An Unusual Presentation of Hemorrhagic Disease in an Infant: A Probable Case of Abetalipoproteinemia

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Summary: We report a probable case of abetalipoproteinemia in an infant who presented with unusual symptoms of late-onset vitamin K deficiency. Abetalipoproteinemia is a rare autosomal recessive disease caused by mutation of the microsomal triglyceride transfer protein gene, resulting in the absence of microsomal triglyceride transfer protein function in the small bowel. It is characterized by the absence of plasma apolipoprotein B-containing lipoproteins, fat malabsorption, hypcholesterolemia, retinai pigmentosa, progressive neuropathy, myopathy, and acanthocytosis. A biopsy of the small intestine characteristically shows marked lipid accumulation in the villi of enterocytes. Large supplements of fat-soluble vitamins A, D, E, and K have been shown to limit neurologic and ocular manifestations. Dietary fat intake is limited to medium-chain triglycerides.

Key Words: abetalipoproteinemia, Bassen-Kornzweig syndrome, late-onset vitamin K deficiency bleeding

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CASE PRESENTATION

We report a case of a female baby from South India, who presented at 1 month of age with multiple soft swellings over the entire body with discoloration of the skin over the swellings for the past 15 days. She was born at term (birth weight = 2.8 kg) to consanguineously married parents. The mother’s antenatal period was uneventful. The baby’s neonatal period was unremarkable except for a history of minimal but prolonged bleeding from the umbilical cord. The baby was delivered at a peripheral hospital and received parenteral vitamin K at birth. Physical examination revealed that the baby had failure to thrive (weight: 2.92 kg, length: 48 cm, Z score = –4.4; length: 48 cm, Z score = –4.6) and had multiple subcutaneous nodular swellings over the entire body. Clinical differential diagnoses included blue berry muffin rash, leukemia cutis, and subcutaneous hematomas. Laboratory investigations revealed hemoglobin was 9.4 g%, total leukocyte count of 12,400/mm3, normal differential count, and a platelet count of 613,000/mm3. There was prolonged prothrombin time (PT > 2 min, normal: 10 to 12.5 s) and activated partial thromboplastin time (APTT > 3 min, normal: 25 to 34.8 s). Fibrinogen was 290 mg/dL (normal: 150 to 450 g/dL). Liver function test, erythrocyte sedimentation rate, and TORCH screen were normal. Nodular skin lesions were considered to be subcutaneous bleeds. An initial diagnosis of late-onset vitamin K-dependent bleeding (VKBD) was made. She received fresh frozen plasma transfusion and parenteral vitamin K1 after which her PT and APTT normalized. She was planned for further workup for VKBD including a complete coagulation workup after 6 weeks, but the patient did not return for timely follow-up.

At 4.5 months of age, the infant presented with recurrence of similar symptoms and pallor. She had failure to thrive (weight: 3.9 kg, Z score = –4.8; length: 56 cm, Z score = –2.9). Hemoglobin was 6.6 g%, PT and APTT were prolonged as before (PT > 2 min and APTT > 3 min), complete coagulation profile revealed low levels of vitamin K-dependent factors, and liver function test was normal. The child was stabilized with fresh frozen plasma and packed cells. Incidentally, a resident on duty noticed the baby to have bulky stools, but this was not considered abnormal by the mother and hence was not reported earlier. Fat malabsorption was considered, and stool for fat globules was positive. Her lipid profile revealed a low total cholesterol of 65 mg/dL (normal: 150 to 200 mg%), triglycerides of 15 mg/dL (normal: 50 to 150 mg%), high-density lipoprotein of 41 mg/dL (normal: 35 to 60 mg%), and low-density lipoprotein (LDL) was 7 mg/dL (normal: 80 to 150 mg%).

