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Hypertriglyceridemia associated with anticancer therapy based on asparaginase and steroids: a retrospective single center study of children with acute lymphoblastic leukemia and lymphoblastic lymphoma

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Abstract

Introduction: Hypertriglyceridemia (HTG) is one of the common complications of the regimens based on steroids and asparaginase used in the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in children. The aim of this cross-sectional retrospective study was the analysis of the prevalence, clinical course and management of hypertriglyceridemia following the administration of asparaginase and steroids according to the binding protocols.

Material and methods: A cohort of 75 children with ALL or LBL was analyzed with reference to anthropometric and laboratory parameters, clinical symptoms, implemented treatment, and complications.

Results: The prevalence of HTG in the analyzed cohort was 29.3%. Risk factors for HTG development were older age, cachexia and lower body mass index, but there was no correlation with high risk group. Patients with HTG presented with elevated lipase acivity and total cholesterol concentration and decreased antithrombin, albumin, sodium and high-density lipoprotein cholesterol. Reported symptoms were unspecific. Management of HTG included: omega 3 fatty acids, fibrates, insulin and plasmapheresis.

Conclusions: Hypertriglyceridemia is a significant complication of ALL and LBL treatment, and can lead to acute and late complications and cause unwelcome interruptions to therapy that can lead to poorer outcomes of treatment. As the course of HTG is oligosymptomatic, but can have undesirable repercussions, every patient receiving asparaginase with steroids should be monitored for HTG. It is also noteworthy that HTG can occur three or more weeks after asparaginase administration.
Key words: hypertriglyceridemia, acute lymphoblastic leukemia, lymphoblastic lymphoma, asparaginase, steroids

Introduction

Acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) are the most frequent malignant neoplasms in the pediatric population. The treatment is based on multi-agent chemotherapy and sometimes radiotherapy or bone marrow transplantation. The curability rate in neoplasms of the lymphoid tissue in children is satisfactory and exceeds 85% [1].

However, the treatment has its costs and adverse effects of treatment are inevitable. The combination of asparaginase and steroids, which are two of the crucial drugs in lymphoid tissue neoplasms therapy, often leads to metabolic complications, in particular diabetes mellitus, hyperlipidemia and/or electrolytes imbalance.

One of the most common sequelae is hypertriglyceridemia (HTG) defined as a triglycerides level exceeding the 95^{th} percentile for age and sex [2]. The epidemiology, management and significance of this complication remain controversial issues.

The aim of this cross-sectional retrospective study of children treated for ALL and LBL was to analyze the prevalence, clinical course and management of HTG following the administration of asparaginase and steroids according to binding treatment regimens.

Material and methods

This study was conducted at the Department of Pediatrics, Hematology and Oncology of the Medical University of Gdansk, Poland. All patients newly diagnosed with ALL or LBL from October 2018 to June 2022 were included. The participants were aged between 0.16 and 18 years.

The patients were treated according to the binding therapeutic protocols (AIEOP BFM ALL 2017 for ALL, or EURO LB-02 for LBL). Both protocols assume multi-agent chemotherapy with steroid therapy. The glucocorticoids used in the treatment are prednisone in a dose of 60 mg/m^2 or dexamethasone in a dose of 10–20 mg/m^2 depending on the phase of the course and the diagnosis. The induction protocol lasts for 33 days, and most patients receive prednisone, with only patients diagnosed with T-cell ALL (T-ALL) with a good prednisone response being switched to dexamethasone 10 mg/m^2 since the ninth day of the induction phase. The re-induction protocol following the consolidation phase assumes dexamethasone (10 mg/m^2) administration for all patients. Both the induction and the re-induction protocols envisage continuous administration of steroids in full doses every day for 28 or 21 days respectively. Dexamethasone (10 or 20 mg/m^2) is also given in shorter periods (five days) in extended consolidation or high risk (HR) cycles for patients stratified to higher risk groups according to protocols.

Asparaginase is given in the same phases as steroids in two doses every two weeks in induction and one dose in other phases (re-induction, extended consolidation, every HR-block). In the analyzed group, all patients received pegylated asparaginase (PEG-ASP) in a two-hour infusion in a dose of 2,500 U/m^2, with a maximal dose of 3,750 U/m^2. One patient was switched to crisantaspase (L-asparaginase derived from *Erwinia chrysanthemi*) due to hypersensitivity.

