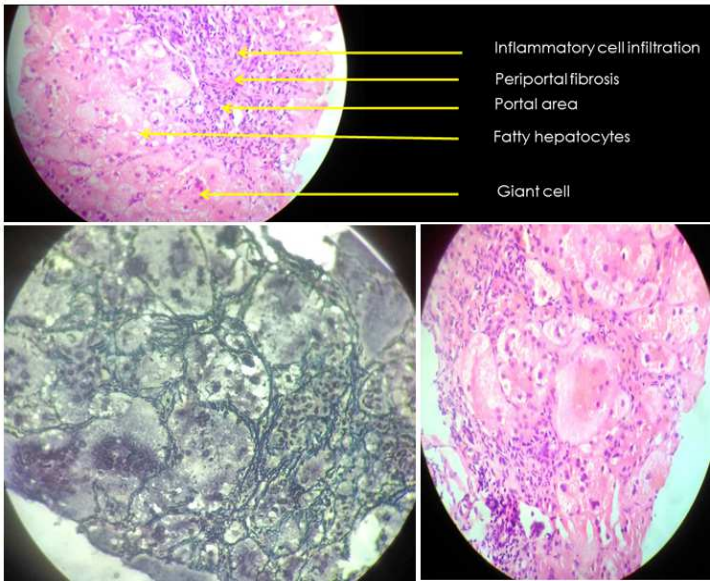

Figure: Histopathology of liver biopsy

Ultrasound guided percutaneous liver biopsy was performed at 5 months of age- Altered architecture of liver, ill-defined nodules, fibrous bands extending from portal areas to lobules.

Lobule s showing plenty of lymphocytes, few eosinophils, neutrophils and proliferating bile ductules. Hepatocytes shows micro-vesicular fatty changes, intrahepatic and canalicular cholestasis and interphase hepatitis-

Features of cholestatic liver disease with dense periportal fibrosis and early cirrhosis.

Laboratory tests were done to rule out various causes of jaundice. Most tests were done between 3 and 7 months of life. AST-Alanine aminotransferases, ALP-Alkaline phosphatase, GGTP- Gamma-glutamyl transpeptidase, INR-International normalized ratio, CMV- Cytomegalovirus, Ig- immunoglobulin, HCV- Hepatitis virus, HBsAg- Hepatitis B surface antigen, HEV- Hepatitis E virus, HAV- Hepatitis A virus, ANA- Antinuclear Antibody, ASMA- Anti Smooth Muscle Antibody, LKM-1- Liver Kidney Microsomal type 1 Antibody, pANCA- Peri-Neutrophilic Cytoplasmic Antibody.

Table-1: Summary of laboratory investigation.

Summary of investigations			
Investigations	**Results**		
	1st value	**Worst value**	**Follow-up investigations**
Hemoglobin g/dl	12	6.8	9.4
Total cell count /cumm	12000	34200	10600
Serum bilirubin (direct) mg/dl	12.4 (7.5)	15.3(7.7)	7.3(5.5)
AST	1312	-	87
ALT	1176	-	37
ALP	882	2142	335
GGTP	50	148	72
Albumin	3.8	-	4.4
INR	1.28	-	1
Anti-rubella IgG. IU/mL		Non-reactive	
Anti CMV IgM		Non-reactive	
Anti CMV IgG		Non-reactive	
Anti Toxoplasma antibody IgM		Non-reactive	
Anti Toxoplasma antibody IgG		Non-reactive	
HBsAg		Negative	
Anti HCV		Negative	
Anti HAV IgM		Negative	
Anti HEV IgM		Negative	
ANA		Negative	
ASMA		Negative	
Anti LKM-1 antibody		Negative	
pANCA		Negative	
Urinary gas chromatography		Normal	
Galactosemia screening		Normal	
Tendam mass spectrometry serum amino acids		Normal	
Genetic study		Homozygous single base pair deletion in exon 6 of the **AKR1D1**	

Discussion

Inborn errors of bile acid synthesis constitutes up to 1–2% of cases of neonatal cholestasis [1]. These patients develop conjugated hyperbilirubinemia within the first few months of life. Two complementary chemical pathways are present in hepatocytes for synthesis of these bile acids. The classic 'neutral' pathway is the main pathway for bile acid synthesis and it produces both cholic acid and chenodeoxycholic acid. Bile acids are physiologic FXR ligands and chenodeoxy cholic acid is the most potent activator of human FXR [2]. FXR activation by primary bile acids ultimately leads to decreasing the negative feedback signal [3] An alternative 'acidic' pathway is the second pathway described [4].

