Original Article

Inherited Lipid Disorders in Children: Experience from a Tertiary Care Centre

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Abstract

Background: Primary dyslipidaemia in children is a rare inherited disorder of lipoprotein metabolism with debilitating sequelae and poor outcomes. Lipid-lowering drugs have less often been used in children and long-term outcome studies are scarce. The purpose of this study was to understand the clinical and laboratory profile, response to treatment on follow up and outcome of primary dyslipidaemia in Indian children. **Methods:** Clinical records, including historical details, examination features and laboratory and radiological evaluation of children diagnosed with primary dyslipidaemia, presenting over the last 9 years were studied. Cascade screening was done for family members of the patients to detect dyslipidaemia in parents and siblings. All children were followed up 3 to 6 monthly for clinical and laboratory evaluation. Diet and drug therapy, initiated as appropriate, were modified as necessary. **Results:** Of nine children with primary dyslipidaemia, seen over the last 9 years, homozygous familial hypercholesterolaemia (HoFH) (n = 4/9), familial hypertriglyceridaemia (FHT) (n = 3/9), familial combined hyperlipidemia (FCH) (n = 1/9), mutation proven chylomicronaemia syndrome (n = 1/9) were the phenotypes seen. Multiple xanthomas (n = 4/9), recurrent pancreatitis (n = 2/9) and incidentally found biochemical abnormality (n = 3/9) were the chief presenting features. Medical nutrition therapy and lipid-lowering drugs, as appropriate, were instituted in all. Follow-up over 16 months (range 4 to 90 months) revealed no deaths and no new onset of symptoms. Atherosclerotic plaques in the carotid artery were seen in one child, who presented late, despite fair compliance to treatment. Interestingly, lipid levels decreased in all cases and were normalised in two. **Conclusion:** Primary dyslipidaemia when detected early and treated aggressively can improve short-term outcomes.

Keywords: Familial hypertriglyceridaemia, homozygous familial hypercholesterolaemia, lipid-lowering drugs, primary dyslipidaemia

Introduction

Dyslipidaemia is an important risk factor in the development of coronary artery disease. There is strong evidence that lipoprotein levels track from childhood into adulthood. Although secondary dyslipidaemia due to obesity, type 2 diabetes mellitus, hypothyroidism and alcohol intake is exponentially increasing in children with changing diet and lifestyle attributes, primary dyslipidaemia is rare and results from genetic defects in the production, transport or degradation of lipoproteins.[1] Lipid-lowering drugs have less often been used in children and long-term outcome studies are scarce. The purpose of this study was to understand the clinical and laboratory profile, response to treatment on follow up and outcome of primary dyslipidaemia in Indian children. The clinical profile, therapeutic response and follow-up of nine children with primary dyslipidaemia diagnosed at our centre, over the last 9 years, are presented here.

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Materials and Methods

This retrospective observational study was conducted between March 2012 and March 2021. Ethical clearance was obtained from the Institutional Ethics Committee and the study was performed in accordance with the ethical standards as laid down in the 1975 Declaration of Helsinki and its later amendments. Children registered at our division and diagnosed with dyslipidaemia were considered for potential enrolment. These children and their parents were invited to join the study after personal counselling and offering them

