Hypertriglyceridaemia; a rare cause for severe acute pancreatitis

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Acute pancreatitis is a common cause for acute abdominal pain. Its aetiology is multifactorial with gallstone disease and alcohol abuse being common causative factors. Hypertriglyceridaemia (HTG) is a rare yet well known cause for acute pancreatitis. HTG pancreatitis (HTGP) is associated with severe multi-organ involvement increasing the morbidity and mortality. Prompt lipid lowering therapy and multi-organ support in intensive care is essential for such patients to achieve a good outcome. However, randomised clinical trials evaluating the efficacy of specific lipid lowering measures for HTGP is lacking due to its relative rarity.

Keywords: Acute pancreatitis; hypertriglyceridaemia; lipid lowering strategies

Introduction

Acute inflammation of the pancreas leading to acute pancreatitis is a common cause of acute abdominal pain.¹ Acute pancreatitis is documented as one of the leading causes of hospital admission for acute abdomen in Sri Lanka.² The incidence in the UK is approximately 56 cases per 100,000 people per year. In 25% of cases, acute pancreatitis is severe and associated with complications such as respiratory or kidney failure, or the development of abdominal fluid collections. In these more severe cases, people often need critical care and a prolonged hospital stay, and the mortality rate is 25%. The overall mortality rate in acute pancreatitis is approximately 5%.

Information regarding the incidence of acute pancreatitis and its outcomes in Sri Lanka is not readily available.²

Disease classification

In 1992, at the Atlanta Symposium consensus was agreed for the classification of severity of acute pancreatitis.³ Better understanding of the pathophysiology of organ failure and necrotising pancreatitis necessitated revision of the Atlanta classification in 2012⁴ and 2016.⁵ Current definitions classify acute pancreatitis as; mild acute pancreatitis, moderately severe acute pancreatitis and severe acute pancreatitis (Table 1).

Table 1 Classification of severity of acute pancreatitis.

Mild acute pancreatitis	No organ failure
	No local or systemic complications
Moderately severe acute pancreatitis	Transient organ failure (resolves within 48 hours) and/ or
	Local or systemic complications without persistent organ failure
Severe acute pancreatitis	One or more local or systemic complications with
	Persistent single or multiple organ failure (>48 hours)

Aetiology

Aetiology of pancreatitis is multifactorial.⁶ Around 50% of cases are caused by gallstones, 25% by alcohol and 25% by other factors.¹ Hypertriglyceridaemia (HTG) is one of the rare yet well-known metabolic causes triggering pancreatitis being most common after gall stones and alcohol.⁷ This review is focused on hypertriglyceridaemic pancreatitis (HTGP). The author has seen and managed 3 new cases of HTGP within a period of 3 years in the UK. In the author's experience it is debatable whether HTG is the cause or an effect of severe acute pancreatitis.

HTG is diagnosed based on a fasting plasma triglyceride concentration above an agreed upper limit and severe HTG is defined as plasma levels more than 1000mg/dL (11.3 mmol/L).⁸ Primary and secondary lipid metabolic abnormalities are associated with HTGP. Risk factors for HTGP include pre-existing lipid disorders (type I, III, IV, and V hyperlipoproteinaemias), poorly controlled diabetes (both type 1, 2 and diabetic keto-acidosis), alcohol abuse, drugs (oestrogens,

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tamoxifen, clomiphene, protease inhibitors, antiretroviral agents, propofol, olanzepine, mirtazapine, retinoids, thiazide diuretics and beta blockers), pregnancy, hypothyroidism and genetic predisposition.⁹

A study of 400 pancreatitis patients revealed HTGP patients are usually younger (average 42 years), have a high BMI, male predominant and having diabetes.¹⁰ The study showed that HTGP patients more frequently developed persistent organ failure compared with patients with non-HTG aetiology. The rate of persistent organ failure increased proportionally with the severity of HTG levels.

Pathophysiology

In acute pancreatitis increased quantities of pancreatic lipases escape into the circulation. These lipases are responsible for breaking down circulating triglycerides into toxic free fatty acids.¹¹ Free fatty acids further damage the pancreas and is causative in precipitating HTGP. Such lipotoxicity increase the severity of severe acute pancreatitis by adding to the inflammatory response due to pancreatitis alone. It could be argued then HTG as an effect of pancreatitis secondary to another aetiology.

