

Atypical Infantile Familial Chylomicronemia Syndrome: A Milky Mess

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| Received: 20.12.2019 | Accepted: 27.12.2019 | Published: 20.11.2020

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Abstract

Case Report

Familial Chylomicronemia was formerly known as type 1 hyperlipoproteinemia, it is a type of severe hypertriglyceridemia characterized by the accumulation of chylomicrons in fasting plasma. Chylomicrons in a patient with health are responsible for carrying the absorbed Triglycerides (TG) into tissues via the activation of Lipoprotein Lipase (LPL) by Apo CII, thus causing the TG to be stored. In cases of Chylomicronemia, the TG is not carried into the tissue and stored thus increasing the level of Chylomicron carrying TG in plasma. This disease has a prevalence of 1 in 1 million for homozygotes and 1 in 500 for heterozygote. The most common mutations are found in the genes LPL, ApoA5, GPIHBP1, and ApoC2 among others. Loss-of-function mutation in these genes renders the LPL-dependent pathway inefficient [1].

Keywords: Atypical infantile familial chylomicronemia.

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INTRODUCTION

Familial Chylomicronemia Syndrome (FCS) results from inactivating mutations in both alleles of the LPL gene in approximately 80% of genetically confirmed cases but can also result from mutations in other genes that are required for the correct localization and function of LPL (Illustration 1). LPL forms a homodimer and is biologically active on the luminal side of the capillary endothelium in adipose and muscle tissue. Intravenous injection of heparin releases LPL from the capillary endothelium allowing determination of LPL mass and activity. More than 180 pathogenic mutations have been described in the LPL gene, with some mutations clustering regionally secondary to founder effects. Apolipoprotein C-II (APOC2) is an essential activator of LPL and bi-allelic mutations in the APOC2 gene leads to functional LPL deficiency and phenotypic FCS. Apolipoprotein A-V (APOA5) also enhances the activity of LPL, and rare mutations in the APOA5 gene have been described as causing FCS, although penetrance is often incomplete and hypertriglyceridemia may be noted only later in life. Besides LPL gene mutations, mutations in genes involved in cellular processing and/or endothelial binding of LPL can also cause FCS. Lipase maturation factor 1 is involved in maturation and transport of LPL through the secretory pathway in endothelial cells and LPL is translocated across and subsequently anchored to the capillary endothelium by

glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1). Recently, it has been reported that autoantibodies targeting GPIHBP1 may also result in an FCS-like phenotype. Finally, a rare patient with a phenotype resembling that of FCS was found to have compound heterozygous mutations in the glucokinase regulator (GCKR) gene [2].

Gene ID on NCMI database discusses the function of a recently studied protein called Apolipoprotein C-III (Apo C3) which is similar to ApoC1. Apo C3 is metabolized in the liver and is a major structural component of VLDL, HDL, and chylomicrons. It acts as an inhibitor of LPL. Apo C3 was also found to inhibit hepatic uptake of chylomicrons and VLDL particles by interfering between the hepatic receptor-ApoE interactions. High plasma Apo C3 levels were also found in patients with high plasma triglyceride concentration [3]. Further in a report published in NEJM three patients with the familial chylomicronemia syndrome and triglyceride levels ranging from 1406 to 2083 mg per deciliter (15.9 to 23.5 mmol per liter) were administered an inhibitor of APOC3 messenger RNA (mRNA), called ISIS 304801. The aim of this study was to see the effect of Apo C3 on TG levels. 13 weeks after the administration of ApoC3 inhibitor it was found that plasma APOC3

levels were reduced by 71 to 90% and triglyceride levels by 56 to 86%. This data supports the important role of APOC3 as a key regulator of LPL-independent pathways of triglyceride metabolism [1].

Familial Chylomicronemia is often discovered incidentally by lactescent plasma during routine blood sampling. The age at presentation is usually in infancy or childhood with clinical sign/symptoms of episodes of eruptive xanthomas on the trunk and extremities, lipaemia retinalis, recurrent abdominal pain, acute and/or chronic pancreatitis and hepatosplenomegaly. The signs and symptoms when present are typical of this condition and makes diagnosis favorable but this is not true for all cases. According to a study by Nagar and Arora, LPL deficiency was demonstrated in 16 infants in Quebec, Canada it was noticed that not all infants presented with typical symptoms/signs. Some of the atypical features seen were heterogeneous features, irritability, pallor, anemia, and gastrointestinal bleed [4]. This was also demonstrated in case one where a 1 month old was accidentally found to have severe hypertriglyceridemia while being evaluated for pallor and jaundice. Due to the effect of this condition on liver and spleen seen clinically as hepatosplenomegaly, destruction of RBCs by the spleen was majority responsible for these atypical symptoms seen in infants [5]. This raises the concern of physician awareness to typical and atypical symptoms seen in FCS in infants versus adults.

