CASE REPORT

Hypertriglyceridaemia in adolescents may have serious complications

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Acute pancreatitis is an often-overlooked cause of acute abdominal pain in children and adolescents. Severe hypertriglyceridaemia is an important cause of recurrent acute pancreatitis. Monogenic causes of hypertriglyceridaemia, such as familial chylomicronaemia caused by lipoprotein lipase deficiency, are more frequently encountered in children and adolescents, but remain rare. Polygenic hypertriglyceridaemia is more common, but may require a precipitant before manifesting. With the global increase in obesity and type 2 diabetes, secondary causes of hypertriglyceridaemia in children and adolescents are increasing. We report two cases of severe hypertriglyceridaemia and pancreatitis in adolescent females. Hypertriglyceridaemia improved markedly with restriction of dietary fat. An inhibitor to lipoprotein lipase was found to be the cause in one patient, while in the other limited genetic investigation excluded chylomicronaemia owing to deficiency of lipoprotein lipase, its activators and processing proteins.

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Acute pancreatitis due to severe hypertriglyceridaemia should be considered in children and adolescents presenting with acute abdominal pain. Unrecognised recurrent hypertriglyceridaemic pancreatitis may cause significant morbidity and mortality, and early recognition and appropriate referral to specialised clinics is advisable to prevent complications. Lipaemia noted on a laboratory report should be investigated.

This report presents two adolescent females with diabetes mellitus (DM), hypertriglyceridaemia and acute pancreatitis. Hypertriglyceridaemic pancreatitis is an often-overlooked cause of acute abdominal pain, especially in children and adolescents. The first patient developed DM after recurrent episodes of pancreatitis and severe pancreatic destruction. The second developed acute hypertriglyceridaemic pancreatitis as a result of poorly controlled DM. The first patient has polygenic hypertriglyceridaemia and the second patient has an inhibitor to lipoprotein lipase (LPL). Both patients responded well to dietary fat restriction.

Case presentations

Case 1

A 12-year-old lean girl of normal stature presented to a peripheral hospital with recurrence of abdominal pain, 5 months after an appendicectomy for presumed appendicitis; however, the appendix had been histologically normal. The serum was grossly lipaemic on admission. On the 3rd day of admission, the triglyceride (TG) level was 12.6 mmol/L, total cholesterol 5.9 mmol/L and high-density lipoprotein cholesterol 0.3 mmol/L. The patient responded to intravenous fluid therapy and was discharged.

One month later the patient was readmitted to the peripheral hospital with acute pancreatitis based on epigastric pain and tenderness, and elevated serum lipase activity (140 U/L (normal 4 - 29)), amylase (94 U/L (normal 19 - 76)) and C-reactive protein (CRP) (131 mg/L (normal <10)). The serum was again lipaemic and the TG level was 37.8 mmol/L. The patient improved and was discharged, only to be readmitted 4 months later with similar symptoms. She was transferred to Tygerberg Hospital (TBH) for further investigation of the recurrent abdominal pain. An enlarged head of pancreas was found on an abdominal ultrasound scan. Recurrent pancreatitis was ascribed to hypertriglyceridaemia, although alcohol consumption was considered to be a contributory cause. Chylomicronaemia due to LPL deficiency, a recessively inherited disorder, was suspected. Fasting lipid profiles of her parents were normal. A fat-restricted diet, supplemented by medium-chain TG, was advised on discharge.

The patient attended TBH for treatment of acute-on-chronic pancreatitis with multiple pancreatic cystic collections, which required drainage. Splenic vein thrombosis was also noted on a computed tomography scan. Adherence to the low-fat diet was difficult, at least in part because of socioeconomic factors, and the TG level remained elevated (38.2 mmol/L). The patient was therefore referred to a paediatric care facility, with a request for continuation of a fat-restricted diet and advising the use of medium-chain TGs to substitute for some of the fat intake.