Direct activation of toll-like receptors (TLR-2 and TLR - 4) by circulating free fatty acids are also associated with HTGP. Hence, patients with severe HTG are at risk of triggering pancreatitis. This explains how severe HTG could act as a cause for pancreatitis. An objective biomarker to identify the effects of direct lipotoxicity in HTGP has not yet been identified. However, severe hypocalcaemia is identified in several studies associated with HTGP.¹² In the author's experience one patient required a continuous infusion of IV calcium to maintain the ionised calcium levels above 1mmol/L.

Clinical presentation

Patients will present with symptoms and signs of severe abdominal pain, nausea and vomiting as common to pancreatitis of any aetiology. There could be evidence of xanthelasma, xanthomata, hepatosplenomegaly secondary to fatty infiltration and lipaemia retinalis due to chylomicrons in retinal arterioles and venules. Patients with HTGP were more likely to develop persistent multi-organ failure than those pancreatitis patients with normal lipid levels.

Figure 1 Schematic representation of pathophysiology of HTGP.

TGL – Triglycerides, FFA – Free Fatty Acids, CM – Chylomicrons.

Blood investigations will show raised white cell count, CRP levels, amylase and lipase levels as common with pancreatitis. High circulating triglyceride levels will lead to lipaemic serum characterised by milky discoloration of plasma. Lipaemic serum interferes with measurements of serum amylase, sodium and other biochemical parameters indicating falsely values. Special dilution techniques are required to mitigate such interference.⁸

Figure 2

Blood separates into lipaemic serum on standing. Half the volume of blood consists of lipaemic serum. Blood remains without clotting due to severe hypocalcaemia.

Following the diagnosis of pancreatitis on clinical suspicion, raised amylase or lipase levels and CT confirmation a high index of suspicion should be maintained for at risk patients to confirm HTGP. It is important to request early serum triglyceride levels since HTG levels tend to normalise within the first 2-3 days.¹³

Severe hypertriglyceridaemia characterised by serum triglycerides levels of more than 1000 mg/dl (11.2 mmol/L) is suggestive of HTGP.

Figure 3.
Spontaneous separation of lipaemic serum in the blood discard bag of LidCo cardiac output monitor.

Graph 1: Rapid drop of serum triglyceride levels within first few days following the diagnosis of HTGP.

Management

Managing HTGP requires general measures of management as for pancreatitis of any other aetiology including multi-organ support in higher level of care and specific measures to reduce the circulating triglyceride levels.

Specific measures

Evidence from randomised clinical trials evaluating the efficacy of specific measures for HTGP is lacking due to its relative rarity. However, more invasive measures like plasmapheresis is considered in worsening clinical situations.

Lipid lowering pharmacotherapy with fibric acid derivatives should be initiated early when HTGP is suspected. Such treatment is continued upon discharge from hospital with regular lipid level monitoring. One practical difficulty the author encountered is non-availability of intravenous fibrates for these patients. Since these patients are post pyloric fed via naso-jejunal tubes fibrate preparations stable to be used via NJ route should be considered. The author recommends seeking early help from a clinical pharmacist with regards to this.

Insulin is used in HTGP aiming to lower circulating lipid levels.¹⁴ Normally 0.1 to 0.3 units/kg/hour as a fixed continuous infusion is suggested. Blood sugar levels should be monitored hourly and where necessary concurrent dextrose infusion should be commenced to prevent hypoglycaemia. Insulin activates the peripheral tissue bound lipoprotein lipase (LPL) enzyme. LPL breaks down the circulating chylomicron and triglycerides to free fatty acids and glycerol. Insulin also facilitates entry of these products into peripheral tissues and enhances their breakdown reducing the circulating lipid load. Insulin reduces adipocyte fat breakdown by inhibiting the hormone sensitive lipase in adipocytes which further helps to reduce the circulating lipids. In addition to this, insulin helps to achieve normoglycaemia in diabetic patients.

