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Case Report
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Chylomicron Retention Disease: An Infant Presenting with Vomiting and Failure to Thrive without Diarrhea

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Abstract

Chylomicron Retention Disease (Anderson's disease) is a rare autosomal recessive disorder caused by mutation of the SAR1B gene that leads to hypercholesterolemia and accumulation of lipoproteins in the enterocytes. This can lead to deficiencies of fat soluble vitamins with serious clinical sequelae. Patients most commonly present in infancy with nonspecific symptoms such as vomiting, diarrhea and failure to thrive. Diarrhea is reported to be universally present in all cases. We report a case of an infant who presented with vomiting and growth failure and no diarrhea. Upper gastrointestinal endoscopy showed whitish appearing duodenal mucosa and small intestinal biopsies revealed steatosis of enterocytes. Genetic testing confirmed chylomicron retention disease. The child was treated with nutritional supplements and fat-soluble vitamins with good clinical results. High index of suspicion for a disorder of hypercholesterolemia and a timely diagnosis and treatment is essential to avoid serious clinical sequelae, especially neurological impairment.

Introduction

Chylomicron Retention Disease (CRD) or Anderson's disease is one of the disorders in the group of familial Hypercholesterolemia's. It is an autosomal recessive disorder caused by mutation of the SAR1B gene and is extremely rare, with fewer than 60 cases reported. Familial hypercholesterolemia's can lead to intestinal fat malabsorption. Within the last 20 years, three main disorders classified as familial hypercholesterolemia have been identified namely abetalipoproteinemia, hypobetalipoproteinemia, and CRD. These disorders can be distinguished based on clinical features, types of lipid abnormalities present and genetic testing.

Approximately 95% of dietary lipids are absorbed in the small intestine. After digestion, the fatty acids and monoacylglycerides within the lumen of the gut are taken up by the enterocytes. The absorbed lipids are delivered to the Endoplasmic Reticulum (ER) where re-esterification to Triacylglycerol (TAG) occurs. Within the ER, TAG combines with a single Apolipoprotein B (Apo B) to form pre-chylomicrons. The Apo B molecules are essential for chylomicron structure and circulate in two distinct forms: ApoB100 and ApoB48. The ApoB100 is exclusively secreted by the liver in Very-Low-Density Lipoproteins (VLDL), and ApoB48 is secreted by the intestine. The pre-chylomicron is transported to the *cis*-Golgi apparatus *via* a Pre-Chylomicron Transport Vesicle (PCTV). Fusion of the PCTV with the *cis*-Golgi apparatus is dependent on formation of a Coating Protein Complex (COPII). SAR1, a guanine tri-phosphatase, initiates the assembly of COPII [1-3].

In CRD, mutations in the SAR1B gene results in the inability of the PCTV to fuse with the *cis*-Golgi apparatus. This generates an accumulation of PCTVs in the cytoplasm of enterocytes and thus chylomicrons are not absorbed into the lymphatic system for utilization. In addition to the significant reduction in calories, serious complications may result from reduced fat-soluble vitamin absorption from the gut, most notably vitamin E [1].

Case Presentation

A 5-month-old baby boy of French Canadian descent was referred from a community hospital with severe failure to thrive. He was born at term by cesarean section due to fetal distress. Pregnancy was normal and there were no complications after birth. The birth weight was 3.1 kg. Newborn screen was normal. By 2 months of age, he had only grown to 4.8 kg and was seen by a pediatrician. He was exclusively breastfed for the first 3 months of life but had been transitioned to a formula due to poor growth. By 4 months of age, there had been no increase in length or head circumference. There was no history of diarrhea. He was having one stool daily though it was described as "fatty". There was spitting up of small amounts in the first few weeks of life which progressed to frequent

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Table 1: Results of laboratory investigations at diagnosis.

Test	Result	Reference Values
Hemoglobin	132 g/L	96-124 g/L
Total white blood cells	12.72 × 10^9/L	6.51-13.32 × 10^9/L
Platelet	449 × 10^9/L	244-529 × 10^9/L
Albumin	31.5 g/L	36-49 g/L
Vitamin A	0.9 umol/L	1.2-2.8 umol/L
Vitamin E	2.0 umol/L	5.0-14.0 umol/L
Vitamin D (25-OH)	42.7 nmol/L	>50 nmol/L
International Normalized Ratio (INR)	1.0	1.0-1.2
HDL-Cholesterol	0.73 mmol/L	0.74-2.25 mmol/L
LDL-Cholesterol	0.25 mmol/L	1.67-5.72 mmol/L
Triglycerides	0.4 mmol/L	0.28-1.4 mmol/L
Alanine aminotransferase	103 u/L	5-45 u/L
Aspartate aminotransferase	112 u/L	20-60 u/L
Alkaline phosphatase	168 u/L	145-320 u/L

non-bilious vomiting. There was no consanguinity amongst parents and family history was unremarkable.

The child was admitted twice to local hospital, first to investigate constipation and vomiting. A barium enema was normal with no evidence of Hirschsprung's disease. The upper gastrointestinal barium study showed minimal reflux. Sweat chloride was normal. Treatment with PEG3350 for presumed constipation and lansoprazole had been initiated along with nightly naso-gastric tube feeds with a partially hydrolyzed formula. The baby was admitted again for failing to thrive. With continuous nighttime feeds, the daily caloric intake was up to 137 kcal/kg/day, but no significant weight gain occurred.