One year later, after three further hospital admissions with acute pancreatitis, the patient presented to the paediatric emergency unit at TBH in diabetic ketoacidosis (DKA): the capillary blood glucose level was >27.8 mmol/L, the β-hydroxybutyrate level was 6.9 mmol/L (normal <0.6), venous blood gas analysis revealed a pH of 7.23 (normal 7.31 - 7.41), the partial pressure of carbon dioxide (pCO_2) was 3.5 kPa (normal 5.5 - 6.8), and standard bicarbonate was 13.1 mmol/L (normal 23 - 29). After acute management with insulin

and intravenous fluids, she commenced a subcutaneous insulin regimen comprising human soluble and neutral protamine Hagedorn (NPH) insulin at a total dose of 1.5 U/kg/d. The anti-glutamic acid decarboxylase and islet antigen 2 antibody combo test was negative. The fasting serum C-peptide level at diagnosis was 0.3 µg/L (normal 1.1 - 4.4), but normalised 10 months later (2.1 µg/L). As her blood glucose control was good (glycated haemoglobin (HbA1c) ranging between 5.0% and 5.8%), the insulin dosage was reduced to 0.8 U/kg/d. The patient returned home after a short stay at a paediatric care facility, with a serum TG level of 1.28 mmol/L. Four months later, she presented to the peripheral hospital with hypoglycaemia and a fasting C-peptide level of 3.0 µg/L. She was not adherent to a very low-fat diet, and the serum TG level was 2.15 mmol/L. However, there were no symptoms of malabsorption, and this was confirmed by faecal elastase and steatocrit testing.

The clinical course and TG results of case 1 are summarised in Fig. 1. In case 1, the TG level varied between 1.3 and 71 mmol/L.

Case 2

A 15-year-old overweight girl, known to have had type 2 DM for 4 years, also had non-alcoholic fatty liver disease, hypertension, and a previous fasting TG level of >12 mmol/L. Her management included lifestyle modification, metformin, insulin, bezafibrate and enalapril, but glycaemic control remained suboptimal (HbA1c 11.8%). Right-sided abdominal pain and constipation prompted re-attendance at the hospital. On physical examination, she had a body mass index of 26.0 kg/m² (95th percentile on the UK body mass index chart) and acanthosis nigricans, but neither eruptive xanthomas nor features of lipodystrophy were present. Abdominal examination revealed hepatomegaly of 3 cm and palpable faeces. The capillary blood glucose level was 22.1 mmol/L, and the β-hydroxybutyrate level was 3.7 mmol/L. Urinalysis showed 4+ glycosuria and 4+ ketonuria. Venous blood gas could not be measured owing to severe lipaemia. The uncorrected serum sodium level of 116 mmol/L was ascribed to pseudohyponatraemia.[1] The sample was insufficient for TG measurement, but the lipaemic index was 4+. In a follow-up specimen, serum TG levels were found to be 100.0 mmol/L after a 1:50 dilution. She

