Chylomicron retention disease in a 2-year-old girl with a novel deletion in the *SAR1b* gene: A case report and literature review

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ABSTRACT

Chylomicron retention disease (CMRD) is a rare disorder of lipid absorption, and its prevalence is <1/million. It is an autosomal recessive disorder with a genetic mutation in the *SAR1B* gene. We report a case of a girl who had the typical symptoms in the early infancy, in whom CMRD was strongly suspected clinically and due to the endoscopy findings. Unfortunately, the treatment was delayed, waiting for genetic confirmation, which was not available in her country. When we first saw the patient at the age of 2 years, she had severe failure to thrive. She recovered very fast with a trial of a fat-restricted diet and medium chain fatty acid supplementation. The working diagnosis of CMRD was later confirmed genetically. We conclude that a therapeutic trial is essential in this type of disease once the diagnosis is suspected to avoid further damage to the patient. This applies especially to resource-restricted environments.

Key words: *Anderson's disease, Chylomicron retention disease, Failure to thrive, Fat-soluble vitamin deficiency, Lipid transport defect, Steatorrhea*

Chylomicron retention disease (CMRD or CRD), also called Anderson's disease (AD), is a rare autosomal recessive disorder of lipid absorption (OMIM 246700). Anderson *et al.* first described it in 1961 [1]. More than four decades later, in 2003, SAR1B gene was identified as the responsible gene [2]. Our patient had a new variant of mutation in the *SAR1B* gene that was not described before as per the American College of Medical Genetics and Genomics (ACMG).

The diagnosis of CMRD often gets delayed due to the rarity of the disease and the non-specific presentation, as happened in our case. We are reporting this case also to explain the avoidable delay in initiation of treatment, which happened due to waiting for genetic confirmation.

CASE REPORT

A 2-year-old girl was referred to our clinic for failure to thrive and chronic diarrhea. She was born in Egypt at full term by a C-section due to a previous C-section, and her birth weight was 2.5 kg. At the age of 1 month, she faced the bleeding problem as a result of ear piercing due to this complication; she was admitted to the hospital and treated with a transfusion of fresh frozen plasma as well as Vitamin K supplementation. Her bleeding workup afterward included coagulation profile, factor assays, and platelet function tests which were within normal limits.

Around the age of 4 months, she suffered from diarrhea and was passing stool up to 5 times/day; the stool was described as oily, bulky, and foul smelling. She was only on breastfeeding at that time; her mother had tried formula supplementation, after which the baby had persistent vomiting. This resolved by the age of 6 months. By the age of 9 months, there was obvious failure to thrive and the family started seeking medical advice. Initially, she was investigated and started on a high-calorie formula through nasogastric tube, but her weight and height remained below the third percentile. The child also had features of rickets; frontal bossing, protrusion of the abdomen, and bowing of legs. The child was started on Vitamin D supplement. The family also gave a history of recurrent infections; one of which required pediatric intensive care unit for 1 week along with this. She also had persistent oral thrush.

The patient's parents were 4th-degree cousins; she had one sibling, an elder brother, who was healthy. Her development was delayed for all her milestones; she was able to sit independently at the age of 18 months and started walking independently at the age of 22 months. She could hold a pen and scribble but could not take off her shoes. She was only using single words, had a very limited vocabulary of around 10 words and knew only one body part.

On examination; her weight was 8.2 kg (below 3rd centile on CDC growth charts, z-score - 3.82), length was 73 cm (below 3rd centile, z-score - 3.27), and head circumference was 44 cm (on 2nd centile, z-score - 1.99). She had been on those centiles since the age of 7 months, but she was vitally stable and generally well, with no distinctive features. She had frontal bossing as mentioned

earlier and her limbs were wasted and bowed, and her abdomen was distended. Her gait was clumsy, no truncal ataxia. Rest of the physical examination was unremarkable.

An initial work-up revealed normocytic normochromic anemia (hemoglobin = 105 g/L, hematocrit = 0.32 L/L, mean corpuscular volume = 75.5 fL, and mean corpuscular hemoglobin = 24.5 pg) with no acanthocytes on blood smear. Her prothrombin time was 21.1 with international normalized ratio of 1.8 (0.86–1.22), which normalized with oral Vitamin K. The other fat-soluble vitamins were also low: Vitamin A 135 μg/L (194–421), Vitamin E <1.40 mg/L (3.02–9.05), and Vitamin D 35.9 nmol/L (52–250). Total cholesterol was 1.99 mmol/L (1.15–4.70), high-density lipoprotein 0.42 mmol/L (0.91–2.12), and low-density lipoprotein (LDL) 1.05 mmol/L (1.63–3.63), but triglyceride levels were 1.14 mmol/L (0.31–1.41); these levels did not change significantly after a fat challenge. ApoA1 level was 0.7 g/L (1.08–2.25), ApoB level was 0.84 g/L (0.6–1.17), and ApoB/ApoA1 was 1.2.