Total of nine defects of bile acid synthesis are known so far. These defects in enzymes are known to cause liver disease.Liver disease can be due to impaired hepatocyte production of primary bile acids leading to reduced canalicular bile acid secretion, thereby affecting bile acid dependent bile flow or accumulation atypical bile acid precursors in hepatocytes, which are hepatotoxic in causing cellular injury [5].

The clinical features, liver histopathology, diagnostic procedures and response to therapy for each of 9 bile acid synthesis defects have been characterized. Bile acid synthesis defects share three important clinical features. 1) Normal or low total serum bile acid concentrations 2) Serum level of γ-glutamyl trans-peptidase (GGTP) is normal or minimally elevated. 3) Pruritus is usually absent [12]. A high index of suspicion is required to diagnosis bile acid synthesis defect. Many bile acid synthesis defects are readily treatable and therefore have an excellent prognosis if recognized and treated early in life.

Our patient had deficiency of Δ4-3-oxosteroid-5β-reductase (5β-reductase deficiency), which is an auto somal recessive condition and causes defective bile acid steroid nucleus synthesis [6]. The enzyme 5β-reductase, is encoded by the gene *AKR1D1*.

Deficiency of this enzyme leads to impairment of reduction of the double bond between C4 and C5 of the steroid nucleus. Because of this impairment, low levels of normal primary bile acids are present in the urine and serum of affected patients. The intermediate products of bile acid synthesis gets accumulated in body, which can be detectable by fast atom bombardment -mass spectrometry (FAB-MS) [1].

The 5β-reductase deficiency was first described by Setchell *et al.* in 1988 [7]. There is paucity of data from India about this condition. The typical presentation of this disorder is neonatal cholestasis, which is characterized by increased concentrations of amino-transferases, normal GGTP concentration, conjugated hyperbilirubinemia, and coagulopathy that worsens with disease progression [1,8]. Mortality rate can be as high as 50% in infants for whom diagnosis is delayed [1].

It can also present with neonatal liver failure resembling neonatal hemochromatosis [9].

Molecular analysis of *AKR1D1* to determine the presence of mutations can be helpful in firmly establishing the diagnosis of primary 5β-reductase deficiency [10].

The histopathology of 5β-reductase deficiency is typical of that of neonatal hepatitis, giant cell can be seen, pseudo-acinar transformation, hepatocellular and canalicular cholestasis, and extramedullary hemato-poiesis. Therapy for 5β-reductase deficiency is by replacement of primary bile acids to stimulate bile flow and limit the production of toxic bile acid precursors through feed-back inhibition [11].

Treatment with cholic acid (10–20 mg/kg daily) can be titrated to ensure that urinary excretion of Δ4-3-oxo bile acids stops [1]. Ursodeoxycholic acid has also been used as therapy because of its choleretic and hepato-protective properties. Ursodeoxycholic acid stimulates the bile flow but it does not inhibit the first step in bile acid synthesis. Therefore it is ineffective as sole therapy for this condition [1]. Overall treatment response is good if the diagnosis of Δ4-3-oxosteroid-5β-reductase deficiency is made early in the course of the disease. In our case child presented with jaundice with altered sensorium and refusal to feeding.

His workup showed cholestatic jaundice with elevated amino-transaminases which settled on follow-up. His CT scan of brain large spontaneous subdural hematoma, this can be due to coagulopathy secondary to liver disease. His urinary gas chromatography and FAB- MS does not showed any bile acid precursors, this may be explained as patient was started on treatment with ursodeoxycholic acid.

Conclusions

Defects in bile acid synthesis are important group of hepatic disorders. These conditions resemble many other causes of neonatal cholestasis and chronic liver disease clinically. High index of clinical suspicion is required when making a diagnosis. Early diagnosis is important because most of these disorders can be treated effectively with bile acid replacement therapy. The current gold standard for definitive diagnosis are FAB-MS and gas chromatography- mass spectrometry (GC-MS) analyses of serum and urine [12]. Genetic testing may help in cases where suspicion of bile acid synthesis disorder is high and above tests are negative.

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