ORIGINAL ARTICLE

L-asparaginase induced hyperlipidaemia in acute lymphoblastic leukaemia

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Abstract

Objective: To evaluate hyperlipidaemia in patients with acute lymphoblastic leukaemia (ALL) receiving L-asparaginase.

Methods: A case-control study carried out between October 2007 and October 2010 with 77 patients undergoing chemotherapy at a teaching children's hospital in Babol, Iran. Patients were treated with anti-leukaemic agents according to the protocols for standard-risk and high-risk ALL. Those patients who received asparaginase represented the cases and those who did not receive it were the controls. Biochemical markers were checked during the induction phase chemotherapy. Lipid profile of patients was recorded. Data was analysed using SPSS 16.

Results: Of the 77 patients, 37 (48.05%) received asparaginase therapy and 40 (51.94%) patients did not. The mean peak triglyceride and cholesterol levels during asparaginase therapy in the first group were significantly higher than the levels in the second group.

Conclusion: Severe hyperlipidaemia may be the cause of some morbidity in children receiving asparaginase. Asparaginase-induced hyperlipidaemia should be monitored in ALL patients during the induction phase of treatment.

Keywords: Hyperlipidaemia, Asparaginase, Acute lymphoblastic leukaemia. (JPMA 63: 324; 2013)

Introduction

L-asparaginase, an important component of therapy for acute lymphoblastic leukaemia (ALL), inhibits protein synthesis. It has typically been administered intramuscularly rather than intravenously because of concerns regarding side-effects, but some centres have tried to use the intravenous route.[1,2] Many of its side-effects, such as allergic reaction, coagulopathies, encephalopathy, seizures, pancreatitis, hepatotoxicity and hyperglycaemia, are familiar to oncologists.[3-5] Conversely, the possibility of therapy-induced hyperlipidaemia generally is not appreciated. Otherwise thromboembolic complications may be associated with L-asparaginase therapy.[6,7] Thromboembolic disease in haematological malignancies is complex and can result from various factors such as tumour cell-derived procoagulant, fibrinolytic or proteolytic factors, inflammatory cytokines, chemotherapy and anti-angiogenic drugs increase this phenomenon. Leukaemic patients may be affected by other prothrombotic factors, including hyperleukocytosis, increased tissue factor (TF) expression, and finally the prothrombotic properties of therapeutic agents such as L-asparaginase.[8,9] Some researchers showed that hypercholesterolaemia and hyperlipidaemia are risk factors for vein thrombosis.[10,11] Thrombosis risk in ALL patients is surely exacerbated by chemotherapy, but is not exclusive to the remission induction period.[12] There was a correlation between asparaginase-induced fall of antithrombin and occurrence of new thromboses.[13] Hyperlipidaemia and thrombosis is not common in childhood, but the overall thrombotic risk in ALL is significant.[14] There are different methods to treat asparaginase-induced hyperlipidaemia, including close clinical monitoring instead of modifications in asparaginase therapy; plasmapheresis and administration of fibrate and heparin in severe cases of hyperlipidaemia; neither fresh frozen plasma (FFP) nor cryoprophylaxis, temporary discontinuation of asparaginase are more common.[15-17]

This study evaluated the fasting triglycerides (TG) and cholesterol levels of paediatric ALL patients before and during asparaginase therapy, and compared it with long-term survivors of childhood ALL who were off-treatment at the time of the study.

Patients and methods

The case-control study was carried out at a teaching children's hospital in Babol, Iran. The patients were treated with anti-leukaemic agents according to standard-risk

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and high-risk therapy protocols that included asparaginase. The estimated number of study subjects for a group was calculated by the formula: n=(Z1-α 1 + Z1-α1-β)2(δ12+δ22) ÷ (X1-X2) 2, (α error =5%, power+80%, δ1 =50, δ2= 200) = 34. All the 37 cases in the study had received 7-9 doses of asparaginase during the induction therapy. Fasting TG and cholesterol levels were obtained in consecutively diagnosed children with ALL before and during the asparaginase therapy. A second population of 40 long-term survivors of childhood ALL who did not receive asparaginase during the current study were also evaluated for fasting TG and cholesterol levels. Doppler sonography was done of great vessels in patients whose serum TG and cholesterol levels were abnormal. Data was analysed with SPSS 16. Statistical comparison was done with Student's t-test.