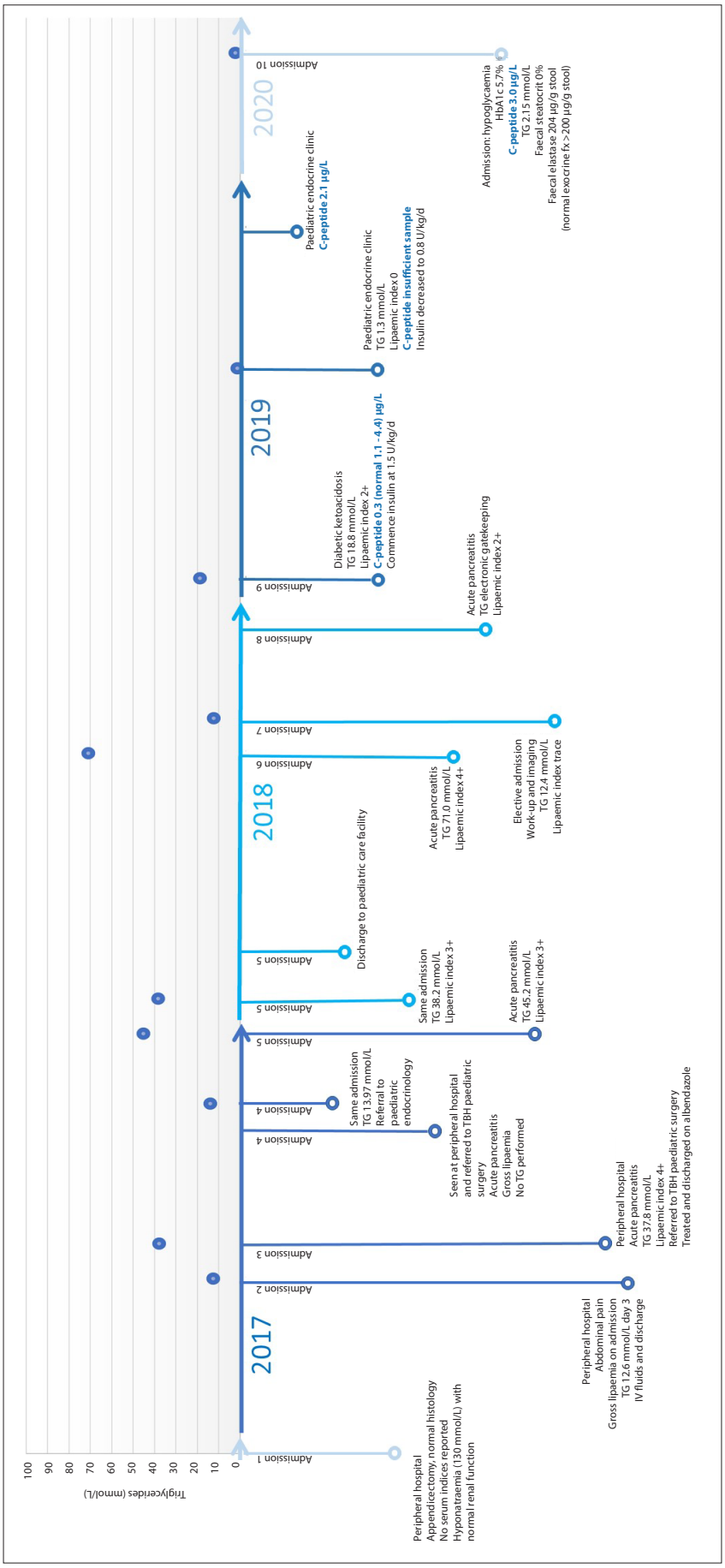

Fig. 1. Clinical course and triglyceride results in case 1. (TG = triglycerides; IV = intravenous; TBH = Tygerberg Hospital; HbA1c = glycated haemoglobin; fx = function.)

was clinically euthyroid, with a biochemical profile compatible with euthyroid sick syndrome.

The patient was treated for DKA with hourly subcutaneous insulin, and her hyperglycaemia speedily recovered. The hypertriglyceridaemia was treated with a 'rescue diet' of <10 g of fat per day and supplemented with medium-chain TGs. Bezafibrate was continued, the insulin therapy was optimised, and the family was re-educated regarding adherence to management. The lipid profile of her obese mother was suggestive of a metabolic error in TG metabolism (TG 5.27 mmol/L), while her father had a desirable lipid profile. As family support of the strict diet could not be ensured, the child was referred to a paediatric care facility. Six months later she was admitted with her first attack of acute pancreatitis and a serum TG level of 29.3 mmol/L. She did not have DKA during this presentation: arterial pH 7.41 (normal 7.35 - 7.45), pCO_2 4.72 kPa (normal 4.26 - 5.99) and bicarbonate 22 mmol/L (normal 19 - 24). A low-fat diet was re-established together with improving glucose control.

The clinical course and routine lipogram results of case 2 are summarised in Fig. 2. In case 2, the TG level varied between 9.2 and 100 mmol/L.