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the patient information sheet. Participants were included after written informed consent was obtained from them/their parents. Secondary dyslipidaemia was ruled out by history including intake of causative drugs or alcohol, anthropometry, clinical examination, fasting blood sugar, thyroid function tests, renal and hepatic function tests, respectively, to exclude obesity, type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, chronic renal failure and hepatitis as the possible aetiology. Children with secondary dyslipidaemia, patients not willing to participate and those cases where the data was insufficient were excluded. All data available in the case record file of the enrolled cases were recorded. Historical details including age at onset of disease, age at presentation, sex, consanguinity, family history of early onset cardiovascular disease in first-degree relatives, anthropometric details, examination features at presentation including manual blood pressure, evidence of xanthomas, detailed ophthalmological examination were recorded. Investigations conducted as per protocol were noted. Fasting lipid profile done after an overnight 12 h fast, to include serum total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol was performed in all patients by enzymatic method from a quality control accredited laboratory. Data regarding radiological evaluation including abdominal ultrasound to look for fatty liver and pancreatic morphology were recorded. Carotid Doppler performed by a single radiology consultant was recorded. Echocardiography performed by in house consultant paediatric cardiologist, as indicated, was noted. Ophthalmological evaluation to look for lipaemia retinalis and visual acuity was recorded. Cascade screening to detect dyslipidaemia was done in both the parents and siblings of all patients. Dyslipidaemia was diagnosed based on fasting lipid profile values as per National Cholesterol Education Program (NCEP) Expert Panel on Cholesterol Levels in Children references.[2] Fredrickson classification was used to categorise the dyslipidaemia phenotype.[3] Details of treatment provided as per standard of care were noted. All children received a diet prescription. Cardiovascular Health Integrated Lifestyle Diet (CHILD)-1 diet for 3 months and if unsuccessful in lowering the lipids, then CHILD-2 cholesterol lowering/CHILD-2 triglyceride lowering diet by an expert nutritionist was advised.[4] Children 5 years and older were advised at least 1 h of moderate-to-vigorous physical activity daily. Gemfibrozil, niacin and omega-3 fatty acids were advised in hypertriglyceridaemia and cholesterol-lowering drugs like atorvastatin and ezetimibe, in children with hypercholesterolaemia, were initiated with prior informed consent. All children were followed up 3 to 6 monthly as per unit protocol.

On follow-up, any new onset of symptoms, clinical examination including anthropometry and pubertal staging as per age, blood pressure, presence of xanthomas and ophthalmological examination were recorded. All children were investigated 3 monthly for the initial year of follow-up and subsequently every 6 months. Laboratory evaluation included fasting lipid profile, liver function test, checking for pancreatic enzymes (in children with hypertriglyceridaemia), ultrasound of the abdomen, carotid artery Doppler and two-dimensional (2D) echocardiography. Diet and drug therapy were modified as necessary. Details at the last follow-up, including growth characteristics, new onset symptoms, laboratory profile, morbidity, complications, if any and response to treatment, were reviewed.

Ethical clearance statement

The study was approved by Institutional Ethics Committee - Bai Jerbai Wadia Hospital for Children vide letter no. IEC-BJWHC/AP/2021/042-V2 on 8th December, 2021. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The procedures follows the guidelines laid down in Declaration of Helsinki 2008.

Results

Nine children (8 males) between 5 months and 9 years of age presented with primary dyslipidaemia. Four (45%) were products of consanguineous union and seven (78%) had a significant family history with either the parents or first-degree relatives diagnosed with dyslipidaemia. One child had lost a sibling due to myocardial infarction and another child had lost a sibling to acute pancreatitis. Tendinous xanthomas in four (45%), recurrent pancreatitis in two (22%) and incidentally found lipaemic serum during blood tests in three (33%) cases were the presenting features. Growth characteristics were normal in all except one child who was short for the population but within mid-parental height targets. None of the children were overweight or obese and all were normotensive [Table 1].

Secondary causes of dyslipidaemia like hypothyroidism, diabetes mellitus, obesity, intake of causative drugs or alcohol and renal or hepatic pathologies were excluded in all cases. Based on clinical and laboratory features, four children were classified as homozygous familial hypercholesterolaemia (HoFH; type IIa familial dyslipidaemia), one child as chylomicronaemia syndrome due to GP1HBP1 homozygous mutation (c.320C>G) (type I familial dyslipidaemia), three children had familial hypertriglyceridaemia (FHT; type IV familial dyslipidaemia) and one child had familial combined hyperlipidemia (FCH; type IIb familial dyslipidaemia) phenotype [Figure 1].

