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L-asparaginase-induced biochemical toxicities in young adults with acute lymphoblastic leukaemia and T-lymphoblastic lymphoma

Sir,

For over 50 years, extracellular depletion of asparagine using L-asparaginase has been used successfully as a chemotherapeutic treatment for haematological malignancies.¹ More recently, asparagine has been shown to play a critical role in regulating cellular adaptation to glutamine depletion and that glutaminolysis induces apoptosis.² First trialled in a child with acute lymphoblastic leukaemia (ALL) in 1966, L-asparaginase produced a marked reduction in circulating lymphoblasts, but was associated with severe haemolysis and fatal pulmonary haemorrhage.³ Its use has substantially reduced the mortality due to ALL. However, its short therapeutic plasma half-life and toxic side effects including hypersensitivity reactions, coagulation disturbances and anaphylaxis, remain ongoing challenges for treating physicians.¹ In the short-acting or pegylated forms, L-asparaginase is a backbone of current paediatric protocols for ALL, but has only recently been added to young adult protocols due to the excess of treatment-related toxicities observed in older when compared with younger patients.⁴

We report a case series demonstrating some of the biochemical toxicities experienced by four young adults receiving L-asparaginase as part of their treatment protocols at

our institution and discuss the need to monitor for these complications in this patient group.

Case 1 was an 18-year-old male with no prior history of diabetes. He presented to the emergency department unwell and obtunded during salvage therapy for his second relapse of T-ALL, requiring admission to the intensive care unit. He was febrile, neutropenic, in supraventricular tachycardia, hyponatraemic (Na 127 mmol/L) and in severe diabetic ketoacidosis (DKA) (pH 6.99, HCO₃⁻ 4.0 mmol/L, anion gap 34 mmol/L, glucose 48.7 mmol/L) (Table 1). His initial therapy (HyperCVAD, POMP) and treatment for first relapse (BFM: phase I and phase II consolidation, maintenance) had not included L-asparaginase, as this was prior to its inclusion in standard young adult protocols. A suitable stem cell donor was not identified. His treatment at second relapse included re-induction with the BFM protocol with the addition of peg-L-asparaginase 3750 units IM on day 1 and dexamethasone 16 mg orally for 21 days, leading to the presentation with DKA. He recovered following appropriate management and required long-term insulin therapy. At review, he reported a preceding one month history of polydipsia and polyuria. His C-peptide level was undetectable and islet antibody testing was negative. A diagnosis of *de novo* type 1 diabetes mellitus, unmasked by chemotherapy and sepsis was made. Treatment with L-asparaginase was abandoned.

Case 2 was a 17-year-old female with T-ALL who was treated with L-asparaginase and long-term corticosteroids as part of the Children's Cancer Group (CCG) AALL0232 study protocol. The intensification and consolidation phases were complicated by the development of type 2 diabetes and marked hyperlipidaemia. A random blood glucose level of 30 mmol/L was detected upon a presentation to the emergency department with polyuria, polydipsia and fatigue (Table 1). There was no associated ketonuria and her C-peptide level was normal. Glutamic acid decarboxylase (GAD) and islet cell antibody testing was negative. She required subcutaneous insulin therapy that was able to be ceased following completion of the steroids and L-asparaginase. The hyperlipidaemia became apparent due to subsequent markedly aberrant biochemical blood test results, including hyponatraemia, which proved discordant with a concurrently run

Table 1 Laboratory biochemical and molecular findings

	Case				Reference interval/limit
	1	2	3	4	
Gender (M/F)	M	F	M	M	
Age (years)	18	17	17	17	
Glucose (mmol/L)	48.7	30.0	14.4	ND	3.0–5.4
Amylase (U/L)	820	295	18	504	<100
Lipase (U/L)	ND	83	28	666	<40
Cholesterol (mmol/L)	ND	14.6	17.5	3.0	<5.5
Triglyceride (mmol/L)	ND	45.7	44.5	2.3	<1.8
APOE genotype	ND	ε4/3	ε4/3	ND	
LPL	ND	No mutation	No mutation	ND	
APOC2	ND	No mutation	No mutation	ND	
APOA5	ND	No mutation	c.-1131T>C heterozygote	ND	

F, female; M, male; ND, not done.

venous blood gas sample. The sample was noted to be lipaemic on gross inspection, causing pseudo-hyponatraemia. A lipid profile revealed triglycerides of 45.7 mmol/L and total cholesterol 14.6 mmol/L. The patient was contacted with a plan to start lipid-lowering therapy; however, given a history of several hours of abdominal pain, she was advised to attend the emergency department. She was subsequently diagnosed with acute pancreatitis [amylase 295 U/L (<100)] that was attributed to the L-asparaginase-induced hyperlipidaemia. She recovered with conservative management and lipid-lowering therapy including gemfibrozil, atorvastatin and fish oil capsules, which was ceased upon normalisation of her lipid profile following completion of the L-asparaginase. Subsequent doses of L-asparaginase were changed from the pegylated to the short-acting formulation, and her lipid profile and pancreatic enzymes were monitored closely. There were no further episodes of severe hyperlipidaemia or pancreatitis. Hypertriglyceridaemia genetic testing for mutations in *LPL*, *APOA5* and *APOC2* were negative.