Blood picture was reviewed, and it showed acanthocytes. A diagnosis of abetalipoproteinemia (ABL) was being considered, and intestinal biopsy was performed. An intestinal biopsy showed duodenal mucosa with preserved crypt villous ratio, focal branching and broadening of villi, and diffuse and extensive vacuolization of enterocytes over the villi suggestive of ABL (Fig. 1). Electron microscopy also showed villous epithelium with multiple small and large non-membrane-bound vacuoles containing fat in the cytoplasm of the enterocyte (Fig. 2). Serum levels of apolipoprotein (apo) was not carried out, as the test was not available in-house. The drop in hemoglobin could have been because of the bleeds, or leukemia secondary to vitamin E deficiency, as the test was not available in-house. The child’s hemoglobin was stable after that. Serum levels of fat-soluble vitamins was also not performed. Eye and neuromuscular examination was normal. She was started on megadose vitamins (vitamin E 50 mg once daily, vitamin A 20,000 U thrice a week, vitamin D granules 10,000 on alternate days, vitamin K1 [5 mg thrice a week] and medium-chained triglycerides’ diet [1 g/kg/d in 3 divided doses]), as recommended in fat malabsorption states. She had been under regular follow-up for 4 months and had gained weight and attained normal milestones.

Given the clinical picture, ABL, homozymous familial hypocholesterolemia with dominant transmission (mutations in the APOB gene), and chylomicron retention disease with recessive transmission (mutation in the SARIB gene) can be considered as possible differential diagnoses. The parents were asymptomatic, and hence familial hypobetalipoproteinemia was unlikely. A low triglyceride level made chylomicron retention disease also unlikely. ABL was the most probable diagnosis. Molecular genetic testing to detect mutations in the microsomal triglyceride transfer protein (MTTP) and APOB genes was advised, but the parents were unwilling.

DISCUSSION

ABL is a rare autosomal recessive disorder of lipoprotein metabolism with an incidence of <1 in 1 million persons.1 It is caused by a mutation in the MTTP gene located in chromosome 4, resulting in the absence of apoB.2,3 ApoB is useful in the synthesis and exportation of chylomicrons and very low-density lipoproteins. ABO and CMR occur with a frequency of 1 in 20,000 persons but are not associated with bleeding diathesis.

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lipoprotein (VLDL), and it is necessary for the absorption of dietary fats, cholesterol, and fat-soluble vitamins. This disorder is grouped under ‘familial hypocholesterolaemia’, which includes abetalipoproteinaemia, hypobetalipoproteinaemia, and chylomicron retention disease.

ABL usually presents in infancy and is characterized by fat malabsorption syndrome, retinitis pigmentosa, and progressive ataxic neuropathy. Infants with ABL present with failure to thrive, developmental delay, distended abdomen, intestinal symptoms, and absent deep tendon reflexes. Ataxia usually develops after 10 years of age. Hence, this disorder is also grouped under causes of autosomal recessive cerebellar ataxia. Neurologic symptoms occur in the form of peripheral neuropathy and is due to deficiency of liposoluble vitamin E. Although the above-mentioned features are more commonly seen, patients with ABL can present with any symptom of fat-soluble vitamin deficiency, and, in our case, bleeding due to vitamin K-dependent factors.

The diagnosis of ABL can be made by measuring fasting lipid profile, which will show low total cholesterol (< 70 mg%) and low levels of LDL (< 0.10 g/L), triglycerides (< 0.20 g/L), and apoB (< 0.10 g/L). There may even be absent LDL and VLDL. Red cells show a peculiar "thorny" deformation called acanthocytes. Other examinations should include a neurologic examination to look for features of demyelination, hepatic ultrasound to look for fatty liver, and an eye examination to look for retinitis pigmentosa and vitamin A deficiency. Identification of mutations of the MTTP gene or the APOB gene confirms the diagnosis.

Treatment includes high doses of fat-soluble vitamins and limiting dietary fat intake to medium-chain triglycerides. Using high doses of vitamins E and A, especially from age younger than 18 months, has been shown to reduce the incidence of ataxia and retinitis pigmentosa. This shows the importance of early diagnosis and treatment to prevent permanent devastating symptoms. Frequent neurologic and eye examination is necessary as a part of follow-up.

Coagulopathy due to vitamin K deficiency has been observed in patients with ABL. Few cases of severe upper gastrointestinal bleeding have been reported. This is the second reported case of an infant with ABL who presented with features of severe hemorrhagic disease of the newborn or VKDB. Hence, infants who present with late-onset VKDB should be evaluated for fat malabsorption. Simple tests such as peripheral blood smear for acanthocytes and stool for fat globules could give valuable clues for diagnosis.

REFERENCES