Investigations

All routine analyses were performed in ISO15189 accredited laboratories in the National Health Laboratory Service. TG analyses were performed using the TRIGL assay (no glycerol blanking step) on the Roche cobas 6000 analyser (Roche Diagnostics, Germany) at TBH. Total cholesterol, CRP, lipase, and serum indices were also determined on this analyser. HbA1c was determined with an immunoassay (Roche cobas A1C-3). Point-of-care testing of blood glucose and ketones at TBH was performed on a FreeStyle Optium Neo (Abbott, Australia). Point-of-care urinalyses were performed using RightSign test strips (Biotest, China).

The lipoprotein derangement was investigated further at a research laboratory by performing a non-denaturing gradient gel electrophoresis describing lipoproteins containing apoprotein B.[2] Additionally, post-heparin lipolytic activity from the patients was determined by measuring the change in turbidity of a lipid emulsion.[3] Ultraviolet light is most sensitive to the change in micellar size over 2 hours compared with a baseline. A standard curve is derived by mixing pooled pre- and post-heparin samples from six healthy normolipaemic volunteers. Mixing post-heparin samples of healthy volunteers with a patient's plasma corrects apolipoprotein C-II (apoC-II) deficiency. In autoimmune inhibition of LPL, the patient's pre-heparin plasma inhibits the activity of LPL in control post-heparin samples.

Locally prevalent mutations in LPL, apoC-II, apoprotein A-V (apoA-V), glycosylphosphatidylinositol-anchored high-density