Case 3 was a 17-year-old male with T-lymphoblastic lymphoma who was treated with the CCG AALL0232 protocol following initial induction with a cycle of HyperCVAD. The HyperCVAD with pre-phase dexamethasone was given while awaiting confirmatory diagnostic pathology due to an urgent need to commence therapy for thoracic outlet obstruction secondary to a mediastinal mass. He subsequently received a modified re-induction followed by standard therapy as per the CCG protocol. No complications occurred during the initial HyperCVAD and dexamethasone induction. Within one week of commencing the CCG protocol, which included first dosing of peg-L-asparaginase, he developed a coagulopathy [INR 1.0 (0.9–1.3), APTT 61 s (27–36), fibrinogen 1.1 g/L (2–4)] and moderate hyperglycaemia (glucose 14.4 mmol/L) (Table 1). The coagulopathy was consistent with L-asparaginase-induced dysfibrinogenemia. He was treated with appropriate blood product replacement and monitoring whilst the hyperglycaemia was managed with a diabetic diet and monitoring. Lipid analyses during this time showed a triglyceride of 20.6 mmol/L (which had been normal at baseline) and total cholesterol of 6.4 mmol/L. A further dose of peg-L-asparaginase was administered prior to commencement of any lipid-lowering strategies and subsequent blood samples were found to be grossly lipaemic causing laboratory analytical interference and revealed a triglyceride of 44.5 mmol/L and total cholesterol of 17.5 mmol/L. He presented concurrently with mild generalised abdominal pain, however, serum lipase and amylase were normal. He commenced lipid-lowering therapy with gemfibrozil, atorvastatin and fish oil capsules to good effect. Hypertriglyceridaemia genetic testing revealed the *APOA5* c.-1131C>T variant (rs662799), which is associated with increased fasting triglyceride levels and increased risk of severe hypertriglyceridaemia.⁵

Case 4 was a 17-year-old male with Philadelphia chromosome positive (Ph) ALL who was treated with the CCG protocol and imatinib. His treatment was supplemented with exogenous erythropoietin, folic acid and iron supplements to boost his bone marrow reserves as he was a Jehovah's Witness and had declined most therapeutic blood products. On one occasion the patient agreed to receive cryofibrinogen due to the development of L-asparaginase-induced dysfibrinogenemia with associated severe thrombocytopenia. Within 4 days of his first dose of peg-L-asparaginase he presented with severe back pain, epigastric tenderness,

fever and tachycardia. He was diagnosed with acute pancreatitis [lipase 666 U/L (<40), amylase 504 U/L (<100)] (Table 1), which resolved with conservative management. His lipids were not assessed at this time, but were normal at baseline.

The relatively recent addition of L-asparaginase to adolescent and young adult protocols for the treatment of ALL has shown promising effects on disease response in these patient groups. However, compliance in the setting of a prolonged treatment protocol and additional drug-related toxicities in young adults could prove problematic for adult haematologists outside of the trial setting.⁶ Experience in our local setting has revealed several biochemical toxicities attributable to L-asparaginase, occurring more frequently in this patient group than would be expected in a similarly treated paediatric population. Hyperlipidaemia, particularly severe hypertriglyceridaemia, with or without acute pancreatitis, has been a recurring theme in our young adult patients treated with the drug. Although hyperlipidaemia is relatively common in paediatric patients receiving L-asparaginase, severe hypertriglyceridaemia with associated acute pancreatitis is not.^{7–9}

The lipid abnormalities seen during L-asparaginase-containing chemotherapy for ALL in paediatric populations have been reported to be benign, transient and self-remitting. However, the rare development of severe hypertriglyceridaemia (>11.3 mmol/L) in paediatric patients is considered high risk for the development of acute pancreatitis and intervention and frequent monitoring has been recommended once this threshold is reached.^{8,9} L-asparaginase-related acute pancreatitis has been reported to also occur in the paediatric population in the absence of associated hypertriglyceridaemia.⁹ In one study where 7 of 31 asparaginase-treated children with ALL were diagnosed with asparaginase-associated pancreatitis, there was no difference in triglyceride levels in patients diagnosed with pancreatitis compared to those who were not.¹⁰ The other rare clinical complication of severe hypertriglyceridaemia that has been reported in paediatric populations treated with asparaginase is that of cerebral thrombosis associated with hyperviscosity.^{7,8}

