Unusual presentation of more common disease/injury

Case series of type III hyperlipoproteinemia in children

Michelle Fung,¹ John Hill,² Donald Cook,³ Jiri Frohlich⁴¹University of British Columbia, Vancouver, British Columbia, Canada;²Healthy Heart Program, St Paul's Hospital, Vancouver, British Columbia, Canada;³Department of General Internal Medicine, Rockyview General Hospital, Calgary, Alberta, Canada;⁴Department of Pathology, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence to Dr Michelle Fung, michelle.fung@vch.ca

Summary

Type III hyperlipoproteinemia (type III HLP) rarely manifests in childhood. Long-term follow-up (37 years) of the first patient revealed hypothyroidism at diagnosis requiring thyroxine replacement, palmar xanthomas requiring surgical removal, splenomegaly requiring splenectomy, 18 episodes of pancreatitis and premature coronary artery disease. Investigation revealed an apolipoprotein E phenotype of E2/E2 and partial lipoprotein lipase deficiency. Investigation of the second patient revealed a combination of apoE2/E2 phenotype and heterozygous familial hypercholesterolaemia. The third patient had a complete deficiency of lipoprotein lipase activity, an abnormal thyroid stimulating hormone on diagnosis (with subsequent normalisation without treatment), and apoE2/E2 phenotype. Type III HLP is a serious disorder with lifelong consequences of premature vascular disease and recurrent pancreatitis. Early presentation of disease in our patients was associated with additional precipitating factors. Drug treatment of paediatric type III HLP is indicated if dietary modifications alone are insufficient in managing the dyslipidaemia.

BACKGROUND

Childhood manifestation of type III hyperlipoproteinemia (type III HLP) is extremely uncommon. Because of the long-term consequences of type III HLP, early onset of the disease has serious implications. There is currently little understanding of the precipitants, natural history and management of paediatric onset type III HLP.

Type III HLP is a disorder characterised by the accumulation of remnant cholesterol-rich intermediate density lipoprotein particles. The underlying mechanism is related to an autosomal recessive polymorphism of apolipoprotein E (usually apoE2/2 genotype) and an independent aggravating environmental or genetic factor leading to overproduction of apoB-containing lipoproteins.¹ Clinical manifestations include palmar and tuberoeruptive xanthomas. Major complications include recurrent pancreatitis, peripheral vascular disease and premature coronary artery disease. One in 10 000 persons have type III HLP, and as many as 1 in 100 have the apoE2/E2 genotype in the general population.²

We document that children affected by this condition experience lifelong consequences of premature vascular disease and recurrent pancreatitis. Early presentation of the disease in our patients was associated with additional precipitating factors such as hypothyroidism, partial or complete deficiency of lipoprotein lipase activity, or concurrent familial hypercholesterolaemia (FH). Drug treatment of paediatric type III HLP is indicated if dietary modifications alone are insufficient in managing the dyslipidaemia.

CASE PRESENTATION

Over the past 25 years, three patients with a clinical history and signs of paediatric type III HLP were identified in the Lipid Clinic at St. Paul's Hospital, Vancouver, British Columbia, Canada.

Case 1A 10-year-old boy presented with multiple tuberoeruptive xanthomas in between the toes, in the creases of the buttocks, in the cubital and popliteal fossa and in the creases of the palms and fingers. Plasma lipoprotein electrophoresis in agarose gel showed a broad β -band consistent with type III HLP. The very low-density lipoprotein fraction upon electrophoresis showed β -migrating lipoproteins. Heparin testing showed that he also had a partial deficiency of lipoprotein lipase (LPL) activity. Furthermore, he was found to be hypothyroid at age 11 and was treated with levothyroxine that commenced in his mid 20s.³

He received initial treatment with dietary changes for type III HLP. Despite diet and subsequent medication therapy, he had multiple complications including xanthomas requiring surgical removal, splenomegaly requiring splenectomy, 18 episodes of pancreatitis, myocardial ischaemia starting at age 42 requiring a stent, followed by two additional stents at age 43 and a third stent at age 50 years with now stable angina at age 55 (table 1). The elevation in triglyceride levels ranged from moderate to severe while on treatment with diet, fibrates, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and cholesterol reuptake inhibitors (table 1). His current lipid profile and investigations are summarised in table 2.