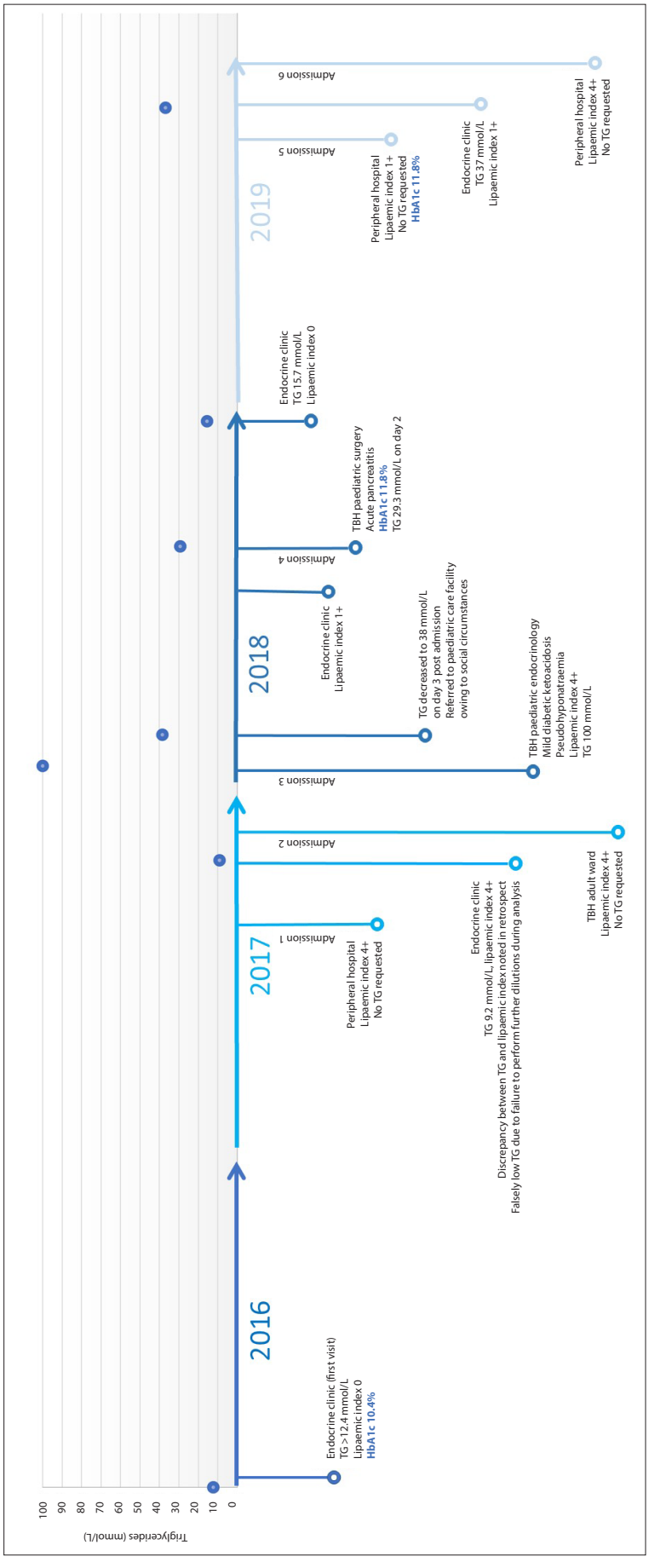

Fig. 2. Clinical course and routine lipogram results in case 2. (TG = triglycerides; HbA1c = glycated haemoglobin; TBH = Tygerberg Hospital.)

lipoprotein-binding protein 1 (GPIHBP1) and lipase maturating factor 1 (LMF-1) were sought by polymerase chain reaction testing and high-resolution melting.

Results

The first lipoprotein electrophoresis in case 1 demonstrated large TG-rich lipoproteins (chylomicrons and large very low-density lipoprotein (VLDL)) and neither intermediate-density lipoprotein (IDL) nor low-density lipoprotein (LDL). These findings indicate that triglyceride-rich lipoproteins were not undergoing significant lipolysis and VLDL was not processed to LDL. At the patient's last admission, the electrophoresis revealed that LDL, though of small size, was the dominant lipoprotein, but some large VLDL remained present. The in-house LPL assay initially demonstrated <10% LPL activity when compared with normal plasma, but performing such an assay on grossly lipaemic plasma is not ideal. At her last admission, the plasma was clear, and the LPL assay revealed activity between 20% and 30%, suggesting that there is impaired lipolysis that makes her vulnerable to hypertriglyceridaemia under dietary and/or metabolic stress.

The discrepancy of the TG level in 2017 (9.2 mmol/L) compared with the lipaemic index (4+) is unexplained, but the reported result was near the upper limit of the assay (measuring range 0.1 - 10.0 mmol/L) and may not have been diluted for a more accurate TG level to be obtained. The lipaemic index is a semi-quantitative measurement of serum turbidity and is reported on laboratory reports as part of the serum indices (haemolysis, icterus and lipaemia).

The lipoprotein electrophoresis in patient 2 demonstrated large TG-rich lipoproteins with possible remnant lipoproteins (IDL), and LDL was detected. The presence of LDL excludes complete LPL deficiency. The patient's LPL activity was ~12% of heparin-activated normal plasma. The complementation assay with normal plasma excluded apoC-II deficiency. The patient's pre-heparin plasma partially inhibited LPL activity of post-heparin normal control plasma, suggesting an inhibitor that is most likely to be an antibody as part of autoimmune disease.

No pathogenic variants were identified in either patient by exon-by-exon analysis of LPL, apoC-II, apoA-V, LMF-1 and GPIHBP1.

Discussion

The purpose of this article is to raise awareness of hypertriglyceridaemia causing abdominal pain and pancreatitis. The incidence of pancreatitis is increasing in children and adolescents, possibly owing to increased awareness.[4,5] Hypertriglyceridaemia from multiple causes may also precipitate pancreatitis, and hypertriglyceridaemia-associated pancreatitis confers a worse prognosis than other causes.[6] While LPL deficiency may present with pancreatitis caused by hypertriglyceridaemia in infancy, pancreatitis in childhood is more commonly due to other causes, including worm infestations and biliary pancreatitis.[7] In adolescence, hypertriglyceridaemia may again be a more important cause for abdominal pain and pancreatitis.