The patient was transferred to our institution for further investigations. On physical examination at admission, he was alert but appeared emaciated with poor muscle mass. The weight was 4.8 kg (<3rd percentile), length 62 cm (<3rd percentile) and head circumference 40 cm (3rd percentile). The abdomen was distended but soft, with no masses or organomegaly. Muscle strength was significantly decreased, and he was unable to push up from a prone position or sit with support. The remainder of the examination, including a formal ophthalmological assessment, was unremarkable.

The patient underwent multiple investigations. Blood gas, electrolytes, glucose, bilirubin, ammonia, renal function, organic acids and urine were normal. The results of other the hematological investigations are listed in Table 1. The LDL-cholesterol was markedly reduced; HDL-cholesterol was borderline low with normal triglycerides. The liver transaminases were mildly elevated. Vitamin A, D and E levels were low. Stool microscopy revealed fat globules. An abdominal x-ray demonstrated distended bowel loops with multiple air-fluid levels. Abdominal ultrasound revealed intestinal wall thickening. An upper gastrointestinal endoscopy showed a milky white "snow storm" appearance of the duodenal mucosa. Duodenal biopsies demonstrated normal villous height and architecture with significant steatosis of the enterocytes. Electron microscopy confirmed large amount of lipid droplets in the cytoplasm of the enterocytes.

Genetic testing revealed, two different heterozygous variants in the SAR1B gene: c.537T>A and c.409G>A. Both variants are pathogenic based on American College of Medical Genetics guidelines, and both have been reported in multiple families with CRD, including in French Canadian families. Both parents were carriers of the variants in SAR1B, confirming that each variant is on a separate copy of the SAR1B gene.

The patient was started on a partially hydrolyzed formula with a higher medium chain triglyceride content administered orally and by nasogastric tube. Supplementation with high dose vitamin A, D, E and K was initiated. In follow-up at 10 months of age, he was doing very well at home and had started eating solid foods. The weight was 7.8 kg (10th percentile) and development was appropriate for age. The fat-soluble vitamin levels were normal.

Discussion

The first clinical description of what is now known as Chylomicron Retention Disease (CRD) was published in 1987 [4]. The authors reported 8 infants who presented with a malabsorption syndrome, hypercholesterolemia, normal fasting triglycerides and deficiency of vitamins A and E. Desaldeleer et al. [5] reported an 8-month old with diarrhea, vomiting and failure to thrive who was diagnosed with CRD. A review by Peretti et al. [1] revealed that 80% of patients with chylomicron retention disease present with failure to thrive in infancy, 60% with vomiting and 100% with diarrhea.

Symptoms such as vomiting, chronic diarrhea and failure to thrive are common in infants and can be seen in a variety of disorders such as gastroesophageal reflux disease, food protein induced enterocolitis, pancreatic insufficiency, etc. As CRD is very rare, it may not be thought of in the initial differential diagnosis. However, if an infant has vomiting with poor growth and basic investigations have been unyielding; one should consider an upper gastrointestinal endoscopy and biopsies. White appearing duodenal mucosa is characteristic of disorders of hypercholesterolemia and biopsies would reveal multi-vacuolated enterocytes. Also, measuring serum cholesterol in such cases may also give a clue towards a disorder of hypercholesterolemia.

In addition to vomiting, our patient had no significant diarrhea and was in fact diagnosed by primary care physician as having constipation. The cause of this is not clear. It could be related to little stool formation due to poor retention of nutrients from frequent vomiting, or from dysmotility of the bowel. Lack of diarrhea has not been described in CRD before and certainly could add to delays in diagnosis as one would not think of malabsorption without this symptom.

Deficiency of fat soluble vitamins can occur in CRD and can have serious consequences. Vitamin A deficiency has been shown to cause ophthalmologic complications in patients with CRD [1]. Poor bone mineralization and delayed growth have been reported and are likely a consequence of vitamin D deficiency [1]. Vitamin K may be mildly deficient or normal. More severe deficiencies will result in a prolonged prothrombin time. Vitamin E plays an essential role in neuronal development. The neurological abnormalities described in cases of CRD include hypo or areflexia, proprioceptive abnormalities, ataxia, myopathy and sensory neuropathy [1]. Patients with the most severe neurological abnormalities also had the lowest vitamin E levels at diagnosis [1]. Of all the fat-soluble vitamins, vitamin E deficiency is the most serious, as the damage caused may be permanent and not reversed fully with supplementation. Therefore, early diagnosis and treatment of CRD is essential to minimize long-term complications.

Conclusion

In conclusion, CRD can present in infants without diarrhea. As the symptoms can be non-specific diagnosis can be missed. Metabolic disorders with hypercholesterolemia though rare, should be considered in infants with failure to thrive, vomiting with or without diarrhea. A timely diagnosis of CRD with nutritional management including fat soluble vitamin supplementation will lead to good outcome and avoidance of serious clinical sequelae, especially neurological impairment.

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