CLINICAL QUIZ (p191) ANSWER

What is the cause of the milky serum and hyponatraemia?

The milky serum is as a result of hypertriglyceridaemia, in relation to combined steroid and asparaginase use. In our patient, the triglyceride level was >50 mmol/L (Reference range: acceptable <1.0 mmol/L, borderline high 1.0-1.5 mmol/L, High >1.5 mmol/L, Very High >5.6 mmol/L, Severely High >11.6 mmol/L). The severe hyponatraemia is due to pseudohyponatraemia secondary to hypertriglyceridaemia which displaces water from plasma and when serum sodium level is measured by the indirect laboratory method. The triglyceride level was controlled to below 10mmol/l with use of insulin infusion and 10% dextrose based intravenous fluid at 120% maintenance rate to maintain adequate hydration, thus reduce chance of hyperviscosity related thrombosis. The serum sodium level rose to above 132 mmol/l on the next day with triglyceride level improved to around 30 mmol/l, which fully normalised on day 5 when triglyceride level was back down to 7.5 mmol/l.

How does the combined use of steroid and asparaginase cause hypertriglyceridaemia?

Asparaginase results in decreased enzymatic activity of lipoprotein lipase, resulting in decreased clearance of triglyceride-rich lipoproteins.[1] In addition, asparaginase also increases endogenous synthesis of very low density lipoprotein (VLDL).[1] On the other hand, systemic corticosteroid therapy increases endogenous production of VLDLs and hepatic cholesterol synthesis.[1] The two drugs work synergistically to cause severe hypertriglyceridaemia.

How common is asparaginase and steroid induced hypertriglyceridaemia and the potential complications?

Mild lipidemic alterations are commonly seen in paediatric patients with acute lymphoblastic leukaemia (ALL) treated with corticosteroids and L-asparaginase. Salvador et al reported 34.5% (41/119) children and adolescents developed hypertriglyceridaemia at two to three weeks of ALL induction therapy.[1] With the recent protocol utilising PEG-asparaginase instead of *E.coli* asparaginase (L-asparaginase), an increased proportion of severe hypertriglyceridaemia has been reported.[2] Severe hypertriglyceridaemia (defined as triglycerides >1000 mg/dL, i.e. 11.3 mmol/L) and very severe hypertriglyceridaemia (defined as triglycerides >2500 mg/dL, i.e. 28.2 mmol/L) were reported in 6.7% patients.[1] In addition to the commonly known acute pancreatitis, other potential complications of persistent severe hypertriglyceridaemia include peripheral neuropathy, central venous thrombosis due to increased blood viscosity, osteonecrosis and thromboembolism.[1,2] However, in the context of transient but severe hypertriglyceridaemia induced by asparaginase and steroid, the chance of developing complications of hypertriglyceridaemia remains to be elucidated.

What are the other common causes of hypertriglyceridaemia?

Cholesterol and triglycerides are 2 main types of lipids in our body. Triglycerides form the basis of our energy stores of fatty acids and may provide fuel for beta-oxidation to generate adenosine triphosphate (energy). Lipids are insoluble and need lipoproteins to transport through the blood vessels to target organs such as skeletal muscle, fat and the liver. There are 5 types of lipoproteins, namely chylomicrons, VLDL, intermediate density lipoprotein, low density lipoprotein and high density lipoprotein.

Triglycerides in the lipoprotein carriers are hydrolysed by lipoprotein lipase into free-fatty acids that are either oxidized by the muscle cells to generate energy, stored in adipose tissue, oxidized in the liver, or used in hepatic VLDL synthesis. Hypertriglyceridaemia occurs when there is accumulation of triglyceride-rich lipoproteins, which is determined by excessive dietary fat uptake from the intestine or hepatic production, with or without reduced clearance of triglyceride-rich lipoproteins, and is classified as primary or secondary (Figure 2 and Table 1).[3-5] Primary hypertriglyceridaemia is of genetic basis.[3,4] Secondary hypertriglyceridaemia is believed to occur when minor genetic variants are exacerbated by conditions or drugs that increase triglyceride levels beyond the saturation point of triglyceride removal system, e.g., high fat diet, uncontrolled diabetes mellitus or insulin resistance, obesity, metabolic syndrome, hypothyroidism, hypercortisolism, renal disease, acute hepatitis, excessive alcohol intake, pregnancy or medications.[3,5]