The experience with these two patients highlights several important points. Unless hypertriglyceridaemia is considered or noted in laboratory reports indicating lipaemia or severe hypertriglyceridaemia, there may be a long delay in diagnosis, and several recurrent episodes of pancreatitis will disrupt schooling and could result in significant hospitalisation, long-term sequelae of malabsorption and DM, and may even prove fatal. Secondary causes that could precipitate severe hypertriglyceridaemia in susceptible adolescents include obesity, an increasingly fatty diet, alcohol intake, retinoids for skin conditions (by influencing transcription of metabolically related genes), oral contraceptives and autoimmune disease, especially in females.[8] Adolescent girls may also become pregnant, and severe hypertriglyceridaemia may be caused by increased VLDL production in response to rising oestrogen levels in the second trimester.[9]

In our first case, no formal diagnosis was made to explain the severe hypertriglyceridaemia that resulted in recurrent pancreatitis with consequent cysts and even splenic vein thrombosis. While it is possible that a fatty diet together with alcohol contributed to her hypertriglyceridaemia, it is likely that her metabolism was more vulnerable with some impairment of LPL activity, probably on a polygenic basis.[10] Primary causes of severe impairment of the lipolytic system for TG-rich lipoproteins are recessively inherited in the following genes. LPL is the commonest gene involved and has been reported in the South African (SA) experience.[11] LMF-1 is required to assemble two LPL proteins before GPIHBP1 can transport the dimeric LPL to the endothelium for it to be activated by apoC-II and apoA-V.[12]

The first patient probably represents a case of multifactorial chylomicronaemia, but a formal polygenic score was not undertaken because it is costly and may not change management significantly.[10,13] In the second patient, it is likely that autoimmune disease targeted LPL or GPIHBP1 to cause severe hypertriglyceridaemia, which was exacerbated by poorly controlled DM. Dietary fat intake can vary among people, but relatively small amounts can cause a significant overload in patients with impaired LPL activity. Drastic reduction of intake to <10 g per day can therefore result in dramatic improvement within days, but is difficult to adhere to in the long term. Subsequent management should still restrict intake to ~30 - 40 g daily in adults. Minimising the contribution of secondary causes to hypertriglyceridaemia, especially poorly controlled DM, is also vital for best outcome. Insulin has a powerful suppressive effect on hormone-sensitive lipase in adipose tissue and in this way limits VLDL production from non-esterified fatty acids released from the adipose tissue to be utilised in the liver.[14,15] Both patients responded well, but significant hypertriglyceridaemia persisted in the patient with suspected autoimmune hypertriglyceridaemia, who fortunately has remained free of pancreatitis, but may require more drastic treatment in the future.

Management of severe persistent hypertriglyceridaemia can be challenging. In the case of severe acute pancreatitis, plasmapheresis may lower the TG level dramatically, but the high turnover of VLDL and the reintroduction of food will rapidly cause a rebound hypertriglyceridaemia. Severe dietary fat restriction as mentioned above is effective, but oil intake in the form of medium-chain TGs may improve palatability without increasing chylomicron production.[16] When there is residual LPL activity, fibrates may add benefit beyond a fat-restricted diet. Up-regulation of LDL receptors by statins improves uptake of LDL, usually absent in severe hypertriglyceridaemia, but does not affect the clearance of chylomicrons and VLDL, which are the cause of severe hypertriglyceridaemia. Infusion of fresh-frozen plasma at critical times of severe hypertriglyceridaemia and impending pancreatitis could supply apoC-II to act as co-factor for LPL in homozygous apoC-II deficiency. Infusion of heparin-activated donor plasma was partially successful in one unreported case of proven LPL deficiency (personal communication). Angiopoietin-like 3 inhibitors are a promising novel treatment that enhances clearance of triglyceride-rich lipoproteins, but are only available in research centres in SA.[17] Gene replacement therapy by intramuscular injection of alipogene tiparvovec (Glybera) has been investigated, but is not available on the market. The prevention of chylomicron assembly by microsomal triglyceride transfer protein inhibitors unfortunately causes fat malabsorption and hepatic steatosis.[18]

Pancreatic lipase inhibitors (lipstatin) decrease the hydrolysis of dietary fat in the gut, but may cause steatorrhoea.[19] In cases of severe autoimmune LPL inhibition, a series of plasma exchanges may improve the hypertriglyceridaemia when diet and fibrates are inadequate.[20] Rituximab can effectively suppress the production of antibodies, while immunosuppression with corticosteroids and cyclophosphamide is less effective.

