Case Report

Neonatal cholestasis – A case report on congenital bile acid synthetic defect type 4 and severe anemia

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ABSTRACT

Congenital defects of bile acid synthesis are rare disorders that cause progressive liver dysfunction. We present a case of alpha methyl acyl-CoA racemase (AMACR) deficiency with non-spherocytic hemolytic anemia who presented with rapidly progressive severe cholestasis and liver failure with normal gamma-glutamyl transferase levels. After extensive investigation, he was found to have AMACR deficiency with HBB gene mutation associated with non-spherocytic hemolytic anemia possibly explaining the severity of the disease. To the best of our knowledge, a similar association has not been reported so far.

Key words: Alpha-methyl acyl-CoA racemase, Anemia, Bile acid synthetic disorder

Bile acid synthesis disorders (BASDs) are a group of rare metabolic disorders characterized by defects in the creation (synthesis) of bile acids [1]. Bile acids are chemical compounds found in the liver that has several roles in the body including promoting the flow, excretion of bile, and assisting in the intestinal absorption of fat and fat-soluble vitamins. Primary BASDs involve congenital deficiencies in enzymes required for bringing about chemical reactions (catalyzing) necessary to synthesize the two main bile acids known as cholic acid and chenodeoxycholic acid. Various enzyme deficiencies in this pathway lead to the disruption in bile acid synthesis [2]. When bile acid synthesis is affected, the accumulation of hepatotoxic atypical bile acids and interruption of normal bile flow leads to liver injury and cholestasis [3]. Alpha-methyl acyl-CoA racemase (AMACR) deficiency or bile acid synthesis defect type 4 has mostly been reported in adults with mild cholestasis and neurological disease. In infants, it usually presents with fat-soluble vitamin deficiencies and mild cholestasis, not many cases of severe cholestasis have been reported.

CASE REPORT

A 4½-month-old male infant born out of non-consanguineous marriage was brought to the outpatient clinic with concerns of jaundice since 1 month of age which was worsening over the past 4–5 days. It was associated with high-colored urine pigmented stool and poor feeding. There was no history of fever, hematemesis, melena, irritability, or seizures. He had a healthy sibling aged 6 years.

On examination, he was deeply icteric with hepatosplenomegaly and a soft systolic flow murmur. He was admitted for further evaluation and management of acute liver failure. He was FT and NVD with a birth weight of 2.8 kg and had a normal Apgar score at birth.

His initial blood investigations showed anemia with high bilirubin levels with coagulopathy. Before he received a blood transfusion, an extensive blood workup was done to look out for the causes of neonatal cholestasis and anemia including tandem mass spectrometry (TMS), gas chromatography–mass spectrometry (GCMS), hemoglobin electrophoresis, and clinical exome. The laboratory results are presented in Table 1.

An ultrasound scan showed hepatosplenomegaly with mild-to-moderate ascites, intra-hepatic biliary radicals were normal, and a contracted gall bladder with a normal common bile duct. Liver biopsy could not be done in view of deranged coagulation profile as well as ascites. His blood sugars were stable throughout.

Serum total bile acids were high, TMS, GCMS, Serologies, and polymerase chain reaction for toxoplasmosis, rubella cytomegalovirus, herpes simplex, and (TORCH) HIV, viral markers B and C were negative, and A1AT levels were normal. Initial Hb was 5.4 g/dl, white cell count was 36,580/cu.mm, and platelet was 510,000/cu.mm. The initial C-reactive protein was 9.96 mg/l which later became negative after starting antibiotics. A peripheral blood smear was microcytic hypochromic with

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Table 1: Blood Investigations of the patient

	Initial presentation	After 1 week	After 2 weeks
Hemoglobin	5.4	8.2	6.7
White cell count	36580	13450	19750
Platelets	510,000	236,000	294,000
Total bilirubin (mg/dl)	33.3	44.5	46.3
Direct bilirubin, (mg/dl)	23.3	29.7	30.9
Serum albumin (g/dl)	2.2	2.9	2.9
Total protein (g/dl)	4.5	5.4	5.1
Alkaline phosphatase (U/L)	226	279	264
Alanine transaminase (U/L)	307	223	253
Aspartate aminotransferase, (U/L)	769	813	705
Gamma-glutamyl transferase (U/L)	71	70	75
Prothrombin time (s/control)	26.5/11.7	29.8/11.7	23.6/11.7
International normalized ratio	2.28	2.56	2.02

no abnormal cell, his blood group was B positive, retic count was 4.5% with a mildly positive direct Coombs test and mildly increased Osmotic fragility. The Hb electrophoresis was normal. Cardiac Echo was normal. There was no evidence of butterfly vertebrae, eye, and hearing examination which was normal.

