Acute Pancreatitis Secondary to Severe Hypertriglyceridaemia in a Patient with Type 1a Glycogen Storage Disease: Emergent Use of Plasmapheresis

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Abstract Acute pancreatitis is a well-recognised complication of hypertriglyceridaemia. High serum triglycerides may develop in the autosomal recessive disorder glycogen storage disease (GSD). Plasmapheresis has been effective in reducing triglyceride levels in pancreatitis secondary to other conditions but not previously described in GSD. We describe a 16-year-old male with type 1a GSD who presented with severe abdominal pain, tachycardia and tachypnoea. Abdominal computed tomography (CT) demonstrated acute pancreatitis. Serum triglycerides were 91.8 mM. Despite intravenous fluids and morphine sulphate, he remained seriously ill, and plasmapheresis was therefore started. After daily plasma exchange for 6 days, triglyceride levels dropped to 5 mM. This was associated with a rapid resolution of pancreatitis. Plasmapheresis is effective in rapidly reducing hypertriglyceridaemia from numerous causes, including glycogen storage disease, and may facilitate recovery from acute pancreatitis.

Introduction

Type 1a glycogen storage disease (GSD) is an autosomal recessive disorder, characterised by fasting hypoglycaemia, hepatomegaly and growth retardation, presenting typically in the first 3–4 months of life (Froissart et al. 2011).

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Deficiency of glucose-6-phosphatase prevents conversion of glucose-6-phosphate to glucose. Intermediaries and alternate pathways lead to the deposition of glycogen and use of alternate fuels. This can lead to severe hypertriglyceridaemia (Wolfsdorf and Weinstein 2003).

We describe a 16-year-old boy with type 1a GSD who developed severe pancreatitis secondary to hypertriglyceridaemia, successfully treated in the acute phase with plasmapheresis. We discuss the possible role of plasmapheresis in the acute management of life-threatening sequelae of hypertriglyceridaemia. We believe this is the first reported use of plasmapheresis in GSD.

Patient Report

A 16-year-old Caucasian boy of non-consanguineous parents regularly attended our service for management of type 1a GSD. Initial presentation was at the age of 3 months, with notably lipaemic serum during an intercurrent vomiting illness. The diagnosis was suggested by an increase of triglycerides and cholesterol, and liver biopsy analysis showed absent glucose-6-phosphatase activity. Genotyping was not a standard practice in the era of diagnosis.

Long-term childhood management included regular 2–3 hourly feeds of uncooked cornstarch and carbohydrate-based food aiming to provide 1.5–2 g/kg carbohydrate and overnight gastrostomy feeds with Maxijul (latterly Vitajoule) delivering 0.2 g/kg/h for 12 h and allopurinol. Growth was adequate, but from the age of 3 years onwards, weight remained persistently on or above the 97th centile. Development was normal. Glycosade was trialled at the age of 12 years and was useful in lengthening the interval in daylight intake to 3.5 h but did not change

Fig. 1 (a) Cholesterol and triglyceride trends 3 years prior to admission. (b) Cholesterol and triglyceride trends with administration of plasmapheresis

the need for overnight glucose or improve serum triglycerides (Fig. 1a). Atorvastatin and bezafibrate were introduced at age 13 following an acute rise in cholesterol and triglycerides, with resolution to the previous (still elevated) baseline (Fig. 1a). Multiple short-term elective hospitalisations throughout childhood confirmed an absolute requirement for supplements, with the most recent occurring 2 months prior to his acute presentation. Triglyceride and cholesterol controls were suboptimal for much of the paediatric time course with uncertainty regarding dietary concordance by the family (Fig. 1a). Shortly prior to admission, lipid control deteriorated with persistent hypertriglyceridaemia (70 mM, normal <1.7 mM) and hypercholesterolaemia (21 mM, normal <5.2 mM).

He then presented acutely with severe abdominal pain. He was tachycardic (130/min) and tachypnoeic (40/min) and required 1 l of oxygen to maintain his saturations above 95%. Abdominal computed tomography (CT) demonstrated extensive inflammatory changes in the peritoneum and retroperitoneum, consistent with a radiological diagnosis of acute pancreatitis, though the pancreas itself appeared normal. Serum triglycerides and cholesterol were markedly elevated at 91.8 mM and 28.3 mM, respectively.

He was initially managed with intravenous fluids with 10% dextrose to reduce glycogenolysis and intravenous morphine sulphate for analgesia. He received 10% dextrose at 5 ml/kg/h for the first few hours of admission and then at a rate sufficient to correct for 5% dehydration over 48 h. In view of ongoing severe symptoms and mortality risk, plasmapheresis was performed on an Aquarius System

(Baxter industries). Five percent human albumin solution was used to exchange 3 l with a final infusion of Octaplas 600 ml at the end of each session. Despite the marked viscosity of the patient's plasma, there were no issues with filtration, and the circuit did not require replacement during any session.

Within 48 h, after two sessions, the patient reported improvement in pain scores, and his tachypnoea and tachycardia settled. TG, cholesterol and CRP levels fell rapidly (Fig. 1b). The macroscopic appearance of his plasma within the machine also cleared. He received daily plasma exchange for 6 days, following which his triglyceride level dropped to 5.0 mM associated with rapid symptomatic resolution of the acute pancreatitis.