All patients were monitored for HTG at least twice i.e. seven and 14 days after the administration of PEG-ASP. At these two time points, asparaginase activity was also evaluated. For the purposes of our study, patients were divided into two groups, with those whose triglycerides level persisted above 500 mg/dL for at least two days being classified as having HTG. This criterion was used to exclude patients with incidentally elevated triglycerides concentration. Other analyzed parameters encompassed coagulation tests, blood urine nitrogen (BUN), electrolytes, albumin, total and high-density lipoprotein (HDL) cholesterol, liver tests (ammonia, alanine transaminase) and lipase. Results were also collected at least twice at the two time points mentioned above, or more often depending on individual indications. The samples were sent to the Main Clinical Laboratory where all tests were performed.

Obtained anthropomorphic details were weight, height and body mass index (BMI). Weight and BMI were also determined using a centile chart [3] to enable a comparison of parameters in patients of different ages. A group of cachectic patients was also identified, defined as patients who had lost at least 10% of their weight and required clinical nutrition.

This study was approved by the Independent Bioethics Committee for Scientific Research of the Medical University of Gdansk (NKBBN/493/2021) and performed in accordance with the guidelines laid down in the Declaration of Helsinki.

The analyzed dataset consisted of both qualitative and quantitative data. Thus, different statistical methods and tests were used to evaluate the statistical relationship. Spearman's coefficient was calculated to explore the correlation between serum triglycerides concentration and the continuous variables from the dataset. To check whether the serum triglycerides concentration was normally distributed, the Shapiro-Wilk normality test was used. The Mann Whitney U Test and Chi-squared Test were used to analyze the non-parametric data. A *p*-value <0.05 was considered statistically significant. The analysis was done using the R Statistical Programming Language.

Results

A total of 75 patients diagnosed with ALL or LBL from October 2018 to June 2022 were included in the study. ALL was diagnosed in 67 (89.3%) patients [56 with B-cell ALL (B-ALL) and nine with T-ALL and LBL in eight (10.7%). No correlation was found between the type of disease and the risk of HTG.

HTG, defined as a persistent triglycerides level exceeding 500 mg/dL, was identified in 22 patients (29.3%). Only one patient had never reached a concentration considered as HTG. The highest result was 3,345 mg/dL (mean triglycerides concentration was 718.6 mg/dL in the whole cohort, 1,546.2 mg/dL in the HTG-group, and 375.11 mg/dL in the control group).

The mean age of participants was 6.97 years [standard deviation (SD) ± 4.77; range: 0.16–18), and patients with HTG were distinctly older (mean 9.36 years vs. 5.98) and this difference was statistically significant. There were 31 females (41.3%) and 44 males (58.7%). Mean weight of patients determined in percentiles was 55.2 kg (50.05 in the HTG group and 57.4 in the group without HTG, no statistical significance). BMI was determined in kg/m^2 as well as in percentiles. Mean BMI was 16.95 kg/m^2 (16.91 kg/m^2 in the HTG group and 16.97 in the control group; no statistical significance was found; 54.08 in percentiles (43.09 in the HTG group and 58.6 in the control group, and this difference was statistically significant. Cachexia was diagnosed in 16 patients (21.3%), seven of whom (43.8%) developed HTG requiring treatment. The detailed patient characteristics are set out in Table I [there were 75 patients diagnosed with leukemia (B or T) or lymphoblastic lymphoma included in the study.

Cachexia was diagnosed in patients who had lost at least 10% of their weight and required clinical nutrition. Patients diagnosed with HTG were older (9.36 vs. 5.98 years; *p*-value 0.004). Patients' weight was marked as a percentile to analyze the weight of patients of different ages. BMI was marked in kg/m^2 and also in percentiles].

Table I. Detailed patient characteristics

Characteristic		**Number of patients — whole cohort [%]**	**Patients with HTG [%]**	**Patients without HTG [%]**	***p*-value**
Total		75 (100)	22 (29.3)	53 (70.7)	
Sex	Female	31 (41.3)	6 (27.3)	24 (45.3)	0.001
	Male	44 (58.7)	16 (72.7)	29 (54.7)	
Diagnosis	B-ALL	56 (74.7)	13 (59.1)	43 (81.1)	0.476
	T-ALL	11 (14.7)	5 (22.7)	6 (11.3)	
	LBL	8 (10.7)	4 (18.2)	4 (7.5)	
Risk group	Standard	66 (88)	20 (90.9)	46 (86.8)	0.100
	High	9 (12)	2 (9.1)	7 (13.2)	
Cachexia	Cachectic	16 (21.3)	7 (31.8)	9 (17)	0.001
	Non-cachectic	59 (78.7)	15 (68.2)	44 (83)	
Mean age, median [range]		5.43 [0.16–17.99]	9.68 [1.04–17.08]	4.49 [0.16–17.99]	0.004
Mean weight in percentile, median [range]		60 [1–100]	51.5 [1–88]	64 [2–100]	0.237
Mean BMI (kg/m^2), median [range]		16.9 [12.9–22.9]	17.5 [12.9–22.3]	16.8 [13.4–22.9]	0.958
Mean BMI in percentile, median [range]		58 [0–100]	45 [0–93]	62 [1–100]	0.05