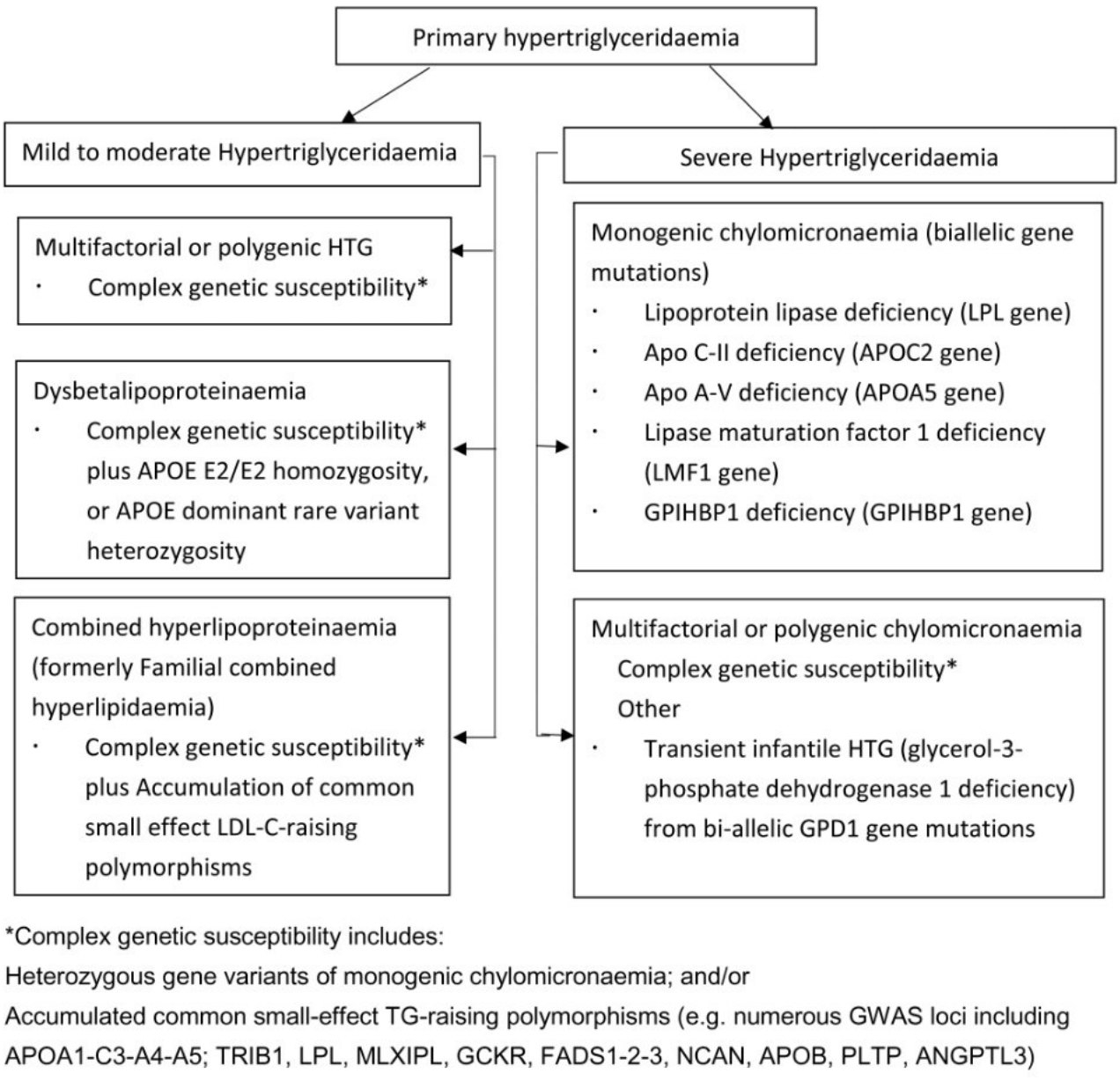

Figure 2 Causes of primary hypertriglyceridaemia.[3,4]

What are the management options of hypertriglyceridaemia induced by asparaginase and steroid?

