CASE REPORT

Lipoprotein lipase deficiency presenting with neonatal perianal abscesses

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SUMMARY

Lipoprotein lipase (LPL), a member of the triglyceride lipase gene family, is synthesised by parenchymal cells of the heart, skeletal muscle and adipose tissues before being transported to luminal surfaces of vascular endothelial cells to exert its main physiological function to hydrolyse plasma lipoproteins. LPL deficiency is a rare autosomal recessive disorder, resulting in severe hypertriglyceridaemia from birth. The effect of marked hypertriglyceridaemia on the immune function in children has not been described. We present a case of a neonate with LPL deficiency and grossly elevated plasma triglyceride levels, presenting with recurrent and recalcitrant perianal abscesses suggestive of underlying immunodeficiency. With reduced levels of plasma triglycerides, the recurrent perianal infections resolved. This case report reviews evidence for potential deleterious effects of hypertriglyceridaemia on immune function, however, underlying mechanisms are poorly understood. Whether hypertriglyceridaemia contributes to immune dysfunction in this context is unknown. If there is a pathophysiological link, this may have implications for hypertriglyceridaemia management.

BACKGROUND

Lipoprotein lipase (LPL) deficiency, resulting from mutations in the gene encoding LPL, which is located on chromosome 8p22,[1] results in marked hypertriglyceridaemia in infancy, with triglyceride levels up to 350 times the upper limit of normal.[2] While the association between hypertriglyceridaemia and acute pancreatitis is well established,[3] the potential effects of markedly elevated triglyceride levels on immune function in children have not been described. We report a case of a neonate diagnosed with LPL deficiency after presenting with recurrent and recalcitrant perianal abscesses, which resolved on correction of marked hypertriglyceridaemia. We hypothesise that hypertriglyceridaemia may contribute to immune dysfunction in individuals with severe hypertriglyceridaemia due to inherited disorders of lipid metabolism. Whether this association may have implications for those with milder hypertriglyceridaemia secondary to obesity and the metabolic syndrome has not been investigated.

CASE PRESENTATION

A 4-week-old male neonate presented to our institution with frequent loose stools. He was the first child of healthy, non-consanguineous parents of Indian descent. He was born by elective caesarean section at 41 weeks gestation for breech presentation following an uneventful pregnancy. The birth and early neonatal course were unremarkable, and he was exclusively breastfed. While he remained systemically well and continued to breastfeed, the loose stools had resulted in perianal excoriation, for which his mother applied a barrier cream.

On clinical examination, he had a low-grade fever (38.0°C) and a tender, erythematous, fluctuant swelling to the right perineum with surrounding cellulitis. The abscess was incised and drained that day, with intraoperative findings including an internal opening within the anal canal with resultant fistula formation. A swab taken perioperatively cultured *Escherichia coli* and a *Klebsiella* spp. The immediate postoperative course was uneventful, and he received broad spectrum intravenous antibiotics (flucloxacillin, gentamicin and metronidazole) for a total of 3 days, followed by oral amoxycillin-clavulanic acid.

During the admission, blood samples were taken to assess inflammatory markers and perform an immunodeficiency screen. Gross lipaemia was identified on serial samples (figure 1A and table 1), with total plasma cholesterol of 40.2 mmol/L (reference interval 1.2 to 4.5 mmol/L) and triglycerides 332 mmol/L (reference limit <1.7 mmol/L), making interpretation of biochemistry difficult.

At this stage, breast-feeding was ceased and a fat-free formula started to provide daily energy requirements through the provision of carbohydrates and protein, resulting in a gradual fall in plasma lipid levels over the next month (figure 1B and table 1). While plasma lipid levels remained elevated, although decreasing, the baby continued to suffer from recurrent perianal abscesses, positive for *Enterobacter* spp, requiring surgical drainage and repeated courses of broad spectrum intravenous antibiotics.

INVESTIGATIONS

The diagnosis of LPL deficiency was suspected based on the presence of chylomicronaemia and confirmed by genetic testing, which showed compound heterozygous mutations in the *LPL* gene. Specifically, the baby was found to have a c.88 +2dupT mutation in intron 1, which disrupts the intron 1 splice donor site,[4] and a c.721C>T mutation in exon 5, which results in p.Pro214Ser missense mutation in a conserved region of the protein,[4] a region thought to affect protein folding and stability.[5] Parental testing revealed normal fasting plasma lipid profile in the father, in the presence of the exon 5 mutation, with mildly

