Familial chylomicronemia: A rare case report

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ABSTRACT

We report a 5-day-old neonate born out of 3rd-degree consanguinity who presented with milky blood, hepatosplenomegaly, and lipemia retinalis (fundus examination). The baby was asymptomatic, euglycemic, and did not have xanthomas. Lipid profile was altered (total cholesterol - 2340 mg/dl, triglycerides (TG) - >10,000 mg/dl, high-density lipoprotein - <5 mg/dl, lipoprotein (a) - <10.1 mg/dl, and apolipoprotein A1 - 795 mg/dl). Lipid profile of mother, father, and elder sibling were normal. The baby was started on skimmed milk powder and medium-chain TGs powder. The baby is under follow-up and lipid profile is improving.

Key words: *Chylomicronemia, Lipemia retinalis, Milky serum, Skimmed milk powder*

Lipid disorders can occur either due to the primary disturbance or secondary to an underlying disease. The primary dyslipidemias are associated with overproduction/or impaired removal of the lipoprotein. The impaired removal of the lipoprotein can occur due to an abnormality in either the lipoprotein itself or in the lipoprotein receptor [1]. Monogenic disorders that cause these abnormalities have received much attention due to their role in metabolic dysfunction and cardiovascular disease (CVD). These disorders often present during adulthood, but some of them can manifest in the pediatric population and can have serious consequences if misdiagnosed or untreated [2]. Hypertriglyceridemia is defined as having plasma triglyceride (TG) above the 95th percentile for the age and sex [1]. According to the National Cholesterol Education Program, normal TG level is <150 mg/dl (<1.7 mmol/l) [3]. The familial disorders of TG -rich lipoproteins include both common and rare variants of the Fredrickson classification system.

Familial chylomicronemia syndrome (FCS) (Fredrickson Type 1) is a rare single-gene defect caused by mutations affecting clearance of apoB-containing lipoproteins. The lipoprotein lipase (LPL) gene is located on the chromosome 8 p22. The mutation in this gene results in either underproduction of the enzyme or makes it catalytically inactive [4]. More than 50 missense and nonsense mutations have been identified. Majority of the mutations are located on exons 3, 5, and 6 which are responsible for the catalytic coding region of the gene [5]. Deficiency or absence of LPL or its cofactor apolipoprotein C-II (ApoC-II), which facilitates lipolysis by LPL, causes severe elevation of TG rich plasma chylomicrons. FCS is the most common example of severe hypertriglyceridemia. The prevalence of FCS is approximately 1 in 1 million for homozygotes and 1 in 500 for heterozygotes [5]. Manifestations include eruptive xanthomas, acute pancreatitis, hepatomegaly, splenomegaly, foam cell infiltration of the bone marrow, and lipemia retinalis. Infants may have heterogeneous presentation in the form of pallor, anemia, jaundice, irritability, abdominal distension, and diarrhea. The manifestations vary with age and severity of presentation [2]. We, hereby, report such a case of FC in a 5-day-old infant.

CASE REPORT

We report a 5-day-old neonate born out of 3rd-degree consanguinity who was referred to our hospital in view of milky blood which was drawn elsewhere to check the serum bilirubin levels after consent from parents. Index case was a male baby born out of normal vaginal delivery at 38 weeks of gestation with a birth weight 3 kg and second in the birth order. Elder sibling is a male child who is 3 years old and healthy. Pregnancy was uneventful, and there was no history of abortions or still births. The baby was roomed in on the day of delivery and was started on exclusive breastfeeds from day 1 of life. On the 4th day of life, the baby was icteric and blood was drawn which was milky, (Fig. 1) and hence referred for further evaluation. On examination, the baby was euglycemic and irritable (Fig. 2). Anthropometry at the admission was normal (weight - 2.9 kg, length - 48 cm, and head circumference - 35 cm). Vitals including non-invasive blood pressure were normal. The baby had hepatosplenomegaly, but he did not have xanthomas. There was no history of convulsions, jaundice, bleeding manifestations, skin rash, premature sudden death, or any known case of hyperlipidemia in family members.