There is no consensus on the acute treatment of hypertriglyceridaemia secondary to ALL treatment. Majority of patients had normalisation of hypertriglyceridaemia with low fat diet (78%).[1] For mild hypertriglyceridaemia, fish oil (omega-3-fatty acids (>2 g/day)) could be considered as an effective option for treatment[3,6] especially in the presence of deranged liver function for which fibrates or niacin are contraindicated. Long chain omega 3 (including eicosapentaenoic acid and docosahexaenoic acid) had been shown to reduce serum triglycerides in a dose-dependent manner.[6] For severe hypertriglyceridaemia not responding to low fat diet or fish oil, insulin infusion has been shown to be effective.[3,7] Insulin works by stimulating the synthesis of lipoprotein lipase by adipocytes and myocytes, which increase the clearance of triglyceride levels within two to three days after initiating insulin therapy. The other options include heparin and plasmapheresis. Heparin works by displacing the lipoprotein lipase into circulation and is a good add-on therapy in cases where hypertriglyceridaemia does not respond well to insulin infusion alone, though after an hour, the lipoprotein lipase is exhausted. Plasmapheresis was effective in treating severe hypertriglyceridaemia but was invasive, costly and with side effects reported as deep venous hrombosis due to a central venous catheter, anaphylaxis, hypocalcaemia and hypokalaemia.[7]

Rebound of hypertriglyceridaemia post plasmapheresis may also be rapid if underlying cause is not managed.[3]

Erwinase was reported to be associated with lower risk of severe hypertriglyceridaemia.[2] However, due to cost and the need for intramuscular injection for Erwinase, its use has been limited to selected patients. This could be considered for those with known pre-existing hypertriglyceridaemia or those with recurrent episodes of severe hypertriglyceridaemia during ALL treatment.

Conclusion

Severe hypertriglyceridaemia can occur in patients receiving asparaginase and steroid during treatment of ALL. Close monitoring of the triglyceride level is important to allow for early intervention to avoid potential complications. Pseudohyponatraemia could be a potential presentation of hypertriglyceridaemia. Since electrolytes are frequently

Table 1 Causes of secondary hypertriglyceridaemia[3,5]

Causes	
High fat diet	
Uncontrolled diabetes mellitus	
Metabolic syndrome	Insulin resistance, obesity
Endocrine disease	Hypothyroidism, Hypercortisolism / Cushing's disease, Growth hormone deficiency, etc.
Renal disease	Proteinuria, Uraemia, Glomerulonephritis, Nephrotic syndrome, etc.
Liver disease	Acute hepatitis, bile duct obstruction, non-alcoholic fatty liver disease, etc.
Rheumatological disorder	Systemic Lupus Erythematosis, Rheumatoid arthritis, etc.
Metabolic disease	Glycogen storage disorder, etc.
Excessive alchohol intake	
Pregnancy	
Medications	Corticosteroids, thiazides, loop diuretics, beta-blockers, oral oestrogen, tamoxifen, retinoids, tacrolimus , cyclosporine, cyclophosphamide, asparaginase, protease inhibitors, antiretroviral therapy, second-generation antipsychotic agents, antidepressants, etc.

measured during the course of ALL treatment, triglyceride level should be checked when hyponatraemia occurs during use of asparaginase and/or steroid.

Declaration of Interest

The authors state that there are no conflicts of interest to disclose.

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