It is important to diagnose this condition early on its course to prevent later complications such as acute - chronic pancreatitis and pancreatic necrosis. FCS can interfere with normal growth and development of infants and result in frequent hospitalizations. This condition can later lead to exocrine or endocrine pancreatic insufficiency, including diabetes [6]. Diagnosis is based on lipid profile evaluation and blood sampling. A lactescent (milky) plasma appearance and a serum triglyceride of >1000 mg/dl are sufficient to make a diagnosis. TG are often 10-fold to 100-fold above the normal value (<150 mg/dl) and may range from 1500 to >15,000 mg/dL [7].

Currently available triglyceride-lowering agents are not completely effective in controlling chylomicronemia in such patients. Recently an LPL gene-replacement therapy (Glybera), was approved in Europe but is not yet made available in the international market. Thus, patients in other countries, the only therapeutic approach is to effectively maintain triglyceride levels below 880 mg per deciliter (10 mmol per liter), levels below this greatly reduce the risk of pancreatitis [8]. The most effective treatment modality is severe dietary triglyceride restriction. As compliance with such requirement if difficult, episodes of chylomicronemia presenting with abdominal pain and recurrent pancreatitis is quite common. Therefore, additional pharmacological therapies are required to

maintain triglyceride levels below 880 mg per deciliter [9].

Here we report a case 3- month- old presenting with atypical symptoms of FCS.

CASE SCENARIO

A 3-month-old infant was brought to the hospital by his parents with a 2-day history of high fever (39 C) which was associated with cough, breathlessness and s/o respiratory infection. He visited a local clinic with the same complaint prior to coming to the hospital. When blood was withdrawn for investigation, lactescent (milky) plasma was noted (Figure 1). Past history includes passage of blood in the stool at 20th and 21st day of the neonatal period, which was followed by spontaneous disappearance of blood on the 22nd day. There was no record of specific diseases running in the family members.

His vitals were: BP 106/84, RR 30/min, PR 126/min, Temperature 40 C and anthropometric measures were: Head Circumference 41cm, Weight 4 Kg, and Height of 63cm. Physical examination revealed a distended abdomen with hepatosplenomegaly (Figure 2). There were no fatty deposits (xanthomas) under the skin. Examination of other organs was unremarkable.

Lab Results revealed Serum cholesterol 361 mg/dl (<170 mg/dl), Serum triglycerides 2146 mg/dl (<150 mg/dl) and a VLDL of 429 mg/dl (<30 mg/dl). Other investigations were Apo B 184 mg/dl (55–140 mg/dl), Apo A 100 mg/dl (110–225 mg/dl), S. lipase 200 mg/dl (0–8 mg/dl), S. amylase 11 U/l, T3 1.78 mg/ml, T4 11.98 mcg/dl, TSH 2.78 μ IU/ml, S. Ca 8.9 mg/dl, S. Phosphorus 3.0 mg/dl, S. Uric acid 4.0 mg/dl. Liver Function test results were Total bilirubin-0.8 mg/dl, SGOT- 22 u/l, SGPT- 394 u/l, and ALP- 56 u/l. Fasting blood sugar was checked and was 84 mg/dl. BUN was 21 mg/dl, Serum Creatinine was 0.7mg/dl and CRP was negative. CBC was done results were: WBC- 20,400/mm³, RBC- 3.47 million/mm³, HB- 9.6 gm%, HCT- 28.3%, PLT- 360000/mm³, MCV-81 mcm³, MCH-27 pg, MCHC-33 g/dl, and RDW-15.8 %. Ultrasonography showed increased size and echotexture of both liver and spleen suggesting hepatosplenomegaly (Liver- 9 cm in and spleen – 6.2 cm) (Figure 4 A). On X-Ray Abdomen liver silhouette was enlarged, displacing bowel loops medially (Figure 4 B). Ophthalmological examination was done and revealed lipemia retinalis. Neurosonogram and Renal Doppler were normal. Lipid profile was done for the mother and father and revealed elevated levels of VLDL, TG and decreased levels of HDL.

The child was started on Simvastatin 10 mg/day, an HMG-CoA reductase inhibitor. Along with this dietary fat restriction and exclusive breastfeeding was advised.

There are no FDA approved statins to use in this age group, in spite they were used in the management of this case. On Follow up after 1 year the patient had developed xanthomas on his right elbow and triglyceride levels were not significantly reduced.