Investigations at the admission revealed a deranged lipid profile (serum enzymatic method) with elevated total cholesterol, TGs, and low-density lipoprotein. Apolipoprotein profile tested by serum nephalometry showed elevated apolipoprotein A1. Serum lipase and

Figure 1: Milky plasma at 15 min and after 6 h refrigeration

Figure 2: Irritable infant

amylase (serum enzymatic method) were normal. Liver function test (IFCC kinetic method) was mildly deranged, and thyroid profile (electrochemiluminescence immunoassay) and coagulation profile were normal. Creatinine, electrolytes, hemoglobin, and bilirubin could not be assessed due to highly lipemic sample. Electrocardiography and two-dimensional echocardiography (2D ECHO) were within normal limits. Fundus examination revealed lipemia retinalis. Lipid profile of the mother, father, and elder sibling were normal. Diagnostic evaluation along with laboratory investigations is given in Fig. 3. Blood investigations are summarized in Table 1. Diagnosis of FCS was based on the lipemic appearance of serum, caking of chylomicrons on serum on refrigeration, and serum TG in excess of 1000 mg/dl [6].

Lipid lowering agents were not started as we could not found any recommendation for its use below 3 months of age. Genetic diagnosis could not be established owing to financial constraints and social reasons. Metabolic workup for other inborn errors of metabolism was not done as baby did not have any other manifestations. The baby was started on skimmed milk and medium-chain triglycerides (MCT) powder. After 15 days of dietary modification, lipid profile showed an improvement. The blood also turned normal (Fig. 4). The baby was continued with skimmed milk powder and simyl MCT powder and was under follow-up. At 6 months of age,

Table 1: Blood investigations at admission

Investigation	Values	Normal range
Lipid profile		
Total cholesterol (mg/dl)	2340	<200
Triglycerides (mg/dl)	>10000	<200
HDL (mg/dl)	<5	>35
LDL (mg/dl	>300	<100
Apolipoprotein profile		
Apolipoprotein A1 (mg/dl)	795	92-151
Apolipoprotein B (mg/dl)	77.8	47-106
Apolipoprotein B/A1 ratio	0.1	0.3-0.9
Lipoprotein (a) (mg/dl)	<10.1	0-30
Liver function test		
SGOT (U/L)	110	25-75
SGPT (U/L)	92	Upto 50
ALP (U/L)	382	<452
Serum lipase (U/L)	100	Upto 65
Serum amylase (U/L)	86	28-100
Thyroid profile		
Free T3 (pg/ml)	3.6	2.6-3.8
Free T4 (ng/dl)	1.22	0.93-1.7
TSH (μiu/ml)	4.6	0.27-4.2

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, ALP: Alkaline phosphatase, TG: Triglycerides

Table 2: Blood investigations at follow-up

Investigation	After 15 days	At 6 months
Lipid profile		
Total cholesterol (mg/dl)	1118	220
Triglycerides (mg/dl)	7000	400
HDL (mg/dl)	20	45
LDL (mg/dl)	220	250

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglycerides

the baby was thriving well with no xanthomas and with normal development. 2D ECHO showed pericardial fat deposit and repeat fundus examination showed progressive lipemia retinalis. Hence, the baby was started on oral Fenofibrate at 160 mg/day once daily. Follow-up assessment has been shown in flow diagram Fig. 3. Blood investigations on follow-up are summarized in Table 2. The baby continues to be under close follow-up.

DISCUSSION

FCS is a rare autosomal recessive disorder that usually manifests in childhood, but 25% of cases can manifest during infancy and rarely in the newborn period [7]. It is caused by the deficiency of extra hepatic LPL or its cofactor ApoC-II. ApoC-II deficiency typically has a later onset of symptoms and is often milder in appearance, whereas patients with LPL deficiency present at an earlier age with more severe hypertriglyceridemia and lower tolerance to dietary fat. Our case was probably due to LPL deficiency as it manifested very early with very high TG levels.