Currently, the patient is 55 years old. He currently meets criteria for metabolic syndrome with elevated triglycerides, abdominal circumference of 125 cm, systolic blood pressure >130 mm Hg and high-sensitivity C reactive protein of 3.52 mg/l. He continues to have stable angina. He quit smoking 27 years ago, and reports drinking approximately six beers per week. There is no history of hyperlipidaemia in his parents. His father died at 82, suffering multiple strokes and had a myocardial infarction at age 46. His father's brother died at 62 years old of presumed acute

Table 1 Case 1: long-term follow-up (55 years) and treatment response

Age (years)	Medications	Total cholesterol <5.2 mmol/l	HDL-C >0.9 mmol/l	Triglycerides <2.3 mmol/l	Complications
10	Diet only	12.8	NA	4.9	Xanthomas
20	L-thyroxine Colestipol Lovastatin Gemfibrozil	38	NA	24	Xanthomas requiring surgical removal every 6 months
33					Splenomegaly requiring splenectomy Eighteen episodes of pancreatitis
42					Unstable angina Percutaneous transluminal coronary angioplasty (PTCA) with stent×3
43	L-thyroxine 300 µg daily	12.6	1.3	8.3	Recurrent unstable angina PTCA with stent×1 Tuberoeruptive xanthomas Xanthalesma Arcus cornealis Acanthosis nigricans Palmar xanthomas regressed
44	Niacin 1 g twice daily Fenofibrate 200 mg daily Atorvastatin 10 mg daily As above Atorvastatin increased to 40 mg daily	18.1	1.3	10.2	
45	As above	7.0	1.5	3.8	
47	As above Atorvastatin increased to 40 mg twice daily Unable to tolerate niacin	9.2	1.5	5.9	Stable angina
55	Rosuvastatin 40 mg daily Ezetimibe 10 mg daily Fenofibrate micro 250 mg daily	6.2	1.2	4.5	Stable angina

HDL-C, high-density lipoprotein cholesterol.

Table 2 Case 1: laboratory results

Laboratory test	1998	2004	2006	2010	Usual result
Age (years)	43	49	51	55	
Total cholesterol	12.6	4.7		6.2	<5.2 mmol/l
HDL-cholesterol	1.3	1.57		1.2	>0.9 mmol/l
Triglycerides	8.3	2.5		4.5	<2.3 mmol/l
Lipoprotein lipase activity	32		31		>90 nmol/l/min/ml
Hepatic lipase activity	76				>90 nmol/l/min/ml
ApoE lipoprotein	E2/E2				E3/E3
ApoB lipoprotein	1.19 (<1.15 g/l)	0.45 (0.6–1.3 g/l)		0.96 (0.6–1.3 g/l)	
ApoA1				1.64	1.04–2.02 g/l
Lp(a)	2310 (<400 IU/l)	1.77 (<0.30 g/l)			
TSH	0.02	0.03			0.5–5.0 µl
Free T4	31				14–25 pmol/l
Homocysteine		20.8			(4.9–13.7 µmol/l)
CRP		3.52			>3 mg/l increased risk
HbA1C		0.061		6.4%	
Treatment					
Complications					

Apo, apolipoprotein; CRP, C reactive protein; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; Lp(a), lipoprotein a; TSH, thyroid stimulating hormone; T4, thyroxine.

myocardial infarction. His mother, now 88 years old, has hypertension. He has one sister who is healthy. He is married and has a 37-year-old male child who has normal lipid levels and a second 34-year-old male child who had a 'brief elevation' of cholesterol that returned to normal.

