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Transient Diabetes Induced by L-Asparaginase

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Abstract

Background: Although hyperglycaemia is one of the known side effects of L-asparaginase, its contribution to the development of diabetic ketoacidosis (DKA) is less well known in the literature. Asparaginase is an essential component of treatment protocols for acute lymphoblastic leukaemia (ALL) in combination with other chemotherapeutic drugs. On further evaluation, she was found to have high anion gap metabolic acidosis, hyperglycaemia and ketonuria. In recent decades, the use of these chemotherapeutic agents has led to a decrease in mortality and disease-free survival in ALL. L-asparaginase is one of the chemotherapy protocols used in the treatment of acute lymphoblastic leukaemia (ALL) and can induce hyperglycaemia which is aggravated by the concomitant use of corticosteroids. We report the observation of a 14-year-old girl treated with chemotherapy (GFA LAL protocol) who developed transient diabetes following the use of L-asparaginase. She was treated at the Donka paediatric haemato-oncology unit by a multidisciplinary team including a paediatric oncologist, a psychologist and a diabetologist. The aim of this study was to highlight blood glucose monitoring before and after the use of asparaginase in acute lymphoblastic leukaemia. Conclusion: We conclude that the occurrence of ketoacidosis following the use of asparaginase is a rare event. We recommend close monitoring of blood glucose levels for hyperglycaemia in patients with ALL receiving L-asparaginase.

Keywords

Asparaginase, Diabetes, ALL, Donka

1. Introduction

L-asparaginase is an essential component of treatment protocols for acute lymphoblastic leukaemia (ALL) and can induce carbohydrate tolerance disorders that are aggravated by the concomitant use of corticosteroids. We report the observation of a 14-year-old girl with no family history of diabetes and a diagnosis of high-risk acute lymphoblastic leukaemia (LAL-GFAOP 2019 protocol), who developed diabetic ketoacidosis (DKA) after the third dose of Intensification 1 L-asparaginase Perfusion. She was successfully treated with insulin.

2. Observation

This was a 14-year-old patient with no family history of diabetes, followed for acute lymphoblastic leukaemia which revealed itself 2 weeks after hospitalisation in the paediatric haemato-oncology unit for bone marrow failure syndrome and tumour syndrome.

Her treatment began in March 2022 with an induction course of Vincristine, Donorubicin, Prednisone, Asparaginase and an intra-spinal injection of Methotrexate.

This induction phase went off without a hitch.

A follow-up myelogram at D38 showed complete remission of the leukaemia, with less than 5% blast cells.

A consolidation phase based on the GFAOP High Risk protocol was started in April 2022 with Vincristine, Prednisone, 6-mercaptopurine, High Dose Methotrexate and Intra Spinal Methotrexate.

This chemotherapy was carried out without any major incidents, with regular checks of the blood count, creatinemia, transaminases and urinary pH. This was followed by the intensification phase (Vincristine, Dexamethasone, L-asparaginase, Donaurubicin and Methotrexate) with blood sugar monitoring before each course of treatment.

10 days after her last treatment, she was admitted to the paediatric haemato-oncology unit with polyuria, polydipsia, weight loss, physical asthenia and dysphagia, all in a state of hypovolaemic shock secondary to diabetic ketoacidosis. Her BMI was 15.25 kg/m^2.

Clinical examination revealed poor general condition, normo-coloured mucous membranes and teguments, apyretic with a temperature of 38.8˚C, respiratory rate 36 cpm, saturation 60%. The abdomen was tender throughout, with no hepatomegaly or splenomegaly. Cardiopulmonary auscultation was normal; lymph nodes were free; ENT was unremarkable.

The diagnosis of hyperglycaemia with ketoacidosis associated with febrile neutropenia was made on the basis of the biology: venous glycaemia at 3 g/l, ketonuria and positive glycosuria with PNN of less than 500/mm^3.

Treatment consisted of Actrapid-based insulin therapy (5 iu per 4 hours) combined with dual antibiotic therapy with Ceftriaxone and Gentamycin. The patient progressed well under treatment and was discharged after 6 days in hospital.

Table 1. Intensification therapy protocol.

Intensification therapy protocol (LAL GFAOP 2019)		
Medicines	Doses	Days
Vincristine	1.5 mg/m^2	J1, J8, J15
Dexamethasone	10 mg/m^2	D1 - D15 then decrease and stop in 1 week
Adriamycin	25 mg/m^2	J1, J8, J15
L-asparaginase	6000 IU/m^2 not to exceed 10,000 IU/injections	J3, J5, J8, J10, J12, J15
Intrathecal methotrexate	15 mg	J1

Background treatment for haematological malignancy and insulin continued, with the definitive withdrawal of asparaginase from his treatment (**Table 1**).

3. Discussion

L-asparaginase is an enzyme that hydrolyses asparagine into aspartic acid and ammonia, causing depletion of asparagine in cells. Insulin incorporates three molecules of asparagine; therefore, L-Asp can inhibit its synthesis in pancreatic beta cells to cause transient hyperglycaemia and diabetes mellitus. The percentage of cases of acute lymphoblastic leukaemia in which hyperglycaemia occurs as a result of

L-asparaginase with corticosteroid therapy is 2.5% to 23%. Hyperglycaemia occurs in the 5 to 10 days following the start of treatment with Lasparaginase [1].

L-asparaginase can induce hyperglycaemia in around 10% of patients, by decreasing insulin secretion and altering the function of insulin receptors.

It should be noted that concomitant corticosteroid therapy can contribute to an increase in hyperglycaemia [2].

In addition to transient glucose intolerance, rare cases develop pancreatic diabetes with L-asparaginase-related pancreatitis. Twentyone per cent of patients with L-asparaginase-related pancreatitis require insulin therapy in the acute phase and 6% of patients continue insulin therapy for up to a year [3].

4. Conclusion

Asparaginase is commonly used for the treatment of acute lymphoblastic leukaemia (ALL). Hyperglycaemia is a well-documented complication and can develop in patients treated with asparaginase therapy, but ketoacidosis is a rare event. The occurrence of ketoacidosis does not require modification of the treatment of ALL in most cases because the hyperglycaemia has resolved after chemotherapy. Persistent hyperglycaemia is rarely seen, particularly in the setting of risk factors and/or underlying infection or pancreatic inflammation. Therefore, we encourage clinicians to educate patients about the symptoms of hyperglycaemia and to closely monitor blood glucose levels during their chemo-

therapy treatment in order to prevent the development of diabetic ketoacidosis and to promptly initiate insulin treatment if necessary.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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