ANDES PEDIATRICA
REVISTA CHILENA DE PEDIATRÍA
www.scielo.cl

Andes pediatr. 2024;95(4):442-448
DOI: 10.32641/andespediatr.v95i4.4940

CLINICAL CASE

Pseudohiponatremia secundaria a hipertrigliceridemia durante tratamiento de linfoma linfoblástico con corticoides y L-asparaginasa

Pseudohiponatremia secondary to hypertriglyceridemia during the treatment of lymphoblastic lymphoma with corticoids and L-asparaginase

Isabel Folatre[a], Mónica Kyonen[b], Daniela Schnettler[a], Mania Yilorm[a], Paula Monzón[a], Pilar Martínez[a], Gustavo Cea[a]

[a]Hemato-Oncología Infantil. Universidad Austral de Chile. Hospital Base Valdivia. Valdivia, Chile.
[b]Químico Farmacéutico.

Received: September 20, 2023; Approved: May 31, 2024

What do we know about the subject matter of this study?

Glucocorticoids (dexamethasone and prednisone) and asparaginase are essential for the successful treatment of pediatric onco-hematological pathologies and can be associated with hypertriglyceridemia. This complication may be transient and benign. However, severe cases of hypertriglyceridemia (triglyceride levels > 1000 mg/dl) generally increase the risk of acute pancreatitis and thromboembolic events. The relative contribution of glucocorticoids versus L-asparaginase (L-asp) in the development of hypertriglyceridemia during acute lymphoblastic leukemia therapy is unclear. The case report shows us that the suspicion of hypertriglyceridemia ADR should be investigated mainly in treatment protocols involving the administration of L-asp and glucocorticoids.

What does this study contribute to what is already known?

The findings observed during the treatment protocol for lymphoblastic NHL in an adolescent with no risk factor made it possible to continue treatment with glucocorticoids and L-asp, accumulating a total of 184,000 IU of L-asp. Treatment protocols for lymphoblastic NHL include laboratory tests, so early detection in clinical practice is likely.

Abstract

L-asparaginase (L-asp) is an antineoplastic drug used in Leukemia and Lymphoma treatment protocols. Alterations in lipid metabolism have been reported in 10-50% of children treated with L-Asp. **Objective:** To report an unusual complication of lipid metabolism associated with the use of L-Asp. **Clinical Case:** We describe the clinical picture of an adolescent who, during treatment for Lymphoblastic Non-Hodgkin Lymphoma (NHL), presented pseudohyponatremia and hyper-

Keywords:
L-asparaginase;
Pseudohyponatremia;
Hypertriglyceridemia;
Lymphoblastic non-Hodgkin Lymphoma;
Causality Algorithm

Correspondence:
Daniela Schnettler
danielaschnettler@gmail.com

Edited by:
Carolina Heresi Venegas

How to cite this article: Andes pediatr. 2024;95(4):442-448. DOI: 10.32641/andespediatr.v95i4.4940

triglyceridemia, suspecting an adverse drug reaction (ADR). This suspicion was evaluated according to the modified causality algorithm (Karch and Lasagna), resulting in a "definitive" ADR for the L-asparaginase and corticosteroids association. He received treatment with a low-fat diet and lipid-modifying drugs; L-asparaginase and prednisone were not suspended since the protocol ended. Hypertriglyceridemia recovered without complications after 14 days of treatment. **Conclusion**: Although the magnitude of the hypertriglyceridemia did not result in clinical pancreatitis, it seems advisable to include ADR suspicion to L-asp among the differential diagnoses, to highlight the need to detect these complications, and to know their prognosis and management in order not to affect the treatment of the patients.

Introduction

Childhood cancer emerges as the second leading cause of death as preventable diseases have been controlled. In Chile, since 1985, childhood cancer has been positioned as the second cause of death in the age group between 1 and 14 years of age. Thus, the group of leukemias accounts for 42.2% of all childhood neoplasms, followed by CNS neoplasms and lymphomas with 17.0% and 8.8%, respectively[1].

The *Hospital Base Valdivia* (HBV) is an accredited center for the diagnosis, treatment, and follow-up of childhood cancer in the southern macro-zone of Chile. Since 2000, it has developed active pharmacovigilance, with onco-hematological patients presenting the most frequent adverse reactions to antineoplastic drugs (39%)[2].