She had a normal absolute neutrophil count and lymphocytes count, as well as normal lymphocytes subset counts, CH50, and immunoglobulin levels on multiple repeated tests. She also had normal celiac profile and a negative sweat chloride test while her detailed ophthalmic examination was normal.

She underwent colonoscopy and histopathology in her country of origin; which reported snowflake appearance of the duodenum. The biopsy reported mild villous atrophy and vacuolated intestinal cells. Thus, at the age of 24 months, child's clinical and para-clinical picture was strongly hinting toward CRD (as was already suspected in her country of origin, but treatment was not started, rather, the child was referred to the hospital for genetic investigations). Due to financial reasons, the process of arranging for the confirmatory genetic study was lengthy. Expecting this delay, we put the child immediately on dietary restrictions which are recommended for CRMD. We started high protein low-fat diet (special formula rich in medium chain fatty acid and low in long chain fatty acid). A follow-up in 1 week showed significant weight gain (i.e., 1.3 kg, 16.3% of her presentation weight). Her diarrhea improved to twice daily and her gait became more stable. The child's feeding regimen was adjusted, and she was followed up closely for her risk of developing refeeding syndrome.

Meanwhile, her genetic studies yielded a normal sequence analysis of the *SAR1B* gene without pathogenic variants, but could not amplify exon 3. A deletion/duplication analysis of the *SAR1B* gene revealed a homozygous deletion encompassing exon 3 (NM_001033503.2; quantitative polymerase chain reaction). It is classified as pathogenic (Class 1) according to the recommendations of the ACMG. According to our lab, it was the 1st time this variant had been detected. Genetic counseling was done, but neither of the parents could undergo genetic testing due to financial limitations.

Gradually over the next year, the child's weight caught up to 35th centile, her diarrhea subsided, and her abdominal distension improved. She had a steady gait and a normal neurological examination follow up. The child had started to achieve her developmental milestones. She was also kept on A, D, E, and K Vitamins supplementation with close monitoring to ensure normal levels.

DISCUSSION

Around 62 cases had been described in literature, of these, 43 have proven alterations in the *SAR1B* gene on chromosome 5; these include 20 different mutations and deletions [3]. Information concerning the *SAR1B* genes in the other patients has not been published [4]. Our patient has a homozygous deletion of exon 3, which has not been described before.

SAR1B gene translates into a protein product belongs to the Sar1-ADP-ribosylation factor family of small GTPases. This family plays a critical role in the transport of proteins from the endoplasmic reticulum to the Golgi apparatus [5]. It is also involved in the hepatic secretion of very LDL. The *SAR1B* protein has another isoform, the SAR1A; however, overexpression of SAR1A found in CMRD patients could not compensate the *SAR1B* suppression [6,7].

There is only one case in which CMRD was not associated with any mutation in *SAR1B* gene, in a 5-year-old Japanese boy with uniparental disomy of chromosome 7, and a normal *SAR1B* gene code sequencing [8]. This suggests that other factors might be contributing to lipid absorption.

AD manifests in infancy or early childhood with steatorrhea, failure to thrive and symptoms of fat-soluble vitamins deficiency. Myopathy has been reported in some patients. Hepatomegaly and hepatic steatosis are also reported in a few published cases [4]. Patients have low total plasma cholesterol level and low LDL but normal triglycerides. There is a selective absence of apoB48 in the postprandial state. Usually, no acanthocytes are seen on blood film unless there is an advanced liver disease. Endoscopy shows normal esophageal and gastric mucosa, whereas the duodenal mucosa looks white with a specific pattern often described as snowflake appearance. Biopsy, generally, shows normal villi, but sometimes mild atrophy is found, as in our patient. Typically, enterocytes are multi-vacuolated, the so-called "fat-filled enterocytes."

The diagnosis of CMRD often gets delayed and the low lipid profile is often attributed to the malabsorption itself. When diagnosed in adulthood, the manifestations are usually more severe. Apart from the malabsorption and the failure to thrive, this disease also causes complications due to the poor absorption of the fat-soluble vitamins. Long-standing Vitamin E deficiency causes degenerative nerve disease such as proprioceptive abnormalities, polyneuropathy, and ataxia. Vitamin A deficiency causes delayed dark adaptation. The complications of Vitamin D deficiency are well known and have been described in patients with delayed diagnosis of CMRD.