Based on the clinical evaluation and normal TMS and GCMS screening, the child was started on the supportive treatment of cholestasis and liver failure with broad-spectrum antibiotics, antifungals, fat-soluble vitamin supplements, and appropriate nutrition. A liver biopsy could not be done in view of the continually deranged coagulation profile despite giving Fresh frozen plasma, Vitamin K, and the presence of ascites.

One of the main clinical features in this patient was very high total bilirubin levels at presentation 33.3 mg/dl which rose up to 46.3 mg/dl in 2 weeks with normal gamma-glutamyl transferase of 71 U/l (with high unconjugated bilirubin level as well) probably related to ongoing hemolysis and also worsening coagulopathy. The child abruptly died of sepsis as further workup and management plan were being discussed.

His exome sequencing report showed the presence of two genetic variants with heterozygous mutation in Hemoglobin Subunit Beta (HBB) and AMACR gene located on chromosome 11 and chromosome 5, respectively, with associated non-spherocytic hemolytic anemia suggesting that the only causative etiology of the severe form is due to associated hemolytic anemia.

DISCUSSION

We present a rare case with an unusual association of neonatal cholestasis caused by a deficiency in peroxisomal 2-methyl acyl-CoA racemase with non-spherocytic hemolytic anemia due to mutation in the HBB gene. To the best of our knowledge, this association has not been reported previously.

BASDs are a group of rare metabolic disorders characterized by defects in the creation (synthesis) of bile acids. The main symptom of most (but not all) BASDs is interruption or suppression of the flow of bile from the liver (cholestasis) and fat-soluble vitamin malabsorption. Additional symptoms such as progressive neurological disease may develop in certain cases and can occur in the absence of liver disease. In many cases, symptoms or signs are present at birth or during the newborn period. If untreated, the more severe forms of these disorders can eventually progress to cause life-threatening complications such as scarring of the liver (cirrhosis) and liver failure. BASDs are caused by mutations in specific genes; most of these mutations are inherited in an autosomal recessive pattern.

AMACR deficiency is an autosomal recessive defect that inhibits cholesterol side-chain oxidation. AMACR is necessary for the racemization of trihydroxycholestanoic acid and pristanic acid into their stereoisomers. Conversion to these stereoisomers is necessary for the subsequent step of peroxisomal β-oxidation of the C27 bile acid side chain [4,5]. Deficiency of AMACR leads to an accumulation of plasma pristanic acid and the bile acid intermediates dihydroxycholestanoic acid and trihydroxycholestanoic acid; therefore, AMACR deficiency affects both the bile acid and fatty acid synthesis pathways [4,5].

The disorder was first reported in three adults presenting with sensory-motor neuropathy. Only five patients with this disorder have been described in the literature [6]. Three of these patients were reported by Ferdinandusse *et al.,* in 2000 [6,7]. Two patients were asymptomatic as children and presented with adult-onset peripheral neuropathy; one of these patients also had retinitis pigmentosa. A third patient had symptoms at 18 months of age that were consistent with niemann-pick disease type C. All three patients had a complete absence of AMACR enzyme activity in cultured fibroblasts. Subsequently, two mutations in the AMACR gene were identified that were present in all three patients.

Two additional patients with AMACR deficiency were later identified and described by Setchell and coworkers. Both infants presented with mild cholestasis, coagulopathy, and fat-soluble-vitamin deficiency [8-11].

CONCLUSION

We conclude that in our patient, the cholestasis was of multifactorial origin, we hypothesized that the HBB gene mutation

may have further led to hepatocellular dysfunction and increased susceptibility of the hepatocytes to insults and progressive liver injury, and hence severe outcome.

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