The most reported drug is L-asparaginase (L-asp) (35%), both locally and internationally (35-45%). This is one of the drugs used in some of the treatment protocols. However, like other antineoplastic drugs, it is not free of adverse effects, among which skin and skin appendages, hepatobiliary, vascular and coagulation, gastrointestinal, metabolic (especially hyperglycemia, hypercholesterolemia, and hypertriglyceridemia), nutritional, and neurological reactions have been reported[3]. Hypertriglyceridemia manifested as pseudohyponatremia is an infrequent adverse drug reaction (ADR), described in less than 1% of the exposures to *E. coli* L-asp, and pseudohyponatremia constitutes a potential factor that needs to be recognized since if it is not correctly interpreted, inappropriate interventions may occur. Knowing the mechanism by which L-asp induces ADR may help to guide treatment by preventing severe complications that need to be treated as soon as possible[4]. The objective of this manuscript is to report the clinical case of an adolescent under treatment for non-Hodgkin's lymphoblastic lymphoma who presented with hypertriglyceridemia presented as pseudohyponatremia during treatment.

Clinical Case

A 14-year-old adolescent, previously healthy, consulted the Primary Emergency Care Service (SAPU) of Osorno, due to an 11-day history of irritative cough, predominantly at night. Symptomatic treatment was indicated, developing dyspnea and orthopnea. He went to the Emergency Department of the *Hospital Base Osorno* (HBO), where severe respiratory distress, intolerance to decubitus position, and abdominal pain were observed.

He was admitted to the pediatric ICU (PICU) with tachycardia, hypertension, polypnea, 96% saturation, FiO2 35%; he looked pink, hydrated and well perfused, and flat jugular veins and small bilateral supraclavicular adenopathies were observed. The chest showed no soft tissue retraction, maintained the knee-chest position, had decreased pulmonary murmur in both bases, and cardiac auscultation had muffled sounds, without murmur. The soft abdomen was slightly depressible and tender in both hypochondria, suspected visceromegaly, and extremities without lesions. Chest X-ray showed an upper mediastinal mass and right middle lobe atelectasis associated with ipsilateral pleural effusion. A chest CT scan with contrast was not performed due to anesthetic contraindication, as stated in the transfer summary from the HBO.

The patient was transferred to the HBV PICU with Mediastinal Compression Syndrome, with clinical suspicion of NHL. He was evaluated by the teams of Pediatric Oncohematology, Pediatric Surgery, Pediatric Intensive Care, Imaging, and Radiotherapy and, given the immediate vital risk associated with the diagnosis, it was decided to administer cytoreductive treatment, with dexamethasone 6 mg/m^2/day and cyclophosphamide 100mg/m^2/day for 5 days, in addition to prophylaxis of tumor lysis syndrome (allopurinol 10 mg/kg/day every 8 hours), overhydration (3000ml/m^2), and treatment for respiratory failure.

Physiopathologically, mediastinal masses compete

for space with vital structures. Negative intrathoracic pressure, which is the sum of anatomical (including intercostal muscle tone) and physiological (respiration) forces, effectively pulls the tumor forward. Gravity exerts an opposing force, pulling the tumor posteriorly. In the supine position, if the intrathoracic pressure is less negative, gravity becomes dominant and pulls the tumor posteriorly over vulnerable structures such as the tracheobronchial tree and the right heart (right atrium and pulmonary artery).

Anesthesia, neuromuscular blockade, and positive pressure ventilation could exert profound effects on this balance as well as the net effect of pressures on the tumor when the patient assumes different positions. This allows predicting changes in the anesthesia effect and developing strategies to prevent and revert cardiorespiratory collapse[5].

The patient evolved with tumor lysis syndrome 24 hours after admission, associated with renal failure, with uricemia (14.6 mg/dL), LDH (2,177 U/L), normal lipid profile (total cholesterol in high normal range, HDL cholesterol in lower normal range, triglycerides 159 mg/dL), fibrinogen 498 mg/dL, D-dimer 1.61 ug/ml, phosphatemia 8.8 mg/dL, and creatinine 0.82 mg/dL. He received rasburicase to treat tumor lysis syndrome (0.2 mg/kg/day), suspending allopurinol and continuing cytoreduction with dexamethasone at half the initial dose (3mg/m^2/day), without cyclophosphamide.

A nephrological evaluation was performed, which confirmed renal failure secondary to tumor lysis syndrome, without dialytic urgency, and tendency to hypertension, with creatinine 1.54 mg/dL, phosphatemia 11 mg/dL, and without hypernatremia. He continued with hyperhydration, diuretics (furosemide), and antihypertensives (amlodipine).

Regarding respiratory aspects, he required oxygen support, with FIO2 35% by Venturi mask, suspending this support on the third day of admission. He evolved with episodes of psychomotor agitation, associated with the diagnosis in process, which was treated according to the institutional protocol of psychomotor agitation, with psychological and psychiatric support, with satisfactory evolution.

On the third day of admission and treatment, a chest, abdomen, and pelvis CT scan with contrast was performed, showing an increase in the size of the thymus, with a homogeneous appearance, probably in the context of a lymphoproliferative process and findings suggestive of right basal pulmonary thromboembolism. Chest CT angiography showed thrombosis of the left jugular vein, extensive bilateral pleural effusion associated with atelectasis in both bases, and signs of bilateral medical nephropathy. Anticoagulation with enoxaparin (1 mg/kg every 12 hours) was indicated for 20 days. Then, a control CT angiography showed resolution of the thrombosis.