Table 3: Previous case reports

Author, year, country	Age	Sex	Clinical features	Consanguinity	Family history	Genetic diagnosis	Treatment
Zhang et al. [13], 2016 China	A-30 days B-48 days	A-male B-male	A-sampling, xanthoma B-sampling	A-none B-none	A-None B-none	A-heterozygote mutation LPL gene B-missense mutation and deletion LPL gene	Both babies dietary modification
Adenwalla et al. [14], 2008, India	15 months	Male	Cleft palate repair-incision site milky blood	None	None	Not done	Dietary modification
Saumyen et al. [15], 2015, India	2.5 months	Male	Tarry stools, abd distension, xanthomas, pallor, HSM	3rd degree	Father elevated TG	Not done	Dietary modification
Manzoor et al. [16], 2015, India	10 days	Female	Refusal to feed, irritability	3rd degree	Parents hyperlipidemia	Not done	Dietary modification
Nampoothiri et al. [17], 2011, India	38 days	Male	Sampling, hepatomegaly, lipemia retinalis	None	None	2 novel mutations in LPL gene	Dietary modification
Azkawi and Alalwan [18], 2010, Saudi Arabia	Siblings A-2 days B-16 days	A-male B-male	A-anemia B-screening	1st degree	Hyperlipidemia	Not done	A-gemfibrozil dietary modification B-dietary modification
Chen et al. [19], 2012, China	A-30 days B-40 days	A-male B-male	A-loose stools, pallor B-pallor, bloody stools	None	None	Not done	Dietary modification
Chaurasiya et al. [12], 2013, India	2 months	Male	Excessive cry, abd distension	None	None	Not done	Fenofibrate dietary modification
Pugni et al. [20], 2014, Italy	23 days	Male	Sampling	None	None	Homozygous mutation LPL gene	Exchange transfusion dietary modification

LPL: Lipoprotein lipase, HSM: Hepatosplenomagaly, TG: Triglycerides

Genetic diagnosis is available only at few centers. Patients with TG levels above 2000 mg/dl are more likely to present with xanthomas, and those with levels above 4000 mg/dl may present with lipemia retinalis (pale pink color to the retinal arterioles and venules due to light scattering of the large chylomicrons) [8].

Xanthomas are asymptomatic, evanescent, yellowish papules over buttocks, shoulders, and extensors of limbs. Phagocytosis of chylomicrons by macrophages in the skin results in the formation of eruptive xanthomas. Skin xanthomas usually regress within a few weeks to months after the lowering of plasma TG. Surprisingly, our case did not have xanthomas despite very high TG levels. Hepatosplenomegaly in our patient is due to ingestion of chylomicrons by reticuloendothelial cells. The mainstay of management is strict adherence to fat restriction which should be continued throughout life. Recommended fat restriction vary from <50 g/day or under 25% of total daily caloric intake to <20 g/day or under 15% of total daily caloric intake [9]. Intake of saturated fats and trans fats should be reduced and should be replaced by polyunsaturated and monounsaturated fats [2].

MCT are preferred source of dietary fat. MCTs' can be either added to infant formula or given as an oral solution to supplement fat calories. Dietary MCTs' are directly absorbed into the portal vein and do not require transport on chylomicrons. Therefore, no increase in TG concentrations is seen. The ultimate aim is to maintain TG values <2000 mg/dL so as to decrease the risk of pancreatitis. FCS resulting from deficiency in LPL or ApoC-II is very difficult to treat with existing pharmacologic agents. The pharmacological agent of choice for severe hypertriglyceridemia is fabric acid derivatives (Fenofibrate). Safety and effectiveness of Fenofibrate has not been established in pediatric patients as per the Food and Drug Administration, especially below 10 years. As monotherapy, fibrates offer the most TG reduction (20-50%), followed by immediate-release niacin, omega-3 methyl esters, extended-release niacin, statins, and ezetimibe [10].

There is a case report in which use of MCT oil and omega-3 fatty acid resulted in complete resolution of clinical symptoms [11]. Hence, we also used dietary fat restriction with use of skimmed milk powder and MCT powder, and this approach resulted in improvement of lipid profile. Early diagnosis is important to prevent complications such as acute and chronic pancreatitis and pancreatic necrosis; although, pancreatic function often deteriorates very slowly. Pharmacologic management is sometimes needed in