BMI — body mass index

Table II. Laboratory test results

Parameter [units]	**Whole group (N = 75); median [range]**	**Patients with hypertriglyceridemia (N = 22); median [range]**	**Control group of patients (N = 53); median**	***p*-value**

			[range]	
Triglycerides [mg/dL])	415 [71–3,345]	1,389.5 [652–3,345]	315 [71–1,290]	0.001
Asparaginase activity [U/L]	772 [47–1,000]	800 [492–1,000]	760 [47–1,000]	0.964
Alanine aminotransferase [U/L]	137 [25–1,052]	165 [32–1,052]	129 [25–761]	0.097
Ammonia [µmol/L]	86 [33–232]	87 [33–227]	81 [46–232]	0.357
Blood urine nitrogen [mg/dL]	22 [6–66]	25 [14–39]	22 [6–66]	0.089
Lipase [U/L]	32 [11–1,465]	47 [19–1,465]	26 [11–1,096]	**0.001**
Antithrombin activity [%]	60 [23–113]	50 [23–82]	62 [36–113]	**0.001**
Fibrinogen [g/L]	0.5 [0.35–2.64]	0.41 [0.35–1.39]	0.55 [0.35–2.64]	0.182
Albumin [g/L]	22 [15–42]	20 [16–34]	23 [15–42]	**0.039**
Total cholesterol [mg/dL]	215 [94–736]	257 [138–736]	205 [94–295]	**0.001**
HDL cholesterol [mg/dL]	20 [5–64]	9 [5–27]	35 [5–64]	**0.001**
Sodium [mg/dL]	132 [121–138]	130 [121–135]	133 [128–138]	**0.001**

HDL — high-density lipoprotein

The analyzed biochemistry results are set out in Table III. We found a statistically significant difference in lipase and antithrombin activity, and in albumin, sodium and cholesterol (total and HDL) concentration. There was no statistically significant difference in fibrinogen concentration, blood urine nitrogen, liver tests (alanine transferase and ammonia) or asparaginase activity].

Pancreas function was monitored with lipase activity. Mean result was 102.53 U/L in the whole group, 190.86 U/L in the HTG group, and 64.43 U/L in the control group, and the difference was statistically significant with a *p*-value of 0.001. The function of coagulation system was evaluated by fibrinogen concentration and antithrombin (AT) activity. Mean AT

was 61.4% in the whole cohort, 47.45% in the HTG group, and 67.19% in the control group. The difference was statistically significant with a *p*-value of 0.001. Mean fibrinogen concentration was 0.67 g/L in the whole cohort, 0.54 g/L in the HTG group, and 0.72 g/L in the control group, but the difference was not statistically significant. Albuminemia was also determined: mean albumin concentration in the whole group was 23.15 g/L, in the HTG group 21.55 g/L, and in control group 23.81 g/L, and the difference was statistically significant with *p*-value of 0.039. Evident differences were found in the concentration of total cholesterol and HDL cholesterol: mean value of total cholesterol in the whole cohort was 226.44 mg/dL and HDL 24.84 mg/dL, in the HTG group 281.62 mg/dL and 10.94 mg/dL, and in the control group 198.86 mg/dL and 32.22 mg/dL respectively, *p*-value was 0.001 for both parameters. Hyponatremia was also seen in patients with HTG: mean sodium concentration in the whole group was 131.99 mg/dL, in the HTG group 129.45 mg/dL (median 129 mg/dL), and in the control group 133.04 mg/dL (median 133 mg/dL), with a *p*-value of 0.001. Analysis of other parameters (i.e. asparaginase activity, blood urine nitrogen, alanine aminotransferase (ALT), and ammonia) did not reveal any statistical significance. Pancreas and liver were also evaluated in ultrasonography. In 36 (48%) patients, the liver was described as normal, while in 39 (52%) some atypical signs were found. In 37 patients, hepatomegaly was found and in 12 higher echogenicity of the liver parenchyma was described. In five (6.7%) patients, features of inflammation were found. In the HTG group in 14 (63.6%) patients the liver was described as abnormal, as was the pancreas in two (9.1%) of them.