Case 2

A 10-year-old girl presented with palmar xanthomas and tubero-eruptive exanthomas of the popliteal fossa and scars on her legs. She was diagnosed with type III HLP based on the clinical signs. The patient was also found to have heterozygous FH secondary to 10-kb deletion in the

low-density lipoprotein (LDL) receptor and a partial deficiency in LPL activity secondary to a Asn291Ser mutation in the LPL gene.⁴ Additionally, her fasting lipid profile consistently shows low high-density lipoprotein (HDL). Her laboratory results and treatment response are summarised in table 3.

Currently, the patient is 18 years old. Her family history is significant for dyslipidaemia and premature coronary artery disease. Her father and two of his siblings had significant hypercholesterolaemia. Her paternal grandfather died at age 30 of a myocardial infarction and was known to have hypercholesterolaemia. Her paternal great

Figure 1 Photograph of palmar xanthomas in case 3.

Table 3 Case 2: treatment response

Laboratory test	1994	1995	2001	2002	2003	2003	2005	Usual result
Age (years)	10	11	16	17	18	18	21	
Total cholesterol	11.85	13.08	4.52	14.43	4.06	8.00		<5.2 mmol/l
HDL-cholesterol	0.82	0.85	0.93	0.89	0.62	0.83		>0.9 mmol/l
Triglycerides	5.68	5.16	2.01	9.86	1.58	2.16		<2.3 mmol/l
Lipoprotein lipase activity							15	>90 nmol/l/min/ml
Hepatic lipase activity							163	>90 nmol/l/min/ml
ApoA1 lipoprotein	1.04							>1.22 g/l for adults
ApoB lipoprotein	1.41	1.8						<1.15 g/l for adults
Lp(a)	36							<400 IU/l
ApoE lipoprotein	E2/E2							E3/E3
TSH	2.78							0.4–4.0 µl
Treatment	Diet alone	Simvastatin 20 mg daily	Atorvastatin 20 mg daily	Atorvastatin 40 mg daily	Atorvastatin 40 mg daily and niacin 1.5 g daily	Atorvastatin 80 mg daily and niacin 1.5 g daily		

Defective LPL activity secondary to a mutation in the LPL gene (Asn291Ser) was present.⁵

Apo, apolipoprotein; HDL, high-density lipoprotein; Lp(a), lipoprotein a; TSH, thyroid stimulating hormone.

grandfather also died of a myocardial infarction at age 50. The family is of French-Canadian ancestry.

Case 3

An 11-year-old girl presented with palmar xanthomas (figure 1) and tubero-eruptive xanthomas of both elbows. Based on these clinical signs, she was diagnosed with type III HLP. Plasma lipoprotein electrophoresis showed a small amount of chylomicrons, increased β -band and decreased α -band. Thyroid stimulating hormone was initially found to be elevated at 80 µl but has since normalised without intervention. She also has elevated total cholesterol and apoB along with a family history of familial combined hyperlipidaemia (FCH).

She was initially treated with diet and salmon oil, and subsequently with fenofibrate supra (table 4). She experienced a dramatic response her dyslipidaemia is well controlled on once weekly fenofibrate supra. The family lipid panels are summarised in table 5.

INVESTIGATIONS

Blood samples from the three subjects were collected in 0.1% EDTA after a 12–16 h fast for lipoprotein measurements. Serum lipids were measured using an enzymatic assay, apolipoprotein (apo) B levels were measured by immunonephelometric method, and apoE phenotyping was performed. HDL and LDL particle size were assessed using the fractional esterification rate of cholesterol in apoB-depleted plasma (FER_{HDL}) in two of the subjects. Blood samples were collected 10 min after an intravenous bolus of 60 IU/kg unfractionated heparin and placed on ice. Testing of samples for postheparin lipase activity were performed at the University of Seattle, Washington DC, USA (by the lab of Dr John Brunzell)⁵ or St. Paul's Hospital, British Columbia, Canada (by the lab of Dr John Hill).

