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Case Report

Rare Genetic disorder presenting as Late onset Vitamin K Deficiency Bleeding in an Infant

Authors:
Dr. Jenish Rajma MD, Dr. Arun AC MD DM
[1]*Assistant professor, Department of Pediatrics, All India institute of Medical sciences Madurai, Tamilnadu*
[2]*Consultant Medical Gastroenterologist, Lily mission hospital , Madurai*
Corresponding Author:
Dr. Jenish Rajma

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ABSTRACT:
Vitamin K deficiency bleeding is a widespread concern affecting newborns globally. Family hypercholanemia is a rare cause of fat-soluble vitamin deficiency. We report an infant who reported multiple episodes of intracranial and gastrointestinal bleeding from the fourth month of life, which was later confirmed to have a bile acid coenzyme A: amino acid N-acyltransferase gene mutation by clinical exome sequence genetic study. Though this baby had subtle signs of itching, the possibility of liver disease was not considered initially, as liver function tests and ultrasound of the abdomen were normal. This case report stresses the importance of evaluating the cause of secondary vitamin K deficiency in all infants with bleeding manifestations despite receiving vitamin K universal prophylaxis at birth.

Keywords: Vitamin K deficiency bleed, Familial hypercholanemia, Liver disease, Hemorrhagic disease of newborn, Bile acids

INTRODUCTION:

Infants frequently encounter vitamin K (VK) deficiency during their first six months. This may be due to the low hepatic stores at birth or the low VK content in human breast milk. Some other conditions, like maternal drug intake or genetic disorders in intestinal absorption of fat-soluble vitamins, can also lead to vitamin K deficiency bleeding (VKDB) (1,2). VK deficiency in liver diseases manifests earlier than other fat-soluble vitamins, given its typically higher turnover rate [3]. We report a rare case of familial hypercholanemia (FH) who presented in infancy with VK deficiency bleeding and vitamin D deficiency rickets but without any other liver-related problems.

One-year-old male infant, first born to third-degree consanguineous parents, presented with complaints of failure to thrive and passing black tarry stools for one week. There was no history of fever, blood vomiting, high-colored urine, or clay-colored stools preceding the illness. He had a history of seizures at four months of age. He was admitted to an outside hospital and was diagnosed with subdural hematoma, requiring a craniotomy. The possibility of late-onset hemorrhagic disease of newborns (HDN) was considered then, and the baby was treated accordingly and discharged after a hospital stay of one month. At eight months of age, he had recurrent episodes of seizures, and a metabolic workup revealed hypocalcemia with low vitamin D levels (Table 1). The child was treated with calcium and vitamin D, along with anti-epileptics. He showed poor weight gain for five months and frequent passage of semi-formed stools. At ten months of age, he had one episode of hematemesis and melena, requiring hospitalization and supportive care for a week. As the child recovered quickly with symptomatic management, he was not fully evaluated. This was the second episode of hematemesis at one year of life. On examination, the child was alert and active but wasted and stunted. He also had pallor, frontal bossing, wide anterior fontanelle, and wrist widening. An abdominal examination showed the presence of scratch marks on the abdomen and limbs. The liver was palpable 3 cm below the right costal margin, without any splenomegaly or free fluid in the abdomen. Because of recurrent episodes of upper gastrointestinal bleeding and a history of intracranial bleeding along with rickets, the possibility of fat-soluble vitamin malabsorption was considered. Conditions causing cholestatic liver disease and pancreatic insufficiency like cystic fibrosis were ruled out. The serum lipid profile was within normal limits. Routine blood investigations done at one year age at the first presentation to us, showed dimorphic anemia, hypocalcemia with high Alkaline phosphatase and low Vitamin D levels. His previous blood reports, done at four months of age, also showed abnormally high alkaline phosphatase (3540 IU/L) with normal GGT.

Blood test	Patients value	Reference range
Hemoglobin	10.3 g/dl	12-15 g/dl
Total leucocyte count	8100 cells/mm^3	4000-11000 cells/mm^3
Serum sodium	135 mEq/L	135-145 mEq/L
Serum chloride	104 mEq/L	96-106 mEq/L
Serum calcium	6.5 mg/dL(low)	9-11 mg/dL
Serum magnesium	1.8 mg/dL	1.7-2.2 mg/dl
Serum parathyroid hormone	409 pg/mL (elevated)	10-55 pg/ml
Serum vitamin D3	5 ng/mL(Low)	20-50 ng/ml
Total protein	6.2 g/dl	6-8 g/dl
Serum albumin	3.7 g/dl	3.5-5 g/dl
Serum bilirubin	0.6 mg/dL	<1 mg/dl
Aspartate aminotransferase (AST	31 IU/L	<40 IU/L
Alanine aminotransferase (ALT	17 IU/L	<40 IU/L
Gamma-glutamyl transferase (GGT)	17 U/L	5-40 U/L
Alkaline phosphatase (ALP)	2835 IU/L(elevated)	80-400