Complaints reported by patients with HTG were nonspecific. No symptoms were declared by four (18.2%) patients. The most common sign was fatigue reported by 15 (68.2%) of patients, while next were abdominal pain (N = 8, 36.4%), diarrhea (N = 7, 31.8%), nausea (N = 4, 18.2%), constipation (N = 4, 18.2%), limb pain (N = 4, 18.2%), vomiting (N = 3, 13.6%), hypertension (N = 3, 13.6%), headache (N = 3, 13.6%), psychiatric symptoms (N = 2, 9.1%), dyspnea (N = 2, 9.1%), ascites (N = 1, 5,5%) and pruritus (N = 1, 5.5%). A summary of declared complaints is set out in Figure 1.

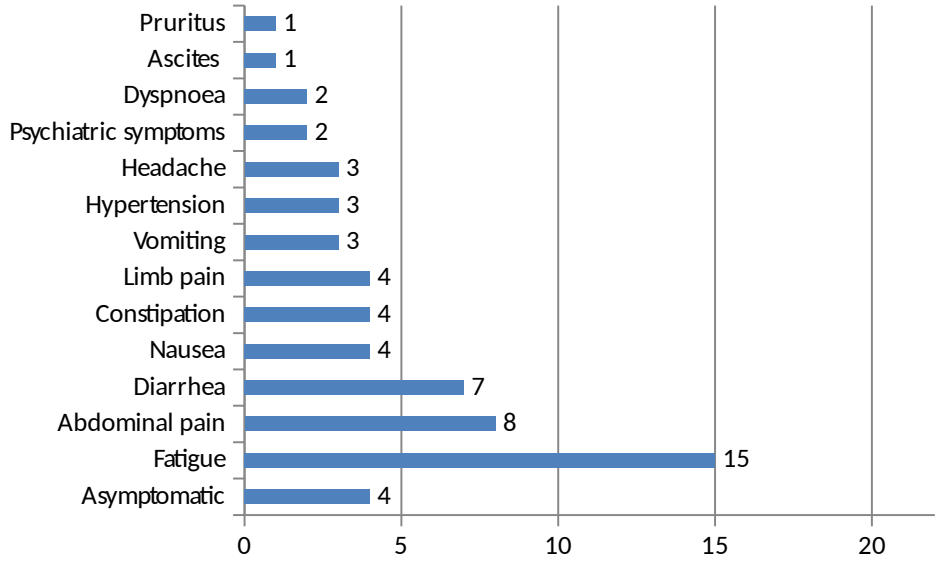

Figure 1. Symptoms declared by patients diagnosed with hypertriglyceridemia. Hypertriglyceridemia was diagnosed in 22 patients. Most frequent complaint was fatigue (68.2%), and all reported symptoms were non-specific. Four patients did not report any ailments

Treatment methods implemented in patients diagnosed with HTG were omega-3 fatty acids, fibrates (fenofibrate), insulin infusion, and plasmapheresis. Omega-3 fatty acids were implemented in 19 (86.4%) patients, fenofibrate in 16 (72.7%), insulin in 20 (90.9%), and plasmapheresis was required by five (22.7%) children. Patients qualified to plasmapheresis had not responded to the insulin infusion. Two of them required plasmapheresis twice — in induction and re-induction phases. All the patients survived and improved after treatment of HTG was implemented.

Acute complications observed after HTG were acute pancreatitis and thrombosis. Pancreatitis occurred in two patients (9.1%) and thrombosis in four (18.2%). In the control group it was three (5.5%) and seven (12.7%) patients, respectively. In patients with HTG history, four (18.2%) had suffered from chronic complications, three from osteonecrosis, and one from pancreas insufficiency. In the control group, late effects were seen in three (5.5%) patients, but no pancreas insufficiency was diagnosed in this group. Another consequence of HTG was unplanned breaks in chemotherapy: the mean duration of treatment withdrawal was 7.9 days, and the longest pause had lasted 24 days. No episode of HTG followed any HR block, 13 episodes were complications of the induction protocol, seven of the re-induction protocol, one occurred in extended consolidation B phase (c.70th day of treatment), and one in

first turnover of III protocol. HTG is a delayed rather than an early consequence of asparaginase: mean time from asparaginase administration to HTG onset was 15.8 days, the shortest time was five days and the longest 26 days. There was no correlation between the type of steroid used (dexamethasone vs. prednisone) and the HTG incidence found.