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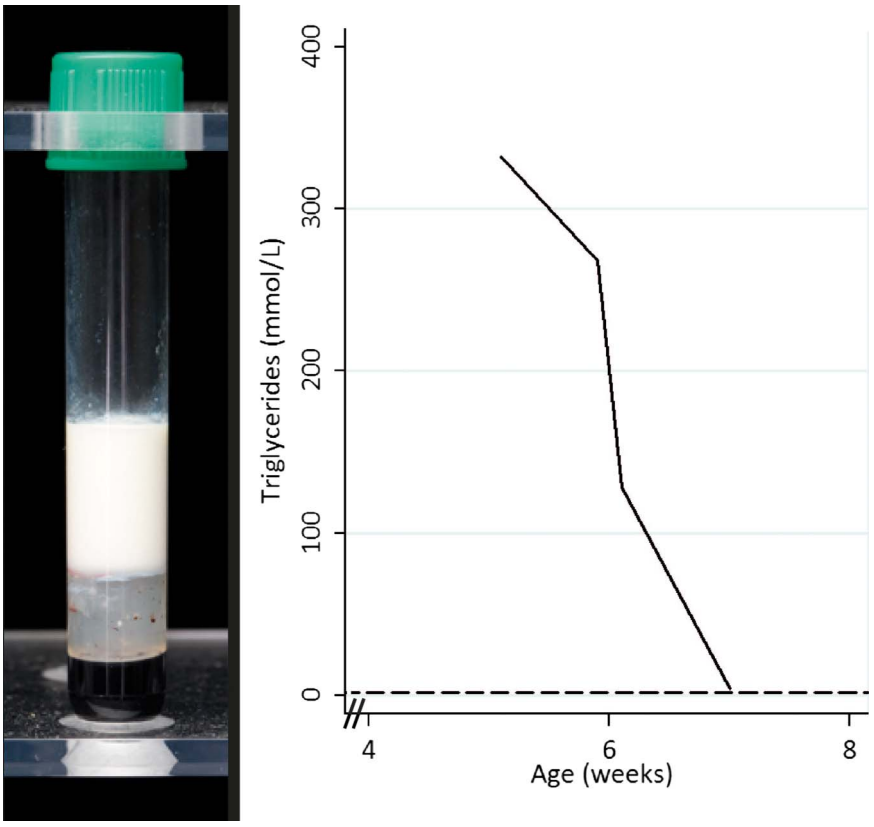

Figure 1 Gross lipaemia in a blood sample collected prior to diagnosis (left), and elevated triglyceride levels at presentation with a rapid fall on appropriate dietary fat restriction (right).

elevated cholesterol and triglyceride levels in the mother, in the presence of the intron 1 mutation (table 2). The patient and his mother had *APOE* genotype 3/2, whereas the father was 3/3. Sequence analysis for the proband and both parents is shown in figure 2.

Immune function studies were attempted during the period of hypertriglyceridaemia, however, the results were difficult to interpret in the presence of gross lipaemia. The presence of hypertriglyceridaemia required an additional step to wash the cells during lymphocyte subset characterisation, with results that were not reproducible. Similarly, the results from the neutrophil burst test were not reliable. It was not clear whether the lipaemia resulted in technical interference with the neutrophil burst assay, or whether elevated triglyceride levels had a direct effect on neutrophil function.

DIFFERENTIAL DIAGNOSIS

Hypertriglyceridaemia presenting in the neonatal period is most commonly due to mutations in the *LPL* gene, which results in elevated levels of chylomicrons, while a number of other genes may be involved in genetic hypertriglyceridaemia presenting in adulthood, including *APOE*.[6] While hypertriglyceridaemia presenting in the neonatal period is most commonly primary (genetic), the differential diagnosis of hypertriglyceridaemia in children and adolescents includes secondary causes such as hypothyroidism, obesity and the metabolic syndrome, cholestasis, nephrotic syndrome, glycogen storage disease type 1, poorly controlled diabetes and medications such as oral retinoids, the contraceptive pill and atypical antipsychotics.[6 7]

Table 1 Plasma lipid biochemical profile over time

	Normal ranges (mmol/L)	Chronological age (days)			
		36 days	41 days	43 days	49 days
Cholesterol	1.2–4.5	40.2	39.7	28.3	7.8
Triglyceride	<1.7	332	268	128.6	4.2
High-density lipoprotein (HDL) cholesterol	0.9–2.0	–	–	–	0.7
Low-density lipoprotein (LDL) cholesterol	Not available	–	–	–	5.2

OUTCOME AND FOLLOW-UP

Following diagnosis of LPL deficiency, our patient has remained on a prescribed low-fat diet, with Monogen for the first year of life, followed by low-fat skimmed cows' milk. His diet is carefully managed to provide a fat intake of 8–15% of total intake, in the form of Monogen, walnut oil and medium chain triglycerides oil. Following this diet, his plasma triglyceride levels have been stable, in the range of 10–20 mmol/L. He has had no further episodes of perianal abscesses nor of other deep-seated bacterial infections, and no episodes of pancreatitis. In the

Table 2 Parental fasting lipid profiles (plasma)

	Normal ranges (mmol/L)	Father	Mother
Cholesterol	<5.5	4.4	5.8
Triglyceride	<1.7	1.5	2.9
High-density lipoprotein (HDL) cholesterol	>1.0	0.9	1.1
Low-density lipoprotein (LDL) cholesterol	<3.0	2.8	3.4