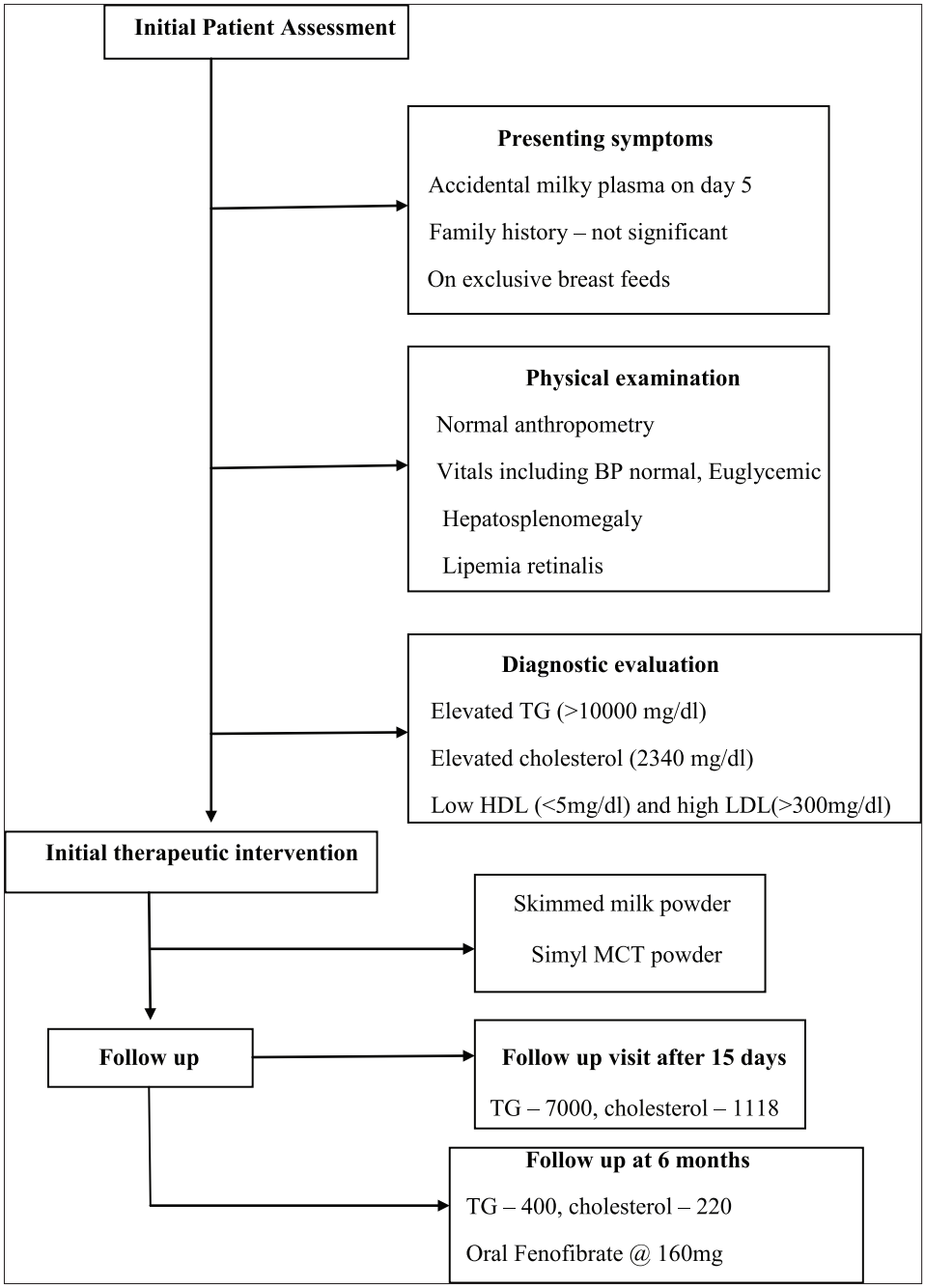

Figure 3: Flow diagram (care guidelines)

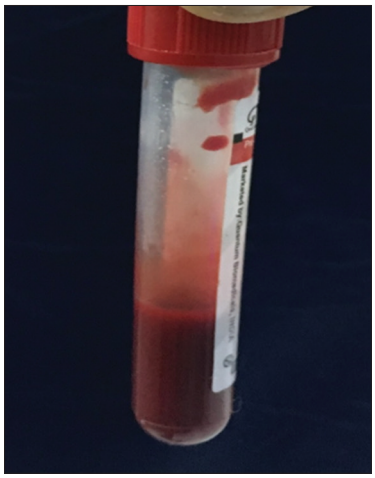

Figure 4: Blood after treatment

primary triglyceridemia to prevent pancreatitis and/or reduce the risk of CVD. Recommendation for their use in children for this particular group of disease needs further studies [12]. Previous case reports have been summarized in Table 3.

CONCLUSION

Literature and case reports on FCS in the neonatal age group are scanty, and there are no specific treatment guidelines in this age group. Hence, it prompted us to report this case. The syndrome presentation is heterogeneous in a very young age group. Early diagnosis and dietary modification can improve the prognosis and maintain a near normal lifestyle for affected children as the risk of pancreatitis and frequency of hospital admissions are significantly reduced.

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