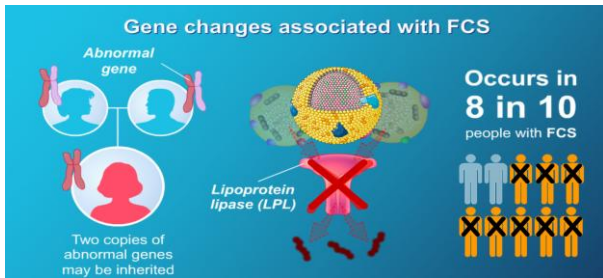


Fig-1: Gene changes associated with FCS



Fig-2: Lactescent Plasma



Fig-3: Distended abdomen with hepatosplenomegaly

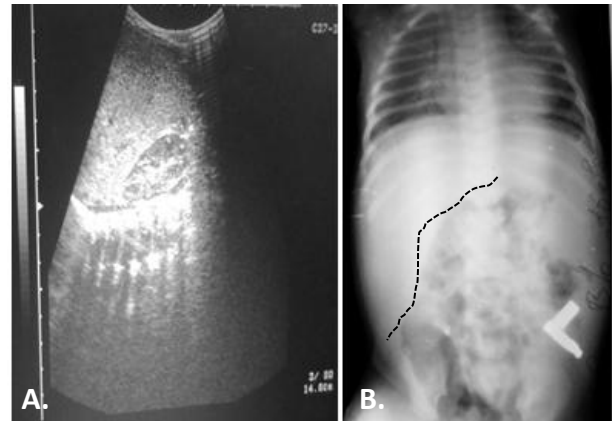


Fig-4: A. Ultrasound showing increased size and echotexture of Liver B. Liver silhouette is enlarged displacing bowel loops medially.

DISCUSSION

Familial Chylomicronemia Syndrome (FCS) is a rare, recessive genetic disorder caused by mutations in Lipoprotein Lipase (LPL) or genes required for LPL functionality. FCS is characterized by hyperchylomicronemia, recurrent abdominal pain, hepatosplenomegaly and recurrent episodes of acute pancreatitis that may result in pancreatic insufficiency along with atypical symptoms as mentioned before which are seen in infants. There are no FDA approved treatments for FCS and patients are managed with a low-fat diet. Due to the rarity of FCS there are few case series describing phenotypic variability in this disorder [10].

In a 2018 retrospective review done at the Cleveland Clinic, Ohio, 70,201 patients that were seen at the Cleveland Clinic Lipid Center from 2006-2016 met the diagnostic criteria for FCS (TG>750 mg/dL. These patients were unresponsive to triglyceride-lowering treatment. They were then compared to patients with TG>750 mg/dL who did not meet criteria for FCS. A total of 36 patients were identified with hypertriglyceridemia and prior pancreatitis. Of those, 14 patients were identified as having FCS (0.02% incidence). Patients with FCS were more likely to be male (79% vs 55%), have higher BMI (mean 32 vs 29, p <0.05), and have lower Hb A1C (mean 6.7% vs 8.7%, p <0.05). The lipid distributions were similar among both groups. Moreover, the risk of cardiovascular (CV) events was also similarly elevated (approximately 50% by age 60) in both groups [11].

The high levels of circulating plasma Chylomicrons can accumulate at multiple locations, such as the skin, producing eruptive xanthomas, or in the retinal blood vessel (lipemia retinalis). The most life-threatening complication of FCS is the occurrence of severe and recurrent episodes of acute pancreatitis [12].

Age-appropriate nutrition

- 0-12 months: Low LCT, high MCT formula or skimmed and fortified expressed breast milk, Introduce low fat table foods when age-appropriate.
- 12-24 months: skim milk and low fat table foods as appropriate. Avoid concentrated sweets, including 100% fruit juice.
- Children and adolescents: continue to provide individualized counseling and modify diet as needed. Special considerations include fussy eating in children and compliance in adolescents [13].

Although control of diet and lifestyle, and management of secondary hypertriglyceridemia risk factors remain the current mainstay of treatment for primary chylomicronemia, the increased understanding of the molecular features that lead to the chylomicronemia state have facilitated the development of targeted therapies. Among the new therapies, LPL gene therapy is the most specific to the underlying genetic disorder; however, MTTP and DGAT1 inhibitors, antisense oligonucleotides directed against APOB, APOC3 and ANGPTL3 mRNAs, as well as other targeted pharmacological agents in development, might also prove useful in the treatment of both monogenic chylomicronemia (which up until now has been an orphan disease with no effective treatment options) and the polygenic form. Close attention must be given to the outcomes of the clinical trials that are ongoing for these agents and their possible role in the management of FCS [14].

CONCLUSION

FCS is a serious inherited lipid disorder associated with chronic, life-altering consequences. Early diagnosis is essential to prevent morbid sequelae of complications such as Acute/Chronic pancreatitis or pancreatic necrosis. Statins should be indicated in the treatment of FCS along with dietary fat restriction. More research should be made for the management of such cases. Consensus on best practice for the diagnosis of FCS is lacking. Cooperation between experts and improved research and knowledge of FCS is essential in improving the diagnosis.

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