Results

There were 44 (57.14%) boys and 33 (42.85%) girls. The mean age of cases was 5.31±3.48 years (range: 0.83-14 years) while the corresponding values for the controls were 6±1.36 years (range: 4-10 years). In the first group of cases, TG and cholesterol levels were normal prior to treatment. During therapy, the mean TG level was 252.68±507.2 mg/dl (range: 25-3000; median=87 mg/dl), and the mean cholesterol level was 322.81±504.20 mg/dl (range: 56-3000 mg/dl). Of the total, 27 (2.97%) patients had normal range of TG and cholesterol — up to 120 mg/dl and up to 200 mg/dl respectively. Six (16.21%) patients had TG and cholesterol levels in the range of 201-600mg/dl; 3 (8.1%) patients had TG and cholesterol in the range of 601-1000 mg/dl. One 10-month-old girl experienced marked hyperlipidaemia (TG and cholesterol levels $\geq$ 3000mg/dl). Abnormal elevation of TG and cholesterol levels was seen after 4 to 6 doses of asparaginase in all patients. In severe cases, TG and cholesterol became less than 1000mg/dl after the discontinuation of asparaginase for 10 days, but TG and cholesterol got elevated after re-starting asparaginase. Asparaginase was discontinued for the girls with hyperlipidaemia for the rest of the treatment. In milder cases, TG and cholesterol became normal after discontinuing asparaginase and did not elevate after re-starting asparaginase. The mean peak TG level during the therapy was significantly higher than the level of 40 controls at the time of study (95% CI; SD=83.56; $p<0.04$). The mean peak cholesterol level during the therapy was also significantly higher than the level of the controls (95% CI; SD=83.11; $p<0.01$). The patient who had TG and cholesterol level more than 3000mg/dl could not walk until 24 months of age, and could not speak until 27 months old. There was no abnormal finding on Doppler sonography.

Discussion

In this study, no patient had an abnormal TG and cholesterol profile before treatment with asparaginase. The 40 controls who had been off the treatment during the study did not have hyperlipidaemia. Hyperlipidaemia is not common in childhood. Ten (27.02%) patients experienced hyperlipidaemia during treatment with asparaginase. There were significant differences in TG and cholesterol levels between the two groups. Though prolonged therapy with corticosteroids and asparaginase seemed to be the probable cause of hyperlipidaemia,[18] our study strongly suggests that asparaginase is an inducer of this hyperlipidaemia because steroids have been used in consecutive courses of ALL therapy. One patient experienced marked hyperlipidaemia (TG and cholesterol level $\geq$ 3000mg/dl). Only a few similar cases were found in the literature during therapy with steroids and asparaginase.[19,20] Severe hyperlipidaemia may be the cause of thromboembolism and ischaemic attack in children who receive asparaginase.[21-23] Although the other evaluation in this patient did not clarify anything for the first time, but she had developmental milestone delay. By discontinuing asparaginase, TG and cholesterol decreased below 1000mg/dl, but increased again after asparaginase was re-started. We continued with the chemotherapy through excluding asparaginase for this patient. In milder cases, TG and cholesterol reduced to the normal range by discontinuing asparaginase and we continued with chemotherapy with asparaginase for them. Fortunately, there was no morbidity in association with milder patients. We suggest checking TG and cholesterol during induction chemotherapy in ALL patients every 3-4 days. In contrast to another study, we suggest that after asparaginase-induced severe hyperlipidaemia, asparaginase should be discontinued and in milder cases it can be re-started with close monitoring.[17] Also in contrast with other studies, we concluded that modifications in asparaginase therapy were necessary.[20] In case of hyperlipidaemia, when the risk of pancreatitis and thrombosis is increased, close clinical monitoring becomes imperative. At the moment, ALL diagnosis is potentially based on atherogenic lipid profile. In severe hyperlipidaemia, plasmapheresis may be considered just as has been the case earlier.[15,24,25]

Conclusion

Severe hyperlipidaemia may lead to morbidity and should be monitored during asparaginase therapy in ALL patients.

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