All children, except infants, were on CHILD 2 diet comprising of low saturated fat, avoiding trans-fat, increased dietary fibre, reduced sweetened beverages, use of complex carbohydrates, the addition of omega-3 fatty acid and increased dietary fish when possible. Children 5 years and older did at least 1 h of moderate-to-vigorous physical activity daily. Gemfibrozil and/or Niacin were given in hypertriglyceridaemia and

Table 1: Profile at presentation

Case No.	1	2	3	4	5	6	7	8	9
Age at presentation (years)	7.8	1.6	9	8.7	0.2	0.7	0.4	8.3	2.3
Sex	M	M	M	F	M	M	M	M	M
Height SDS	0.97	1.15	-0.90	1.55	2	-0.28	-1.21	-0.96	-2.32
Weight SDS	0.05	-0.51	-1.23	-0.07	-0.55	-1.15	-2.5	-2.54	-1.23
Family History+[$]	+	+	+[#]	+	-	-	+	+	+[@]
Clinical presentation	Xanthomas	Xanthomas	Pancreatitis	Pancreatitis	Lipaemic serum xanthoma	Lipaemic serum	Lipaemic serum	Xanthomas	Xanthomas
Laboratory profile on admission*									
Total S. Cholesterol (Normal <170 mg/dl)	719	691	171	124	122	106	236	609	>800
LDL Cholesterol (Optimal <100 mg/dl)	671	442.8	93	106	61.2	59	140	568	>549
VLDL Cholesterol (N- 6-38 mg/dl)	21.6	16	>300	146.5	40.6	-	67.2	23.8	22.2
S. Triglyceride (mg/dl)	108	67	2483.4	2172	6275 Chylomicron present	2287	398	119	111
HDL (mg/dl)	26	23	14	13	6	18	30	41	19
Fredrickson phenotype	Type IIa	Type IIa	Type IV	Type IV	Type I	Type IV	Type IIb	Type IIa	Type IIa
Echocardiography/ Carotid Doppler	N	Mild aortic root dilatation	N	N	N	N	N	Mild intimo medial thickening of b/l carotid	N
Treatment	Statin 30 mg and EZT 10 mg daily	EZT 10 mg daily	Niacin 1 g, Sea cod	Ω 3 fatty acid	Ω 3 fatty acid	CHILD 2-TG Diet, MCT oil	Low-fat diet	Statin 10 mg daily	Statin 10 mg daily

+Mother and/or father had primary dyslipidaemia. *Normal values of lipid profile.[2] [$]Case No 3,4,5,8 were born of a consanguineous union. [#]Older sibling died at 12 years of age due to pancreatitis had increased triglycerides. [@]Older sibling died at 5 years of age due to myocardial infarction. EZT: Ezetimibe ; Statin :Atorvastatin; MCT : Medium-chain triglyceride; Ω 3: Omega-3

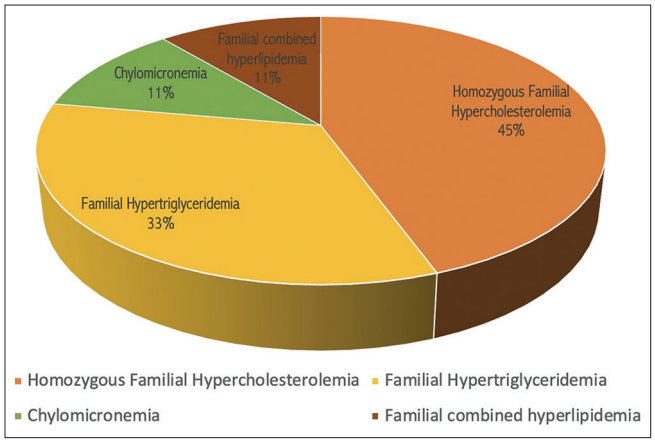

Figure 1: Types of inherited lipid disorders in our study

cholesterol-lowering drugs like atorvastatin and/or ezetemibe, in hypercholesterolaemia. [Table 1]

The median duration of follow-up was 16 months, ranging from 4 months to 7 years 6 months [Table 2]. There were no deaths. All grew adequately and two attained spontaneous puberty. Of the four cases with HoFH, none had aortic stenosis, though, one child, case 1, had early calcific plaque and intimal thickening of the aortic root and arch suggestive of atherosclerosis. He presented to us late at 7 years 8 months, and the atherosclerotic changes were seen at 14 years of age. There were no further episodes of pancreatitis during follow-up, in children with hypertriglyceridaemia [Table 2].