DISCUSSION

This is the first case series of type III HLP in children.

Table 4 Case 3: laboratory results and treatment response

Laboratory test	2001	2001	2002	2002	2002	Usual result	
Age (years)	10	10	11	11	11		
Total cholesterol	7.17	12.01	8.95	8.3	10.34	<5.2 mmol/l	
HDL-cholesterol	1.07	1.17	1.91	1.06	1.25	>0.9 mmol/l	
Triglycerides	3.83	4.87	2.73	3.31	4.56	<2.3 mmol/l	
Lipoprotein lipase activity				186		>90 nmol/lmin/ml	
Hepatic lipase activity				197		>90 nmol/lmin/ml	
ApoA1 lipoprotein				1.36		>1.22 g/l for adults	
ApoB lipoprotein		1.16		1.01		<1.15 g/l for adults	
Lp(a)				595		<400 IU/l	
ApoE lipoprotein				E2/E2		E3/E3	
TSH		80		1.87		0.4–4.0 μl	
Anti-TPO antibody				<10		<36 IU/ml	
Treatment	Salmon oil	Salmon oil	Salmon oil	Salmon oil	Salmon oil		
Laboratory test	2002	2003	2003	2004	2005	Usual result	
Age (years)	11	12	12	13	14		
Total cholesterol	6.53	8.64	7.02	7.47	9.01	<5.2 mmol/l	
HDL-cholesterol	1.04	1.0	0.85	0.63	NSQ	>0.9 mmol/l	
Triglycerides	2.19	5.85	4.39	5.86	6.27	<2.3 mmol/l	
Lipoprotein lipase activity						>90 nmol/lmin/ml	
Hepatic lipase activity						>90 nmol/lmin/ml	
ApoA1 lipoprotein						>1.22 g/l for adults	
ApoB lipoprotein						<1.15 g/l for adults	
Lp(a)						<400 IU/l	
ApoE lipoprotein						E3/E3	
TSH						0.4–4.0 μl	
Anti-TPO antibody						<36 IU/ml	
Treatment	Salmon oil 2 g twice a day, niacin 250 mg twice a day	Fish oil 2–3 g daily, 1500 mg daily non-flushing niacin	Niacin 2–3 g daily, fish oil, policosanol	Salmon oil and niacin, irregularly	Salmon oil 6 g daily		
Laboratory test	2006	2006	2007	2008	2008	2009	Usual result
Age (years)	15	15	16	17	18	19	
Total cholesterol	4.78	5.36	4.87	4.6	5.32	4.64	<5.2 mmol/l
HDL-cholesterol	1.54	1.41	1.59	1.27	1.51	1.49	>0.9 mmol/l
Triglycerides	1.51	1.56	1.25	1.72	1.94	1.80	<2.3 mmol/l
Lipoprotein lipase activity							>90 nmol/lmin/ml
Hepatic lipase activity							>90 nmol/lmin/ml
ApoA1 lipoprotein							>1.22 g/l for adults
ApoB lipoprotein					0.74		<1.15 g/l for adults
Lp(a)							<400 IU/l
ApoE lipoprotein							E3/E3
TSH							0.4–4.0 μl
Anti-TPO antibody							<36 IU/ml
Treatment	Lipidil supra 160 mg daily	Lipidil supra 160 mg every 2 days	Lipidil Supra 160 mg every 3 days	Lipidil Supra 160 mg once weekly	Lipidil Supra 160 mg once weekly		

Apo, apolipoprotein; HDL, high-density lipoprotein; Lp(a), lipoprotein a; TPO, thyroperoxidase; NSQ, Not Sufficient Quantity; TSH, thyroid stimulating hormone.

What factors affect the manifestation of disease in type III HLP in children?