The mechanism of L-asparaginase-associated hypertriglyceridaemia appears related to an increase in endogenous synthesis of very low density lipoprotein (VLDL) and/or a decrease in the activity of lipoprotein lipase, a key enzyme in the catabolism of triglyceride-rich lipoproteins in the circulation. Corticosteroids can also increase hepatic VLDL secretion and thus may compound the effect.^{7,9} Finch *et al.* showed that while genetic risk factors were associated with baseline triglyceride levels in ALL, after treatment with L- or peg-asparaginase these genetic risk factors explained less of the variation in triglycerides, suggesting that hypertriglyceridaemia was driven by drug therapy more than genetics.¹¹

The various different commercial presentations of therapeutic L-asparaginase have differed in their biological activity and thus their dosing regimens, despite being derived from native *Escherichia coli* strains. The development of the pegylated formulation has helped ameliorate some of the difficulties with administering the drug as well as reducing the tendency to antigenic reactions;¹² however, it has made the monitoring for other toxicities even more important due to the prolonged action of the agent. A formulation derived from *Erwinia* bacteria is available for use in patients allergic to the *E. coli* formulations. It has no cross-reactivity, reduced immunogenicity and reportedly less coagulopathy.

However, its cost is prohibitive in many areas and significant dose increases compared to the *E. coli* formulation have been required to achieve therapeutic drug levels; thus, further studies into its pharmacokinetics are required.^{1,12} Finch *et al.* found that the formulation impacted triglyceride levels, with peg-asparaginase associated with higher triglycerides compared to L-asparaginase.¹¹

Interestingly, all four of our patients had T-cell malignancies. Studies involving much larger numbers of young adults with ALL/lymphoblastic lymphoma would be required to determine whether the lymphoid blast phenotype (B- or T-cell) has any causative role in the complications described. Pancreatitis, severe hyperlipidaemia and diabetes have all been reported as adverse events related to use of L-asparaginase, but are rarely problematic in children. Our experience suggests these toxicities may occur more frequently in the young adult population. Thus, we suggest consideration of baseline biochemical screening as well as serial monitoring of triglyceride, glucose and amylase/lipase in this population during L-asparaginase therapy, in addition to current routine blood tests. We would also advise remaining alert to the possibility of hyperlipidaemia first presenting as pseudohyponatraemia or other similar laboratory biochemical abnormalities that seem discordant with the clinical picture. Further review of large study populations may allow the identification of baseline markers to identify those young adults at increased risk of developing such toxicities, as well as clearly identifying the appropriate frequency of monitoring and thresholds for intervention.

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Diagnostically challenging immunophenotypic shift in mantle cell lymphoma following ibrutinib and venetoclax therapy

Sir,

A 57-year-old Caucasian male without a significant medical history presented with B symptoms, widespread lymphadenopathy and peripheral blood lymphocytosis. A diagnosis of mantle cell lymphoma (MCL) was confirmed on bone marrow histology and typical immunophenotype. He was treated with four cycles of R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone) chemotherapy and obtained a complete metabolic remission on positron emission tomography (PET) scan. He then received maintenance rituximab 3 monthly (Fig. 1). One year later while on rituximab maintenance he had biopsy proven relapse of MCL in the right orbit and subcutaneously in the left posterior thigh. This was treated with local radiation to the thigh and orbit and he was commenced on ibrutinib. Six months later, he progressed with central nervous system (CNS) relapse of MCL. This was managed with intrathecal methotrexate and high dose cytarabine, followed by two further cycles of R-HyperCVAD chemotherapy and craniospinal radiation, achieving a complete remission of the CNS disease. He was subsequently recommenced on ibrutinib maintenance. Three months later he presented with multiple skin lesions over the legs and torso, with a biopsy of both the left knee mass and skin lesions demonstrating blastoid MCL. He received palliative radiotherapy to the lower legs and proceeded to venetoclax monotherapy with achievement of complete response on PET. After 5 months of venetoclax therapy a bone marrow aspirate demonstrated no definite evidence of involvement with MCL; however, there were two focal areas of a lymphoid-appearing infiltrate which did not appear congruent with mantle cell lymphoma on immunohistochemistry (CD20, CD79a, PAX5, cyclinD1 negative). Flow cytometry did not demonstrate an aberrant or clonal B-cell population.

One month after this biopsy he presented with widespread bony pain, B symptoms, pancytopenia and a rapidly rising white cell count. Peripheral blood film demonstrated a