Adherence to the prescribed diet was uniformly inconsistent. Lipid profile at last follow-up had significantly improved from baseline though were not normal. Of the four cases with HoFH, low-density lipoprotein (LDL) cholesterol levels declined by 53%, 32% and 44% from baseline in cases 1, 2 and 8, respectively, but increased by 35% from baseline in case 9. This child had poor compliance with dietary and pharmacological therapy. Serum triglyceride levels significantly decreased by 87%, 51%, 86% and 94% from baseline in cases 3, 4, 5 and 6, respectively [Figures 2-4].

Discussion

Secondary dyslipidaemia in children and adolescents is on the rising trend in view of the increasing prevalence of obesity with insulin resistance and metabolic syndrome. On the other hand, primary dyslipidaemia, an inherited genetic disorder of lipoprotein metabolism is rare.

Table 2: Profile at last follow up

Patient	1	2	3	4	5	6	7	8	9
Age at last follow-up (years)	14.2	2.3	16.6	11.1	6.1	1	1.2	8.5	2.8
Height SDS	1.08	1.01	-0.91	1.17	0.14	-0.75	-1.88	-0.75	-1.35
Weight SDS	-0.05	0.30	1.31	-0.05	-0.5	-0.74	-1.76	-1.94	-0.79
Total cholesterol (mg/dl)	346	700	81	142	133	150	137	364	840
LDL cholesterol (mg/dl)	315.2	>300	34	106	17.2	84	75.4	313.4	746
VLDL cholesterol (mg/dl)	-	-	-	111	-	-	-	10.4	32
Triglyceride (mg/dl)	64	11	303	1045	824	115	138	52	162
Morbidity	Early changes of coronary artery disease, atherosclerosis in the aorta	Dilated aortic root	Mild left ventricular dilatation. No further episodes of pancreatitis	No further episodes of pancreatitis	Nil	Nil	Nil	Mild intimo medial thickening of bilateral common carotid arteries	Nil
Treatment	Atorvastatin 80 mg, Ezetimibe 20 mg, Aspirin 150 mg daily	Ezetimibe 20 mg, Cholestyramine 8 g, Omega-3 fatty acids 5 caps daily	Gemfibrozil 1800 mg, Naicin, Sea cod, Omega-3 fatty acids daily	Omega-3 fatty acids, Gemfibrozil 1200 mg daily	Omega-3 fatty acids, Gemfibrozil 900 mg daily	MCT oil, Omega-3 fatty acids	Low-fat diet	Atorvastatin 10 mg BD	Atorvastatin 5 mg, Ezetimibe 10 mg daily

Screening the population for primary dyslipidaemia is imperative for early diagnosis and treatment before serious complications set in. The previous guidelines advocated targeted screening of children with risk factors for HoFH such as a family history of premature cardiovascular diseases, dyslipidaemia and obesity. Cascade screening of children was advised wherein the disease was actively screened for among the first- and second-degree relatives of patients diagnosed by targeted screening. To improve the detection rates further, recent guidelines recommend a strategy of universal lipid screening, which is best performed at 9–11 years of age, whereas screening at any time after the age of 2 years is preferred in those with risk factors.[5]

Fagge identified primary dyslipidaemia more than a century ago as a skin ailment but its correlation with atherosclerosis was first recognised in 1939 by Carl Muller.[6,7] Advances in molecular studies of lipoprotein metabolism enabled the characterisation of various phenotypes of primary dyslipidaemia. Based on electrophoretic lipoprotein phenotype, Fredrickson *et al.*[3] classified primary hyperlipoproteinemia into five major types (types I–V). Goldstein and Brown[8] discovered that mutations in low-density lipoprotein receptor (LDLR) was the cause of monogenetic familial hypercholesterolaemia (FH). In addition to the LDLR defect, defective ApoB100 component of LDL and gain of function mutation in proprotein convertase subtilisin/kexin 9 (PCSK9) which is responsible for the degradation of LDLR are also causes for this disorder.