Apolipoprotein E genotype

ApoE is a protein required for the normal removal of triglyceride-rich particles from the blood, and the usual isoform of apoE is apoE3. Most patients with type III HLP have the apoE2/E2 genotype. However, even though the prevalence of the apoE2/E2 genotype in the population is 1 in 100 persons, only about 1% of individuals who carry the apoE2/E2 genotype manifest type III HLP. The manifestation of type III HLP in children is most uncommon. The expression of type III HLP in individuals with apoE2/E2 genotype is associated with a second metabolic abnormality. In children, this second abnormality has been identified to be one of the following: hypothyroidism, FH or a defect in LPL activity.

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Thyroid dysfunction

Both patients one and three had documented laboratory evidence of thyroid dysfunction. These findings are consistent with a small number of reports of type III HLP associated with hypothyroidism in children.^{6–13} Mechanisms by which the two conditions may be related include decreased cholesterol catabolism by the liver and decreases fecal bile acid, neutral sterol and total steroid excretion causing elevated cholesterol levels in hypothyroidism. Thyroid hormone regulates LDL receptor activity, cholesterol 7 α -hydroxylase and HMG-CoA reductase.

Table 5 Case 3: family studies

Laboratory test	Father	Mother	Brother	Usual result
Total cholesterol	6.63	5.72	4.9	<5.2 mmol/l
HDL-cholesterol	0.71	1.35	0.98	>0.9 mmol/l
Triglycerides	8.81	1.31	2.25	<2.3 mmol/l
LDL-cholesterol	NA	3.77	2.89	<3.4 mmol/l
Lipoprotein lipase activity	146	195	199	>90 nmol/lmin/ml
Hepatic lipase activity	473	185	314	>90 nmol/lmin/ml
ApoA1 lipoprotein	1.19	1.47	1.13	>1.22 g/l for adults
ApoB lipoprotein	0.94	1.06	0.95	<1.15 g/l for adults
Lp(a)	433	128	90	<400 IU/l
ApoE lipoprotein	E4/E2	E3/E2	E3/E2	E3/E3
TSH	0.75	1.92	1.22	0.4–4.0 µl

HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo, apolipoprotein; Lp(a), lipoprotein a; TSH, thyroid stimulating hormone.

Familial hypercholesterolaemia and familial combined hyperlipidaemia

FH is a genetic lipid disorder of the LDL receptor, usually resulting in hypercholesterolaemia without hypertriglyceridaemia. Several reports of FH co-existing with type III HLP have been reported in addition to the patient in case 2.^{14–17} Another genetic disorder of lipid metabolism is FCH where affected families have a polygenic hyperlipidaemia resulting in variable phenotypes among family members, as seen in case 3. The concurrent expression of an inherited defect in lipid metabolism such as FH or FCH in an individual with the apoE2/E2 genotype may accelerate the clinical manifestation of type III HLP in childhood.

Decreased LPL activity

A decrease in LPL with the absence of the normal apoE3 allele may cause retention of lipoproteins leading to the overt expression of type III HLP seen in both cases. Both cases 1¹⁸ and 2 had decreased LPL activity. This finding is significant because LPL and apoE independently enhance binding and uptake of lipoproteins by cells. If apoE is defective, LPL may compensate for the by enhancing lipoprotein binding to these receptors.¹⁹ If LPL activity is also decreased, it may explain the early clinical manifestation of type III HLP in children.

Lipoprotein particle size

Lipoprotein particle size may be smaller in patients with type III HLP that manifest in childhood. HDL and LDL particle size can be assessed using the fractional esterification rate of cholesterol in apoB-depleted plasma (FER_{HDL}).²⁰ The measurement of FER_{HDL} is based on estimation of the radioactivity of free and esterified cholesterol in plasma depleted of apoB lipoproteins. The FER_{HDL} in case 1 was 21.14% and 31.11% in case 3, both of which are higher in comparison to average values of FER_{HDL} in normal men and women (16.8±4.5%/h and 10.6±3.6%/h, respectively),²¹ indicating the presence of smaller particle sizes in these patients with paediatric type III HLP.