In our patient, the diagnosis was suspected early on, but the treatment was delayed. A trial of fat restricted diet resulted in a fast and spectacular improvement. This supported the working diagnosis which could not be confirmed until later on. We suggest that a therapeutic trial should be the preferred approach if genetic

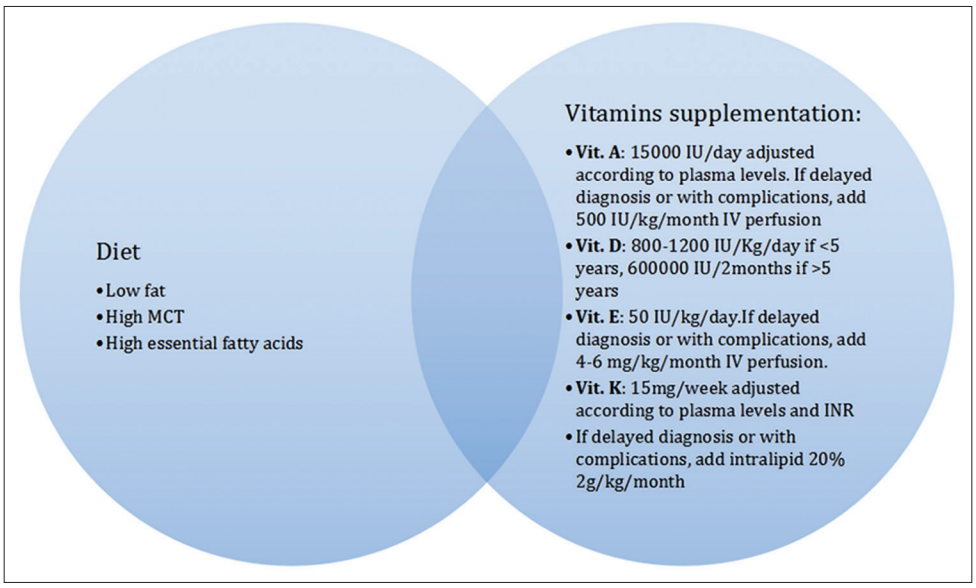

Figure 1: Chylomicron retention disease treatment [10]

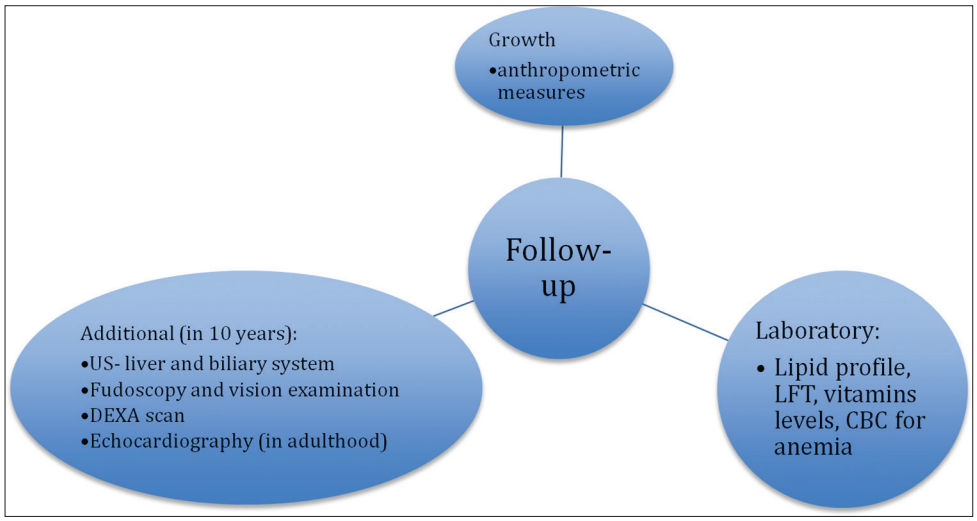

Figure 2: Follow-up of patients with chylomicron retention disease [10]

confirmation is not feasible, as often happens in resource-poor countries.

Management of CMRD focuses on (1) exclusion of long-chain fatty acids from diet, to decrease the fat load inside in the enterocytes and promote absorption, and (2) supplementation with fat-soluble vitamins to prevent vitamin deficiency syndromes, most importantly Vitamin E [3].

A close follow-up of CMRD patients is crucial. The aim is to maintain a sufficient level of Vitamin E and hence prevention of neurologic complications. It is challenging since plasma concentration level usually does not reflect the vitamin status of tissues. It has been suggested to measure the concentrations of Vitamin E in erythrocyte membranes for treatment adjustments, and adipose tissue; as a measurement of vitamin reserve and long-term compliance. Reference values are available in children [9]. Although CMRD is a rare entity, Peretti *et al.* suggested an approach for its diagnosis and management in 2010 based on literature review and experience of two centers (Figs. 1 and 2) [10]

CONCLUSION

CMRD is a rare disease of hypocholesterolemia; more research is required to understand its pathophysiology and contributing factors. When the diagnosis is suspected a therapeutic trial with diet seems indicated, especially in resource-restricted countries. This supports the diagnosis and helps to prevent its devastating complications.

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