HoFH, diagnosed in four cases in this series, is a rare disorder, seen in 1 in 300,000 to 400,000 individuals. Inherited in an autosomal codominant fashion, its severity depends on the level of LDL receptor activity with the null phenotype (<2% activity) even leading to intrauterine death. It presents in the first decade of life with primarily dermatological and ocular manifestations in the form of xanthomas including tuberous, tendon and interdigital xanthomas, xanthelasma and corneal arcus with raised low-density lipoprotein–cholesterol (LDL-C). HoFH results in an almost hundred-fold increased risk of coronary artery disease as a result of excessive accumulation of atherogenic LDL cholesterol in the arterial walls.[9] Heterozygous familial hypercholesterolaemia (HeFH) is more common with a prevalence of 1 in 500 persons. These patients are largely asymptomatic in childhood and adolescence and are typically diagnosed by screening methods. Some may bear peripheral markers of fat deposition. In this series, one of the four cases of HoFH was born of consanguineous union, and cascade family screening in all cases showed elevated LDL-C levels in one or both parents. All children had extensive cutaneous, tendinous xanthomata with TC levels greater than 600 mg/dl and LDL-C levels of more than 400 mg/dl at the time of diagnosis [Table 1]. Parihar in 2012 reported a 3-year-old female who, like our patients, presented with skin lesions as the sole clinical manifestation and her lipid profile was consistent with HoFH.[10]

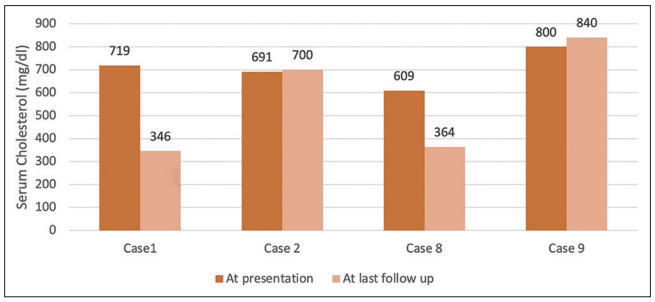

Figure 2: Serum total cholesterol (mg/dl) at presentation and at last follow-up in patients with familial hypercholesterolaemia

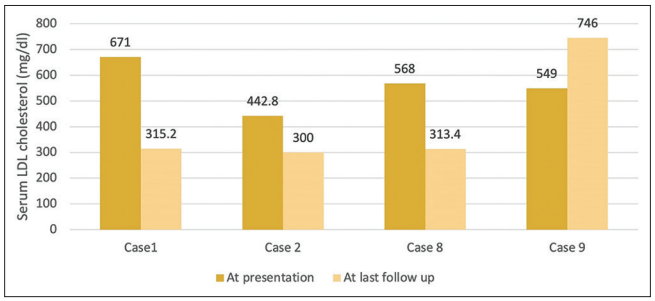

Figure 3: Serum LDL cholesterol (mg/dl) at presentation and at last follow-up in patients with familial hypercholesterolaemia

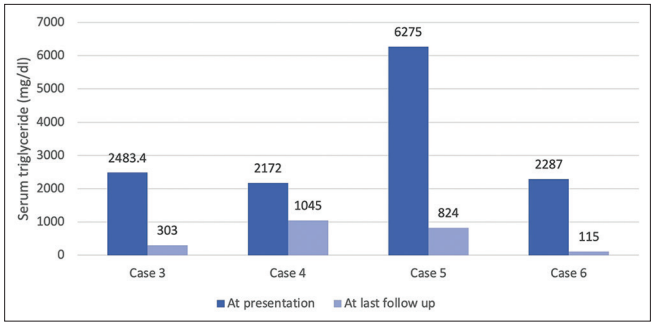

Figure 4: Serum triglyceride (mg/dl) at presentation and at last follow-up in patients with familial hypertriglyceridaemia