Unfortunately he then developed pyrexia. Culture from the central venous catheter identified *Staphylococcus aureus*, so this was removed.

He has not had any further episodes of acute pancreatitis. TGs remain controlled <10 mmol/l, but he has required very high doses of bezafibrate with a significant adverse effect profile. Genetic profiling was undertaken for other dyslipidaemias, but no mutations were identified in *LPL*, *LMF1*, *ApoC2*, *ApoA5* and *GPI-HPB1* and no duplications or deletions in *LPL* MLPA.

Discussion

We report a paediatric patient with markedly elevated triglycerides and cholesterol who developed acute potentially life-threatening pancreatitis. Plasmapheresis was instituted with success to achieve a short-term rapid reduction in hypertriglyceridaemia.

Acute pancreatitis is a recognised complication of hypertriglyceridaemia of any cause; indeed hypertriglyceridaemia is the aetiology in 1.3–3.8% of pancreatitis. Proposed mechanisms include hydrolysis of triglycerides by lipase to free fatty acids with a directly toxic effect on pancreatic acinar cells and elevated serum viscosity from increased chylomicrons predisposing to ischaemia (Kadikoylu et al. 2010; Tsuang et al. 2009; Chen et al. 2004). It is generally accepted that a triglyceride level greater than 11.2 mM (1,000 mg/dl) is needed to precipitate an episode of acute pancreatitis (Kadikoylu et al. 2010; Tsuang et al. 2009; Ewald and Kloer 2012). In our patient, the initial triglyceride level was 91.8 mM (8,123 mg/dl). The chronic management preceding the admission was suboptimal, despite frequent outpatient reviews and discussions.

Conventional management is to reduce triglycerides using lipid-lowering agents, fluids and dietary restriction (Wolfsdorf and Weinstein 2003). However, this is effective over days to weeks as opposed to plasma exchange where the triglyceride level can be significantly reduced in 2–3 h (Tsuang et al. 2009). This may be beneficial in the acute

phase of pancreatitis if the episode is clinically judged to be severe/life-threatening and potentially in acute recurrent pancreatitis, with reported cases of reduction in the frequency of episodes following treatment with plasma exchange (Yadav and Pitchumoni 2003; Stefanutti et al. 2013; Piolot et al. 1996; Kyriakidis et al. 2006).

Plasma exchange has been reported as an effective treatment for reducing serum triglycerides in acute pancreatitis secondary to other causes (e.g. chylomicronemia syndrome (Lennertz et al. 1999), extreme gestational hyperlipidaemia (Saravanan et al. 1996) and drug-induced hyperlipidaemia (Routy et al. 2001)), but we believe it has not previously been described in patients with type 1a GSD. The absence of any randomised controlled trial assessing the role of plasmapheresis in hypertriglyceridaemic pancreatitis has been highlighted (Valdivielso et al. 2014). Consensus guidelines on the use of apheresis suggest a possible role, with caution that a proven benefit on outcome is lacking and that treatment decisions must be individualised (Schwartz et al. 2013). A single controlled trial with historical controls failed to demonstrate superior outcomes, attributed by the authors to delay in initiation of apheresis (Yeh et al. 2003). Recommendations are that plasmapheresis be commenced as early as possible when felt necessary (Ewald and Kloer 2012). In our case, the severity and acuity of the pancreatitis prompted our decision to treat with apheresis within 48 h of admission.

Therapeutic plasma exchange is not without risk (Schwartz et al. 2013; Sanford and Balogun 2011). Central venous access is required, with the potential for catheter-related complications including infection. Apheresis is an extracorporeal procedure requiring suitably trained providers. If serial plasmapheresis sessions are required, consideration must be given to replacement of plasma components. Plasmapheresis may also remove medications, the timing of which may require adjustment in relation to delivery of apheresis. Though the reduction in triglycerides with plasmapheresis may be significant, it is typically transient, and other lipid-lowering strategies should be optimised. Standard of care remains dietary management and medications; plasmapheresis should only be considered when the patient is at a significant risk of imminent clinical harm.

Despite the potential for complications related to the viscosity of the plasma, our patient received a standard plasmapheresis prescription and did not suffer any technical or clinical complications. The only subsequent complication was central venous catheter infection, which was resolved by prompt removal of the infected catheter.

Conclusion

Plasmapheresis is an effective and rapid treatment for hypertriglyceridaemia of a variety of causes and may facilitate recovery in acute severe/life-threatening pancreatitis. This treatment modality appears similarly effective in our patient with a background of glycogen storage disease type 1. Clinicians should consider early short-term use of plasmapheresis in severe acute pancreatitis secondary to hypertriglyceridaemia.

Compliance with Ethics Guidelines

Emma Rivers, Ben Reynolds, Su Bunn, Jayne Straker, Nicola Leech and Heather Lambert declare they have no conflict of interest.

This study does not contain any studies with human or animal subjects performed by any of the authors.

This article has been planned and reported by Emma Rivers and Ben Reynolds, with comments from Su Bunn, Jayne Straker, Nicola Leech and Heather Lambert.

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