Discussion

HTG is defined as a level of triglycerides serum concentration exceeding the 95th percentile. In laboratory results usually an adult range is used, although pediatric recommendations consider 100 mg/dL to be high for children under 10 years and 130 mg/dL for older children.

For analytical purposes, we have used the highest results in our study; nevertheless, only one patient did not achieve 100 mg/dL. Most patients showed a decreased concentration of triglycerides after fasting or the withdrawal of parenteral nutrition. This shows that interpreting results should be cautious and usually requires repetitive tests.

Bhojwani et al. [4] have proved that older age and treatment in accordance to high risk protocols are risk factors of HTG development. Correlation of older age and higher HTG prevalence was also confirmed by our study, whereas the relation between the risk groups was the opposite, 30% of patients stratified to the standard group developed HTG but only 22% of patients treated as the high risk group. No patient was diagnosed with HTG after any HR block, defined as very aggressive multi-agent chemotherapy associated with 5-days long high dose dexamethasone. There have been studies suggesting better outcomes and fewer complications after short therapy with pulses of higher steroid doses rather than continuous therapy [5–8]. This thesis fits with our observation, as all patients diagnosed with HTG received continuous steroid therapy for 3–4 weeks and no patient developed HTG after a cycle with short therapy based on high dose dexamethasone (five days with 20 mg/m^2).

It has been proven that lipid metabolism impairment is often seen in cachectic patients [9]. A similar finding was confirmed in our study. 43.8% of cachectic patients developed HTG but only 25.4% from the group without cachexia. There was also a significant difference in the BMI between the compared groups. This reveals how significant are nutritional care and early intervention.

There are still no explicit guidelines concerning the treatment of HTG in children, especially in children during chemotherapy. Our analysis shows that implementation of any treatment usually depends on the physician’s opinion and experience. Omega-3 free fatty acids and fibrates have been implemented in the majority of patients with HTG, but the most

frequently used method was an infusion of insulin. It is known that insulin can increase the clearance of triglycerides by the activation of lipoprotein lipase and is an effective treatment of HTG. It has also been suggested that insulin infusion should be used only in patients with diabetes, or in other situations connected to insulin deficiency. Indications to plasmapheresis are also a controversial issue. It is definitely an effective method, with a reduction of 40-70% of triglycerides, but it is also fraught with a high risk of complications, most importantly hypovolemia, electrolytes imbalance and/or hypotension. A patient qualified to plasmapheresis requires the insertion of a large catheter which poses a risk of bleeding or thrombosis [10, 11].

Another debatable issue is pancreatitis and its relation to HTG. Most sources claim that a triglycerides level exceeding 500–1,000 mg/dL increases the risk of pancreatitis. On the other hand, pancreatitis can be a complication of asparaginase administration *per se*. Raja et al. [12] showed that HTG was not associated with acute pancreatitis. What is more, they showed a correlation of triglycerides level and pancreatic enzymes activity, but there was no correlation with the onset of pancreatitis.

In our study, acute pancreatitis was more frequent in the group with HTG (9.1% vs. 5.5%) and chronic insufficiency of pancreas was diagnosed in only one patient who suffered from severe HTG twice and required plasmapheresis repeatedly [12, 13].

Conclusions

We have shown that HTG is a significant complication of ALL and LBL treatment, with a prevalence of 29.3%. We have shown that HTG is more often diagnosed in older patients after treatment according to a standard risk regimen, and that particularly vulnerable are persons with lower BMI and cachexia. Symptoms declared by our patients diagnosed with HTG were nonspecific and 18% did not report any complaints.

HTG can lead more often to acute complications, chiefly acute pancreatitis and thrombosis, and also to late consequences such as osteonecrosis, and bring unwelcome interruptions of therapy which can worsen the outcome of treatment [14]. Because the course of HTG is oligosymptomatic but can have undesirable repercussions, every patient receiving asparaginase with steroids should be monitored for HTG. It is also noteworthy that HTG can occur three or more weeks following asparaginase administration, so it should be always considered after that time, even if the patient has already started another block of chemotherapy.

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Author's contributions

NI-J conceived idea. NI-J, MH supervised project. AM gathered necessary data, conducted statistical analysis, and wrote manuscript under supervision of co-authors.

Conflict of interests

The authors declare no conflict of interest.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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