Therapeutic lifestyle adjustments including strict low-calorie, low-fat diets and increased physical activity are important aspects of management. Lipid-lowering drugs like statins, ezetimibe and bile acid-binding agents are being used. Newer modalities of treatment include drugs like lomitapide, mipomersen, serum PCSK9 inhibitors like alirocumab and HDL-bound enzyme cholesterol ester transfer protein (CETP) inhibitors like dalcetrapib. For children who have extremely elevated LDL levels refractory to medications, biweekly LDL apharesis has been utilised successfully. Orthotopic liver transplantation represents the most definitive treatment as it treats the underlying cause of elevated LDL cholesterol. The practical use of gene therapy for patients with HoFH is being researched. In this series, four children with HoFH were treated with atorvastatin and/or ezetemibe besides diet and lifestyle modification. On follow-up, although TC and LDL-C decreased, they remained more than normal. One child who presented late developed calcific plaques in the aortic root on follow-up [Table 2]. Two other children who had aortic root dilation and intimo medial thickening of bilateral common carotid arteries at presentation did not show any progression of these changes, while on treatment. Widhalm *et al.*[11] in 2017 reported a case series of nine patients (youngest 1-year-old) with HoFH diagnosed over the last 30 years, in which two patients had died and four (44.4%) developed arterial plaques, as compared to our series (youngest 5-month-old) in which there were no deaths and one (25%) of the four cases of HoFH had arterial plaques on follow up. Palacio *et al.*[12] reported two cases of HoFH diagnosed in early childhood not responding to maximal medical therapy, who were treated successfully with an orthotopic liver transplant. The poor response to lipid-lowering drugs is also seen in our series [Table 2]. Though studies with a long follow-up of 20 years on a statin (pravastatin) in a large cohort (214 patients) of FH have shown the treatment to target (LDL <100 mg/dl) in only 20% patients, progression of carotid intima-media thickness and cardiovascular events were reduced at 39 years in these patients who started treatment in childhood than their parents.[13]

Hypertriglyceridaemia is defined as an increased plasma fasting triglyceride (TG) concentration, that is greater than 100 mg/dl for children of ages 0 to 9 years and greater than 150 mg/dl for children of ages 10 to 19 years.[14] FHT is a rare inherited disorder of triglyceride metabolism which results from an increase in chylomicrons, VLDL or both. It encompasses hyperchylomicronaemia (Fredrickson type I) which occurs due to mutations in the lipoprotein lipase (LPL) gene which is an enzyme that is essential for the degradation of triglycerides or defective production of cofactors like ApoC2 and ApoA5; FHT (Fredrickson type IV) due to increased concentration of VLDL due to either increased production or decreased catabolism of VLDL with triglycerides between 250 and 1000 mg/dl; and the more severe combined hypertriglyceridaemia and chylomicronaemia (Fredrickson type V) in which both VLDL and chylomicrons are elevated and triglyceride levels are often >1000 mg/dl.

After excluding all secondary causes of hypertriglyceridaemia, three children in this series had FHT/endogenous hypertriglyceridaemia (Fredrickson type IV) which has polygenic inheritance with environmental susceptibility and one child had primary lipohyperproteinemia/familial chylomicronaemia. Although familial chylomicronaemia syndrome is mainly caused by mutations in the LPL gene, few causal mutations in other genes (i.e., APOC2, APOA5, LMF1 and GPIHBP1) have also been reported.[15] Our patient had a GP1HBP1 homozygous mutation. This is a rare cause of familial chylomicronaemia accounting for only 2% of cases (95% of cases being due to LPL gene defect).[15] GP1HBP1 is a critical protein for LPL transportation from the subendothelial spaces to the capillary lumen, where it promotes lipolysis by working as the main site (platform) to bind LPL on the endothelial surface. Dangerous levels of TG up to 38000 mg/dl have been reported in this condition

