Rare disease

'A lipaemic mystery': a patient with hypertriglyceridaemic pancreatitis and cerebral infarction

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Summary

Hypertriglyceridaemia (HTG) causes up to 10% of all cases of acute pancreatitis (AP). It is the third most common cause after gallstones and alcohol. Despite this frequency, there are no clear guidelines for its specific management, mainly due to the paucity of evidence. The authors present a case and discussion of hypertriglyceridaemic pancreatitis (HTGP) complicated by an acute cerebral infarct. The patient's subsequent death secondary to cerebral infarction opens the discussion as to whether HTG should be more urgently treated.

BACKGROUND

This case highlights the serious pathological effects of hypertriglyceridaemia (HTG), which can result in serious sequelae from acute pancreatitis (AP) to cerebral infarction. A hypercoagulable state has been reported in diabetic ketoacidosis, which may have contributed to this lady's demise.

From a review of the current expert opinion and the evidence, there are no clear evidence based guidelines for the management of AP secondary to HTG. The current consensus is to use insulin and heparin, but with caution in using heparin given the controversy in its mechanism of action. The role of plasma exchange is controversial and the most convincing results have been reported in the acute setting, however triglyceride (TG) levels in most patients fall upon starving so the proposed mechanism is unclear.

The chronic phase of treatment is important to prevent TG levels from rising with lifestyle advice and medications.

CASE PRESENTATION

A 37-year-old Scandinavian lady presented to casualty with a 24 h history of severe epigastric pain and vomiting. She had no previous medical history and was not on any medication. She did not smoke, rarely consumed alcohol and volunteered no relevant family history. On examination, she was somnolent but easily rousable. She was sweaty and hyperventilating, but was otherwise haemodynamically stable. On examination, she was tender to the epigastrium but there was no evidence of peritonitis. There were no masses or organomegaly palpated on examination of the abdomen.

INVESTIGATIONS

Her blood glucose was raised at 25 mmol/l; arterial pH was 7.25 with a bicarbonate of 18 mmol/l, base excess

10 mmol/l and lactate 3 mmol/l. Her urinalysis was positive for ketones. Chest x-ray was unremarkable, and abdominal x-ray showed faecal loading. While in casualty she was initially treated as a suspected new diagnosis of diabetic ketoacidosis with intravenous fluid resuscitation and an insulin sliding scale. She also received 5000 IU of prophylactic subcutaneous dalteparin. However, her blood samples were visibly lipaemic, with the turbidity making blood samples difficult to process in biochemistry (figure 1). Her initial haemoglobin was 11.9 g/dl, white cell count $19.85 \times 10^9/l$ (neutrophils $17.11 \times 10^9/l$), platelets $184 \times 10^9/l$, amylase 1085 IU/l, alanine aminotransferase (ALT) 6 U/l, alkaline phosphatase (ALP) 63 U/l, albumin 22 g/dl, and calcium 1.65 mmol/l. In view of her lipaemic blood sample and raised amylase, a lipid profile was requested which showed a serum TG level 20.0 mmol/l and serum cholesterol level 38.4 mmol/l. This helped confirm a diagnosis of hypertriglyceridaemic pancreatitis (HTGP). Based on initial assessment, the patient scored 2 on the Ranson criteria, indicating a low chance of mortality (<2%) related to her HTGP. As a result of the severely lipaemic biochemistry samples, further complete assessment of this scoring was not possible. However, there was no evidence of organ dysfunction. On further questioning, she recalled that her father had high cholesterol but she had never been tested for this before.

A CT abdomen and pelvis with contrast was performed within 48 h. This showed extensive inflammatory change in the peripancreatic fat and upper abdomen with a small amount of free fluid. There was also non-enhancement in the body of the pancreas. This was in keeping with an AP with necrosis (figure 2).

OUTCOME AND FOLLOW-UP

She improved clinically over the next few days with hourly observations, careful fluid balance, an insulin sliding scale,

Figure 1 Lipaemic initial blood sample.

analgesia and prophylactic low molecular weight heparin. Three days later, her acidaemia had resolved and she was mobilising short distances. However, the following morning she was found collapsed and unconscious on the ward. She was intubated and taken to intensive care. A cranial CT angiogram demonstrated a hyperdensity in the basilar artery in keeping with an acute thrombus (figure 3). She underwent emergency angioplasty and stent insertion of her basilar artery. Despite obtaining a good angiographic

Figure 2 CT abdomen with contrast. Black arrow indicates central area of necrosis within the body of the pancreas. White arrow indicates surrounding inflammation.

Figure 3 CT head with contrast. Arrow indicates hyper density in left basilar artery.

result she did not recover. Further imaging demonstrated bilateral thalamic and extensive pontine cerebellar infarction. Her poor neurological outcome was discussed with her family and medical staff and the decision was made to withdraw ventilatory support 8 days post admission.

DISCUSSION

HTG causes up to 10% of all cases of AP, and up to 50% of gestational cases.¹ It is the most common aetiology of AP after alcohol and gallstone-induced disease. Pancreatitis

is thought to be triggered when TG levels exceed 11.3 mmol/l.² Secondary disorders of metabolism are the most common cause of HTG. These most commonly include diabetes and alcohol, but also a number of medications.