What are the complications of paediatric type III HLP?

Except for the patient in case 1,¹⁸ there are no long-term follow-up studies of paediatric patients with type III HLP. Type III HLP in children is likely to be strongly associated with premature vascular disease as well as increased risk of pancreatitis if triglycerides are very elevated.^{22–23} The

premature coronary artery disease seen in case 1 may be secondary to the accumulation of remnant lipoproteins in type III HLP that is associated with premature atherosclerosis in conjunction with metabolic syndrome, increased lipoprotein (a) and homocysteine elevation. The fact that case 1 developed coronary artery disease in the absence of clinically significant peripheral vascular disease is unusual as some clinical manifestation of such disease would be expected in type III HLP. Given the long-term consequences of type III HLP, aggressive treatment of type III HLP with hypolipidaemic agents in these children is justified. Combination drug therapies also appear to be critical and safe to assist in adequate control of these combinations of lipid abnormalities.

Precipitating factors

The identification of this disease in children raises many new questions. How do the biochemical abnormalities relate to clinical manifestations such as palmar xanthomas? What factors determine the extent of hypertriglyceridaemia? Alcohol can significantly raise triglyceride levels, and could potentially be a precipitating cause for pancreatitis. However, the subject in case 1 where the patient had frequent attacks of pancreatitis cannot recall any association between consumption of alcohol and pancreatitis, and currently reports no episodes of pancreatitis in the past 5 years.

We note that in all three cases, the apoB levels were elevated. We suspect that case 1 may have inherited FCH given his positive family history for coronary disease, but we are unable to confirm this. In case 2, the elevated apoB level is the result of FH. The patient in case 3 likely inherited FCH as supported by elevated apoB level and consistent lipid profiles in her parents. As elevated apoB is not expected as part of type III HLP, does the presence of this additional lipid problem contribute to its manifestation in childhood? And furthermore, does FCH exacerbate the clinical symptoms and complications of type III disease?

There remain several questions that remain a quandary. For example, what is the gene-to-gene interaction between LPL and apoE? Also, are there specific mutations of the LPL gene that can cause this problem? There remains uncertainty in our ability to identify potentially important environmental triggers of disease expression in genetically vulnerable individuals.

What are the treatment options?

There is little experience in the treatment of paediatric type III HLP. There are questions pertaining to the management of this condition that remain unanswered. In particular, what are the treatment targets for paediatric type III HLP? And can complications related to type III HLP be prevented? Treatment of secondary causes of dyslipidaemia and dietary control is recommended. Drug treatment may be required to lower lipid levels. Treatment options in type III HLP include fibrates, HMG-CoA reductase inhibitors, high-dose nicotinic acid and ω -3 fatty acids and cholesterol absorption inhibitors classes of drugs. Long-term effects of statins and fibrates in children have not yet been studied, although there have been several short-term studies on the use of statins in children with FH.^{24–28}

Type III HLP rarely manifests in children. The early onset of type III HLP in our patients was associated with a partial deficiency in LPL activity in some cases and may also have been precipitated by concurrent hypothyroidism. Elevated apoB was also present in all cases. It is not definitively known if one or more of these aggravating factors are necessary for the expression of disease. Paediatric onset type III HLP is a serious disorder with lifelong consequences of premature vascular disease and recurrent pancreatitis if left untreated. Drug treatment of paediatric type III HLP is indicated if dietary modifications alone are insufficient in managing the dyslipidaemia.

Learning points

- ▶ Type III HLP is rare in children and is associated with precipitating factors.
- ▶ Paediatric type III hyperlipoproteinemia is a serious disorder with lifelong consequences of premature vascular disease and recurrent pancreatitis if left untreated.
- ▶ Drug treatment of paediatric type III HLP is indicated if dietary modifications alone are insufficient in managing the dyslipidaemia.

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