even in the newborn period.[16] Children with primary hypertriglyceridaemia often get detected incidentally having a lipaemic serum or oily stools as seen in two of our cases. Delayed presentations include pancreatitis, pancreatic necrosis, atherosclerosis and non-alcoholic fatty liver disease. Two cases in this series who presented as late presenters had pancreatitis whereas the one child detected in infancy did not, although had lipaemia retinalis on ophthalmological examination. Serum triglyceride (TG) levels were more than 1000 mg/dl in all of our cases at presentation. A review has noted that the risk of pancreatitis increases from 6.5% with a TG level of >1000 mg/dl to 38% with a level of more than 2000 mg/dl. This is likely due to pancreatic capillary obstruction and subsequent ischaemic damage due to hyperviscosity induced by TG. Pancreatic lipases may also induce damage by local liberation of pro-inflammatory lysolecithin and free fatty acids by the hydrolysis of TG. The most effective treatment modality is dietary triglyceride restriction by restriction of fat, sugars and simple carbohydrates. There are no Food and Drug Administration (FDA) approved triglyceride (TG) lowering medications for use in children younger than 18 years of age. Nevertheless, when fasting TG concentration is greater than 500 mg/dl, pharmacological agents such as fibrates, niacin and omega-3 fatty acids are used to prevent pancreatitis. For patients with moderate hypertriglyceridaemia (200–499 mg/dl), treatment is directed towards reducing the non-HDL cholesterol level by using a statin. Plasmapheresis can reduce serum TG levels rapidly and can be used in symptomatic patients with severe hypertriglyceridaemia and pancreatitis. In this series, besides dietary modifications, we used gemfibrozil and/or niacin with omega-3 fatty acid and medium-chain triglyceride (MCT) oil supplementation. Bhatia *et al.*[17] in 2018 reported a case of neonatal hypertriglyceridaemia, which like the two cases in our series, was incidentally diagnosed in view of viscous, milky blood. Like the other two cases in our series presenting with pancreatitis, Zhang *et al.*[18] in 2017 reported a case of hypertriglyceridaemia induced acute pancreatitis requiring plasmapheresis. Blackett *et al.*[19] reported two siblings with hyperchylomicronaemia who presented at 9 years and 7 years of age, respectively, and demonstrated the beneficial role of orlistat, a pancreatic lipase inhibitor in controlling the triglyceride levels and reducing the episodes of pancreatitis. Infants with GP1HBP1 mutations have required plasmapheresis at a very young age of 1 month for severe hypertriglyceridaemia.[16]

FCH (Fredrickson type IIb) is characterised by an overproduction of VLDL and ApoB100 by the liver and a decrease in the clearance of chylomicron remnants. Patients may manifest with an increase in either TG or LDL-C or both. It is associated with a strong family history of premature cardiovascular disease. Similar history was also present in our case whose maternal grandfather and uncle had an early-onset myocardial infarction. This child, now one year since diagnosis, is well-controlled on dietary restriction alone.

Further long-term follow-up is needed to characterise the outcome of cases in this series.

Conclusions

This series highlights the importance of early diagnosis, intensive management and meticulous follow-up of primary dyslipidaemia syndromes to prevent morbidity and mortality due to life-threatening complications. Physical findings like tendon xanthoma, arcus corneae and xanthelesma are clinical pointers to primary dyslipidaemia. Clinicians should be vigilant to diagnose hyperlipidemia syndromes and screen family members of the index case. Screening for primary lipid disorders in children and adolescents having risk factors like positive family history of elevated cholesterol, premature coronary artery disease and pancreatitis should be practised. Lipid-lowering drugs and strict dietary modification are essential. Genetic analysis could be done only in one patient due to cost constraints. Further follow-up is required to characterise the outcome of cases in this series.

Ethics approval

Ethical clearance was obtained from the Institutional Ethics Committee (IEC) (Bai Jerbai Wadia Hospital for Children IEC) vide letter Ref No IEC-BJWHC/157/2021 for the research project and the study was performed in accordance with the ethical standards as laid down in the 1975 Declaration of Helsinki and its later amendments.

Consent to participate

Participants were included after a written informed consent was obtained from them/their parents.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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