Our patients demonstrate that eruptive xanthomas, a sequel of severe hypertriglyceridaemia, may not precede the onset of pancreatitis. The importance of interpreting laboratory reports related to hypertriglyceridaemia must be stressed, as the risk of pancreatitis becomes significant with levels exceeding 10 mmol/L.[21] Hypertriglyceridaemia >25 mmol/L requires urgent attention to avoid pancreatitis. The TG levels can change dramatically with fat intake in persons with impaired LPL activity. Within hours after ingestion, 85 g (100 mmol) of TG (e.g. 90 mL vegetable oil) can raise the plasma TG level by 33 mmol/L in an adult with no LPL activity. During starvation (before surgical procedures or with decreased intake due to vomiting), TG levels can decrease significantly within days and the association with pancreatitis may be overlooked. The lipaemic index is a crude indicator of turbidity, but should nevertheless alert the clinician to hypertriglyceridaemia and its risks. Severe hypertriglyceridaemia may affect several laboratory investigations, e.g. pseudohyponatraemia.[1,22] Glycerol kinase deficiency causing pseudohypertriglyceridaemia, in which laboratory results report hypertriglyceridaemia in the absence of turbidity and excess lipoproteins, is a rare disorder resulting in high plasma glycerol levels. Since glycerol is generated in the TG assay, the condition causes a falsely high TG level. Excess glycerol ingestion may also cause pseudohypertriglyceridaemia without turbidity or lipaemia.[23,24]

The triad of DKA, hypertriglyceridaemia and acute pancreatitis has been described in previous cases.[25,26] DKA can cause hypertriglyceridaemia and acute pancreatitis, but DKA can also be the result of acute pancreatitis and hypertriglyceridaemia. Insulin deficiency in DKA may cause increased TG levels as a result of increased lipolysis in adipocytes, which may trigger acute pancreatitis by an increased output of triglyceride from the liver.[26] Acute pancreatitis may precipitate transient insulin deficiency, which resolves within a few months after presentation.[27,28] In our first case, severe acute pancreatitis caused hyperglycaemia that resolved within 10 months. Recurrent acute pancreatitis can progress to chronic pancreatitis with chronic abdominal pain, exocrine pancreatic insufficiency or DM.[29] The second patient was known to have poorly controlled type 2 DM and hypertriglyceridaemia. Poor control of both conditions triggered acute pancreatitis.

The experience with these two cases with severe metabolic derangements highlights the problem of the diagnosis and management of metabolic disorders in SA. Ideally, such patients should be referred for expert evaluation at a (regional) dedicated clinic for achieving best control promptly and arranging the best possible management in the community. A national specialised laboratory would provide the necessary diagnostic support and relevant research to improve insight into local metabolic diseases.

Conclusion

Pancreatitis caused by hypertriglyceridaemia must be recognised as a potential cause of acute abdominal pain in all patients at any age. Hypertriglyceridaemia >10 mmol/L or an increased lipaemic index is an important finding. Polygenic hypertriglyceridaemia (multifactorial chylomicronaemia) and secondary causes are far more common than monogenic forms or familial chylomicronaemia after infancy. Importantly, severe hypertriglyceridaemia from any cause may precipitate pancreatitis. Given the potential severe sequelae of pancreatitis and the recurrent nature of pancreatitis with uncontrolled hypertriglyceridaemia, there is a great need for dedicated clinical and laboratory expertise to manage patients, including adolescents, with severe hypertriglyceridaemia.

Teaching points

- Lipaemic serum or plasma should be taken seriously.
- Recurrent pancreatitis due to hypertriglyceridaemia can be avoided by appropriate intervention.
- Dietary fat restriction is the key to successful treatment of hypertriglyceridaemia.
- Identification of the cause of hypertriglyceridaemia may permit more specific intervention.
- Referral of patients with severe hypertriglyceridaemia to specialised clinics with dedicated laboratories affords the best opportunity to avoid recurrent pancreatitis.

Patient consent. Informed consent was obtained from both patients. The Health Research Ethics Committee of Stellenbosch University approved this case report (ref. no. S19/10/269).

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