Table 1: Blood investigations

Ultrasound of the abdomen was normal without any features of cholestasis. Upper gastrointestinal endoscopy was normal. The possibility of bile acid synthetic defects(BASD) was considered, but a serum bile acid level was done, and it was elevated (>50 mEq/L). Clinical exome sequencing revealed a homozygous mutation of the bile acid coenzyme A: amino acid N-acyltransferase (BAAT) gene, confirming the diagnosis of FH, a type of bile acid conjugation defect. He was treated with a high dose of vitamin D at eight months of age, and an x-ray of his wrist showed a white line of calcification. The child is continued on a double dose of fat-soluble vitamins A, vitamin D, vitamin E, weekly injectable VK, and ursodeoxycholic acid. He was started on calorie-dense complementary feeds along with multivitamins and iron supplements. After a follow-up of three years, the child is developmentally normal, gaining weight, and liver function tests were normally done every three to six months during follow-up. A fibro scan was done every six months, which was normal. Serum bile acid levels were between 30 mEq/L and 50 mEq/L.

DISCUSSION:

VKDB is a common problem in childhood, with an incidence of one in 15,000 births [4]. Late VKDB is associated with significant morbidity like developmental delay, epilepsy, or severe conditions such as hydrocephalus or cerebral palsy [5]. Sudden severe intracranial bleeding may also lead to death in such infants. Identifying and treating bleeding early is crucial to mitigating these severe outcomes. One of the rare causes of late VKDB is Familial Hypercholanemia.

FH is a rare autosomal recessive disorder characterized by elevated concentrations of bile acids, typically conjugated, in the blood. This condition leads to itching, fat malabsorption, poor overall growth, and deficiencies in fat-soluble vitamins [6]. There are two types of hypercholanemia described in the literature to date. Familial hypercholanemia type 1 (FHCA-1) is usually caused by a homozygous mutation in the tight junction protein 2 (TJP2) gene on chromosome 9q21 [6,7]. Familial hypercholanemia type 2 (FHCA-2) is caused by a mutation in the solute carrier family 10 member 1 (SLC10A1) gene on chromosome 14q24 [6]. In our patient, neither of these genes were mutated. Rather, we identified the mutated BAAT gene. The BAAT gene is responsible for encoding the enzyme bile acid coenzyme A: amino acid N-acyltransferase, which catalyzes the transfer of C24 bile acids from acyl coenzyme A thioester to either glycine or taurine [8]. This enzymatic step represents the second stage in creating bile acid-amino acid conjugates. These conjugates act as detergents in the small intestine, vital for improving the absorption of lipids and fat-soluble vitamins. BAAT is considered to be a rare gene causing FH [9].In these patients, serum bile acid levels are usually very high, but these patients usually have normal serum bilirubin levels. ALP is also in the normal range in most reported cases. However, in a few cases, it might be raised. If ALP is high, thorough investigations must be done to rule out other common cholestatic diseases or other vitamin deficiencies. In our patient, LFT was normal except for ALP, which was high. We suspect the high ALP was due to a severe vitamin D deficiency causing rickets. These may have raised PIVKA levels in patients with FH, indicating a VK deficiency. In our patient, PIVKA was elevated, and vitamin D levels were low.

Imaging like ultrasonography of the abdomen is usually done to rule out abnormal liver echotexture, biliary radicle dilatation, and any other abnormality suggestive of cholestatic liver disorder. In patients with FH, the liver is normal, and no anatomic abnormality will be noted, similar to the present case. Diagnosis of FH relies on genetic testing and identification of the

genes responsible for the disease. At the same time, genetic testing will rule out other causes of cholestasis and fat malabsorption. Next-generation sequencing (NGS) technology is a new technique for identifying the underlying genetic mutations in rare diseases [13,14].There was the presence of a BAAT mutation in our patient, which was causing hypercholanemia along with features of fat malabsorption and itching.

FH is a genetic disorder and cannot be completely treated [6,7]. Patients with FH can be given ursodeoxycholic acid (UDCA). However, its role in FH is still unclear. Patients with FH should be followed regularly as the effects of increased bile acids on the liver are unknown. Our patient was treated with supplementation of fat-soluble vitamins and UDCA and is under follow-up with regular outpatient visits every six months. Currently he is 4 years old, growing well with normal development

CONCLUSION:

Familial hypercholanemia is a rare cause of fat-soluble vitamin deficiency with raised serum bile acids due to conjugation defects. Though many mutations are reported in the different steps of bile acid synthesis, the BAAT gene mutation is rarely reported worldwide. It usually presents with coagulopathy but without other liver manifestations. Early clinical suspicion and proper diagnosis help us to give life-long treatment with fat-soluble vitamins to avoid complications in the future. We must follow up on the child for decades to identify the long-term hepatic and extra-hepatic consequences of raised serum bile acids in the blood.

Figure 1: Child at 3 years of age with normal growth and development, showing mild features of wrist widening and pot belly

Gene and transcript	Variation	Location	Zygosity	Disorder(OMIM)	Inheritance
BAAT NM_001701.3	c.1036delA (p.Arg346Aspfs*18)	Exon 4	Homozygous	Hypercholanemia, Familial	Autosomal recessive

Table 2: Clinical Exome sequencing showing BAAT mutation

Source of support- nil

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