

Drug-Induced Hyperlipidaemia in a Paediatric Patient with B-Cell Acute Lymphoblastic Leukaemia

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Dyslipidaemias are rarely encountered in the paediatric age group and may be primary, secondary or multifactorial. Secondary causes include endocrinological and chronic inflammatory disorders, renal disease, liver disease, and medications. We report a case of hypertriglyceridaemia in a 3-year-old girl receiving chemotherapy for B-cell acute lymphoblastic leukaemia.

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Hypertriglyceridaemia is infrequently observed in children however is a rare and often asymptomatic side effect of PEG-asparaginase therapy.¹ Our patient developed hypertriglyceridaemia after the second dose of PEG-asparaginase which was given concomitantly with steroids. She presented with significant polyuria and polydipsia which resolved with treatment.

CASE REPORT

A 3 year 10-month-old girl presented in the first instance with a 1-month history of pyrexia and weight loss; on examination pallor and splenomegaly were found. Initial blood investigations showed a white cell count of $3.22 \times 10^9/L$ (normal range $4.86-13.18 \times 10^9/L$) with a neutrophil count of $0.05 \times 10^9/L$ (normal range $1.60-8.29 \times 10^9/L$) and a haemoglobin level of 4.2 g/dL (normal range $10.2-12.7 \text{ g/dL}$). The blood picture showed hypochromia with red cell

anisocytosis. Morphology from a bone marrow aspirate reported infiltration with small to medium sized blasts with a high nuclear to cytoplasmic ratio. These blast cells were positive for CD19(++), CD10(+++), CD34(++) (on 64% of the blasts), CytCD79a(++), TdT(++), CD22(+++), CD24, CD38(++), CD81(+++), CD9(+++), CD13(+), C66c(+), CD58(+), CD123(+++), Lambda(+/-). Approximately 11% of the blast cell population expressed brighter CD81(+++), CD38(++), NG2(+) and weak CD15/CD65. These findings were consistent with a diagnosis of B-cell acute lymphoblastic leukaemia.

The patient was treated as per UK ALL 2019 regimen A protocol. Induction consisted of 28 days of dexamethasone (given per oral route) at a dose of 6mg/m²/day tapered down over 7 days, 4 doses of vincristine (1.5mg/m²) administered intravenously, 2 doses of PEG-asparaginase (1000 IU/m²) given intramuscularly and intrathecal methotrexate at a dose of 12mg on day 1, 15 and 29. The child developed a hyponatremia of 127 mmol/L (normal range 136-145 mmol/L) associated with polydipsia and polyuria on day 24. No hyperglycaemia was documented, and her blood samples were noted to be grossly lipemic. Lipid indices showed a raised total cholesterol (29.29 mmol/L; normal range 2.0–5.0 mmol/L), triglycerides (19.48mmol/L; normal range 0.1-2.26 mmol/L) and LDL (2.87 mmol/L; normal range 0.1-3.88 mmol/L) with low HDL (0.10 mmol/L; normal range 1.15-1.68 mmol/L). Lipid indices were compared to a fasting lipid level taken off steroids and PEG asparaginase; total cholesterol (4.50 mmol/L), triglycerides (0.77mmol/L), LDL (2.88 mmol/L) and HDL (1.27 mmol/L).

The sudden development of hypertriglyceridaemia was likely a result of the concomitant administration of PEG asparaginase treatment and steroid therapy during induction treatment. Management involved increasing the patient's oral fluid intake, a change to a low fat and carbohydrate diet and introduction of fenofibrate at 67mg/20kg/day. Lipid indices showed a drastic improvement within two weeks of treatment with complete normalization within 1 month. Her polyuria and polydipsia resolved. Fenofibrate treatment was stopped upon normalization of lipid levels. During the first part of delayed intensification when she received her third dose of PEG-asparaginase concomitantly with dexamethasone, fenofibrate was added at the previous dose. Lipid levels were monitored closely during this period and the dyslipidemia did not recur after 3 weeks of treatment with fenofibrate. A follow up lipid profile taken when she was off steroids and PEG asparaginase was also within normal. No history of familial

hypercholesterolemia was recorded. In view of this her dyslipidemia was attributed to PEG asparaginase therapy in combination with steroid therapy.

DISCUSSION

Although the combination of steroids and PEG asparaginase is known to rarely cause hypertriglyceridaemia, it has not shown to result in significant long-term complications.² A literature review revealed that although dietary care is only mildly effective in these children, it is still recommended.³ A large study carried out by Bhojwani et al in 2018 compared 257 children with ALL who were given steroids and PEG-asparaginase in combination. Their lipid levels were checked at 4 specific points during their respective chemotherapy protocol. A total of 48 children developed hypertriglyceridaemia, 18 (7%) of which had triglyceride levels of >1000 mg/dL and were classified as severe. 17 of the 18 severely hyper triglyceridemic patients continued receiving PEG-asparaginase and steroids. Following the completion of chemotherapy, lipid levels normalised in all children. No statistically increased risk of pancreatitis or thrombosis was noted. Higher doses of steroids or PEG-asparaginase as well as older age were associated with a higher risk of developing hypertriglyceridaemia. The study highlights that fibrates may reduce the risk of hypertriglyceridaemia as well as improve symptoms. It has been proven to prevent pancreatitis in adults.³ Our case report showed good clinical response to fenofibrate and similarly no pancreatitis occurred. Although hypertriglyceridaemia has been described in similar cases in the literature, little has been reported about the incidence and prognostic implications.⁴

In 2020 Kloos et al studied individualized therapeutic drug monitoring and adjustment of PEG-asparaginase to avoid PEG-asparaginase induced toxicities in children with ALL. The study noted no reduction in toxicity.⁵

Several studies have shown that a child with hypertriglyceridaemia induced by combined PEG-asparaginase and steroid therapy should be closely monitored for pancreatitis [1,6,7]. There is no consensus on the optimal management of hypertriglyceridaemia in these cases. Tried treatment options have included short term fasting, low fat diet, plasmapheresis, omega-3 and oral fibrates.^{6,8,9} Our case represents another successfully treated PEG-asparaginase induced hypertriglyceridaemia with an oral fibrate with no complications.

CONCLUSION

Hypertryglyceridaemia is a rare but known complication of PEG asparaginase treatment, especially when combined with steroids, however in most cases of childhood ALL the benefits of treatment outweigh any short- or long-term risks. There is little evidence on dietary modification or use of lipid lowering agents in such patients however a low-fat diet and fenofibrate therapy proved to be very effective in this case. As symptoms are very nonspecific, a low threshold for lipid investigations should be maintained in children on PEG-asparaginase and steroids. In view of the different treatment modalities that have been used to treat dyslipidaemia, a standardized management plan would aid paediatric oncologists in this potential life-threatening complication.

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