ALBUMIN	(35 - 50)	g/L	*31	*26	*25	*15	*LIPAEMIC	*LIPAEMIC
ALP	(30 - 130)	U/L	110	*LIPAEMIC	78	53	*LIPAEMIC	*LIPAEMIC
ALT	(0 - 63)	IU/L	*LIPAEMIC	*LIPAEMIC	*86	54	*LIPAEMIC	*LIPAEMIC
AMYLASE	(28 - 100)	U/L	*1279	*LIPAEMIC	-	-	*LIPAEMIC	*LIPAEMIC
APTT	(23 - 34)	secs	-	***	-	*42	*171	*147
APTT RATIO			-	-	-	1.4	5.4	4.7
CALCIUM	(2.10 - 2.60)	mmol/L	-	*1.11	*LIPAEMIC	*0.96	*LIPAEMIC	*LIPAEMIC
CALCIUM (CORRECTED)	(2.20 - 2.60)	mmol/L	-	*1.37	*UNSUIT	*UNSUIT	*UNSUIT	*UNSUIT
CREATININE	(60 - 120)	umol/L	69	117	*215	*400	*LIPAEMIC	*LIPAEMIC
HGB	(130 - 180)	g/L	167	166	175	155	*123	*117
INR			***	-	-	1.2	1.0	1.1
LYMPHS	(1.00 - 3.00)	X10 ⁹	-	1.50	-	-	-	1.04
MAGNESIUM	(0.70 - 1.00)	mmol/L	-	-	-	*0.49	*LIPAEMIC	*LIPAEMIC
MCH	(27.0 - 32.0)	pg	*44.9	*44.7	*43.5	*43.1	*40.7	*40.5
MCHC	(310 - 360)	g/L	*399	*395	*379	*378	356	357
MCV	(76.0 - 98.0)	fl	*112.5	*113.1	*114.8	*113.8	*114.4	*113.4
MONOCYTE	(0.20 - 1.00)	X10 ⁹	-	0.30	-	-	-	-
NEUTS	(2.00 - 7.00)	X10 ⁹	-	*9.50	-	-	-	*10.56
PLT	(150 - 450)	10 ⁹ /L	252	228	208	182	*53	*46
POTASSIUM	(3.5 - 5.3)	mmol/L	4.3	4.4	*LIPAEMIC	5.1	*LIPAEMIC	*LIPAEMIC
PROTHROMBIN TIME	(9 - 14)	secs	*UNSUIT	*UNSUIT	-	14	13	13
RBC	(4.00 - 6.50)	X10 ¹²	*3.72	*3.72	4.02	*3.59	*3.01	*2.89
SODIUM	(133 - 146)	mmol/L	133	*131	*LIPAEMIC	138	*LIPAEMIC	*LIPAEMIC
TRIGLYCERIDES	(0.2 - 1.9)	mmol/L	*194.0	-	*171.0	-	-	-
UREA	(2.5 - 7.8)	mmol/L	6.8	*8.5	*LIPAEMIC	*13.4	*LIPAEMIC	*LIPAEMIC
WBC	(4.0 - 11.0)	10 ⁹ /L	*11.8	10.9	*12.0	*12.7	*11.1	*11.6
HCT	(0.401 - 0.541)	L/L	0.418	0.421	0.461	0.409	*0.345	*0.328
MEAN PV	(7.0 - 12.0)	fl	8.8	8.1	8.0	7.8	9.4	9.1

Table 2: Serial blood results of a patient with HTGP. Admission triglyceride level was 194 mmol/L indicating very severe HTG. Most of the blood investigations were unable to perform due to lipaemic serum.

Heparin has been suggested in some case studies, but its benefit in managing HTGP is uncertain. Heparin activates the release of endothelial LPL into the circulation which breaks down the circulating triglycerides into circulating free fatty acids. Even if the circulating lipid levels were lowered the lipotoxicity of circulating free fatty acids could worsen the toxic effects of HTGP.

High volume haemofiltration (HVHF) was compared in a prospective randomised trial over insulin and heparin therapy on a group of patients with HTGP which showed no difference in clinical outcomes.¹⁵ The trial concluded that HVHF can lower HTG levels more efficiently than low molecular weight heparin and insulin therapy, but it is not superior in terms of clinical outcomes and costs.

Plasmapheresis is suggested in clinically deteriorating patient with HTGP. During the extra-corporeal circulation plasma is separated from other components of blood and replaced with albumin or fresh frozen plasma (FFP). Citrate anticoagulation is suggested over heparin for plasmapheresis in HTGP.¹⁶ A study

comparing this demonstrated that the citrate group had significantly lower mortality.

All 3 cases the author encountered were referred to a specialist in metabolic medicine/ chemical pathology to continue long-term management upon discharge. This involved continuation of oral lipid lowering therapy, dietary advice to lower fat consumption, measures to reduce BMI, achieving good glycaemic control and regular follow-up among others.

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