Primary causes of HTG are rare and are mainly genetic, centred on the activity of lipoprotein lipase (LPL). When LPL activity is impaired, TGs in chylomicrons/very low density lipoprotein are not broken down and accumulate in the blood stream. The best-characterised genetic defects are LPL deficiency and apoCII (a cofactor for LPL), which often present in childhood as Friedreich's chylomicronaemia syndrome type 1. ApoA5 gene and GPIIIBP1 have been characterised in a small number of reports.³ In adults, HTGP is likely to be plurigenetic in origin with a strong impact of environmental and lifestyle factors.

There are no clear guidelines for the management of pancreatitis secondary to HTG, but the treatment is traditionally separated into acute and chronic management.

Acute management

The management of AP is to establish the aetiology, exclude gallstones and alcohol as major causes, and investigate if other causes of AP are present. The patient should be kept nil by mouth, hydrated with intravenous fluids and given appropriate analgesia.¹ TG levels fall fast, so it is important to measure these early if suspected.

If HTG is the cause, often there biochemical analysis may demonstrate a spurious pseudohyponatraemia secondary to HTG. However, the concentration of sodium in the plasma is normal. TGs also interfere with certain amylase assays, so amylase levels may be reported as falsely low. Pancreatic lipase activity might be helpful in this case if pancreatitis is suspected.

In most centres, insulin and heparin have been the mainstay of treatment. However, there have been no controlled trials and evidence is from case reports. Insulin activates LPL so is considered helpful in lowering the HTG in both non-diabetic and diabetic patients.¹ Heparin stimulates the release of endothelial LPL into the circulation. However, heparin is subject to greater controversy since there is a transient rise in LPL followed by increased degradation and depletion of plasma stores resulting in LPL deficiency.⁴ In 2009, Cole⁵ listed the evidence for use of heparin versus insulin, which amounted to 9 case reports, only 2 of which just used insulin. A total of 23 patients were involved in all nine reports, reducing the power of the studies. The distinct effects of the two therapies in HTAP are therefore uncertain.

A number of case reports have demonstrated that an acceleration of TG removal can be achieved through plasma exchange.^{6–8} However, the expense of plasma exchange limits its use. Furthermore, TG levels fall quickly in most patients on starving. Therefore the subgroup of patients who have persistently high TG levels may benefit.⁶ However, since the treatment does not work on the underlying cause, plasma exchange may not be definitive.

Chen *et al*⁶ presented the largest study of its kind on plasmapheresis to treat AP. Two groups of patients with HTG

and AP with a Ranson score over 3 were compared. One received apheresis (10 patients) and the other did not (19 patients). No benefit could be found on the rate of overall mortality and complications.

Chronic management

Once the AP has been treated, the first step should be to treat the any underlying disorder and to stop any offending medication.^{1–3} The long-term treatment of HTG should consist of lifestyle advice if necessary in combination with lipid lowering drugs. Lifestyle changes include low calorie intake and low alcohol ingestion. Weight loss is known to result in a decrease of TG by about 22%.³ A diet high in mono- and polyunsaturated fat, supplementation of n-3 fatty acids, increased physical activity and cessation of smoking may improve lipid levels. Medications such as statins, fibrates, niacin and ω 3 fish oils have been shown to reduce TG levels by up to 40% in trials.¹ Combinations may be more effective than individual drugs.

In cases of severe HTG, a genetic cause should be considered.³ It follows that children are more likely to present with extremely high TG levels due to genetic deficits, whereas environmental factors are more likely to affect an adult's presentation. Patients with severe HTG should be referred to a geneticist for LPL genotyping and LPL cofactor assessment.¹

Research into some of the more resistant cases has included prophylactic apheresis.⁶ Piolot *et al*⁹ presented two case reports of patients with LPL deficiencies that were resistant to treatment with lifestyle modifications and oral medications. They found that 4 weekly plasmapheresis treatments significantly reduced their TG levels and incidence of pancreatitis. A criticism to this study would be that such patients would need continual and indefinite treatment, which would not be possible in most centres.

Recent research has focused on the prospect of gene therapy for LPL deficiency. Strokes *et al*⁹ created an adenovirus vector with LPL gene, and injected it into leg muscles of 8 LPL-deficient patients. They found initially that the levels of TGs all fell and remained low up to 36 weeks. However, on long term follow up (18–31 months) the levels of TGs were all higher with less LPL activity than before the trial started. They found antibodies against the viral capsid proteins, but not against LPL, so conjecture that this may be related to an immune response.

This case clearly highlights the serious pathological effects of hypertriglyceridaemia, which can result in serious sequelae from AP to cerebral infarction. Various pharmacological therapies have been shown to have proven benefits in cases of HTG, although for rapid improvement in TG level, apheresis may provide the best clinical outcome. To direct this resource best, rapid diagnosis of HTG needs to be made, including clear identification of those with genetic disorders of lipid metabolism. Once, HTGP is identified, physicians need to be aware of apheresis as a possible treatment option, although further randomised controlled trials are needed to fully establish its true efficacy and benefits.

Learning points

- ▶ It is essential to exclude secondary causes of pancreatitis in those presenting with the clinical features of AP.
- ▶ Assessment of organ dysfunction in admission is crucial in a patient presenting with AP. Assessment of Ranson criteria can also be a useful in predicting the severity of AP.
- ▶ The acute management of HTGP is the same as for other causes of Pancreatitis with insulin and heparin, but note controversy over heparin.
- ▶ Frequent assessment of TG levels is important. Clinicians should consider plasmapheresis for those resistant cases, not responding to first line treatments.
- ▶ Always consider other consequences of HTG such as cardiovascular sequelae.
- ▶ Consider genetic screening of family members if HTG is diagnosed.

Competing interests None.

Patient consent Obtained.

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