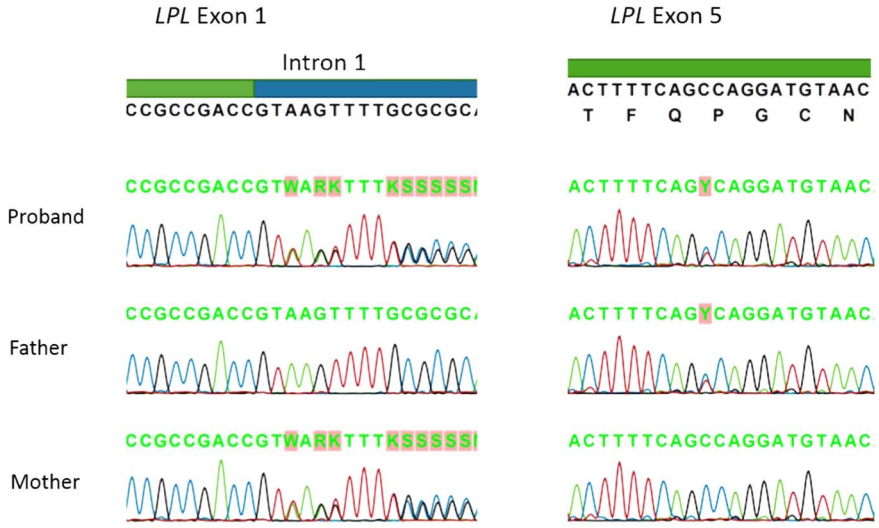

Figure 2 *LPL* genetic sequence analysis for the proband and both parents. LPL, lipoprotein lipase.

absence of ongoing clinical signs of immunodeficiency, immune function studies have not been repeated.

DISCUSSION

This case describes an unusual clinical course for a neonate diagnosed with LPL deficiency. The child developed recurrent and recalcitrant perianal abscesses that were slow to respond to appropriate surgical and antimicrobial therapy. These abscesses occurred during a period of gross hypertriglyceridaemia, and ceased soon after triglyceride levels reached more modestly elevated levels. Coupled with the observation of an unsatisfactory neutrophil burst test in the presence of gross lipaemia, we hypothesise that the child's hypertriglyceridaemia may have contributed to immune dysfunction, possibly mediated through altered neutrophil function, particularly as neonatal perianal abscess has been reported as a presenting feature for autoimmune neutropaenia.[8] However, it is also possible that hypertriglyceridaemia and subsequently LPL deficiency were detected in this case as incidental findings, following routine blood sampling in the context of unrelated neonatal perianal abscesses.

Most individuals with LPL deficiency present in the first decade of life, with abdominal pain, cutaneous xanthomas or hepatosplenomegaly.[9] Only 25% of individuals with LPL deficiency present in the first year of life, with neonatal presentation a rare event.[9] Clinical presentation with severe or recurrent infections has not been previously described.

Potential effects of hyperlipidaemia on immune function and susceptibility to infection have been previously described. Functional activity of monocytes,[10] lymphocytes,[11] antigen presenting cells[12] and neutrophils[13 14] are all impaired in the presence of elevated lipid levels. Further, mice with elevated lipid levels, including *ApoE* knockout mice, have impaired defences against several diverse pathogens, including *Klebsiella pneumoniae*, *Listeria monocytogenes*,[15] *Candida*,[16] *Mycobacterium tuberculosis*[17] and hepatotoxic lymphocytic choriomeningitis virus,[18] but not against *Salmonella* spp.[19] The wide variety of pathogens affected suggests that lipaemia may result in immune dysfunction via several pathways, with evidence to support decreased phagocytic capacity of granulocytes,[20] defective innate immunity[21] and dysregulation of inflammatory cytokines[22] in the presence of dyslipidaemia. This may have implications for treatment of infections, as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have been suggested to confer a survival benefit in influenza, even in the absence of dyslipidaemia.[23] Further research is required to further characterise these pathways and determine whether the effects are likely to be seen in individuals with milder elevations of plasma lipids, such as those associated with obesity.

If immune dysfunction is associated with mild elevations of serum lipid levels, this may have implications for the management of hyperlipidaemia in children as well as in adults. It is unclear whether treatment of patients with elevated triglycerides, including those with familial LPL deficiency, has beneficial effects on immune function. In particular, it would be of interest to know whether alipogene tiparvovec (Glybera, AMT-011, AAVI-LPLS477X), a $Ser^{447}X$ variant of the human LPL gene in an adeno-associated virus vector, developed as an intramuscular gene therapy for the treatment of LPL deficiency,[24] alters immune function in children with elevated lipid levels, including those with familial LPL deficiency. Further research in this area may assist in identifying children and adults at risk of immune dysfunction secondary to dyslipidaemia, and identify novel or existing therapeutic targets to modify this risk.

Learning points

- This is the first case to hypothesise that lipoprotein lipase deficiency may masquerade as immunodeficiency in the neonatal period, with treatment of hypertriglyceridaemia coinciding with the resolution of recurrent perianal abscesses.
- Further research is required to establish the relationship between hypertriglyceridaemia and immune function.

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Competing interests None declared.

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