On the fourth day of admission and treatment, a diagnostic and extension study was performed, which included, among others, complete biochemical profile including lipid profile, granulopoietic hyperplasia of the bone marrow (myelogram), flow cytometry (bone marrow) in which no cells with clonal predominance or neoplastic immunophenotype of hematologic lineage were observed; peripheral blood flow cytometry was negative for neoplastic cells, pleural fluid cytology was negative for neoplastic cells, pleural fluid flow cytometry without evidence of hematologic neoplasia. The patient was presented to the pediatric oncology committee, noting that a biopsy of the tumor could not be taken since the mediastinal mass disappeared with cytoreductive treatment, assuming the diagnosis of lymphoblastic lymphoma due to the clinical picture and the response to treatment, according to the PINDA 0516 protocol. This protocol contemplates in AI Induction 8 doses of *E.coli* L-asp of 10,000 IU/m^2.

Having received 7 doses of L-asp and with a cumulative dose of 90,000 IU plus glucocorticoid (prednisone), he presented symptoms of decay, vomiting, abdominal pain, and mild dehydration. Pancreatitis was suspected, which was ruled out by normal amylase/lipase values and normal liver tests. At that time, he had a plasma electrolyte test with hyponatremia of 126 meq/l, hypertriglyceridemia of 1,115 mg/dL, and total cholesterol of 435 mg/dL (figure 1). Given the persistence of hyponatremia despite adequate replacement therapy, he was evaluated by pediatric nephrology, highlighting the absence of neurological alterations, normal blood pressure, plasma osmolality 272 mOsm/kg, and urinary osmolality 510 mOsm/kg, both normal values. With hyponatremia and hypertriglyceridemia, the suspicion of ADR of pseudohyponatremia secondary to hypertriglyceridemia associated with L-Asp was suggested.

The patient was evaluated by Gastroenterology and Endocrinology, indicating a diet low in refined sugars and rich in fiber, fibrates (ciprofibrate 100 mg oral/day), and omega 3 (4 g oral/day), until triglyceride values of 300mg/dL were achieved. 2 weeks later, the triglycerides decreased to 79 mg/dL. Ciprofibrate and omega 3 were suspended, indicating prophylactic use associated with treatment with corticosteroids and L-asp. 12 doses of L-asp were completed with a cumulative dose of 184,000 IU corresponding to the induction protocol.

Suspected ADR was subjected to causality assessment, with the Karch and Lasagna algorithm modified by the WHO[5], which resulted in "Definite" ADR for the L-asp and Prednisone association (Annex 1).

Discussion

Hyponatremia is defined as a plasma sodium level below 130 mEq/L associated with plasma hypoosmolarity, which can occur in the context of normal, hypo, or hypervolemia. The presentation of neurological symptoms such as seizures is associated with natremia under 120 mEq/L and, under 112 mEq/L, there may be coma. The faster the hyponatremia sets in, the greater the neurological involvement[6].

Normally, serum consists of an aqueous phase (93%) and a non-aqueous phase (7%). Sodium is found in the aqueous phase and, in the non-aqueous phase, glucose, lipids, and proteins. When serum proteins or lipids increase, the relative fraction of non-aqueous serum increases[6].

Since serum sodium is usually measured by indirect ion-selective methods, requiring a dilution of the aqueous phase, which is assumed to be 93%, low serum sodium levels may falsely result, giving rise to pseudohyponatremia. There are formulas to correct the aqueous phase decreased by hypertriglyceridemia: Corrected sodium = Serum sodium + 0.2 x triglycerides g/L[6].

On the thirty-sixth day of induction, the patient showed serum sodium of 126 mEq/L which did not correlate with his state of consciousness, general condition, lack of correction with the administration of physiological saline, normal plasma osmolality (272 mOsm/kg), and hypertriglyceridemia of 1.170 g/L, suspecting pseudohyponatremia secondary to hypertriglyceridemia. The patient's corrected natremia was: corrected sodium = 126 mEq/L + 0.2 x 1,170 g/L = 147 mEq/L.

Causality assessment of suspected ADR according to the modified Karch and Lasagna algorithm, based on a scoring system assigned to the evaluation criteria[5], was performed for each of the drugs associated with ADR. In this case, prednisone and L-asp, noting that for both drugs there was a compatible temporal chronology between administration and ADR. Pseudohyponatremia began on the fortieth day from the start of corticosteroids and on the nineteenth day from the start of L-asp.

The potential mechanism through which glucocorticoids and L-asparaginase lead to hypertriglyceri-

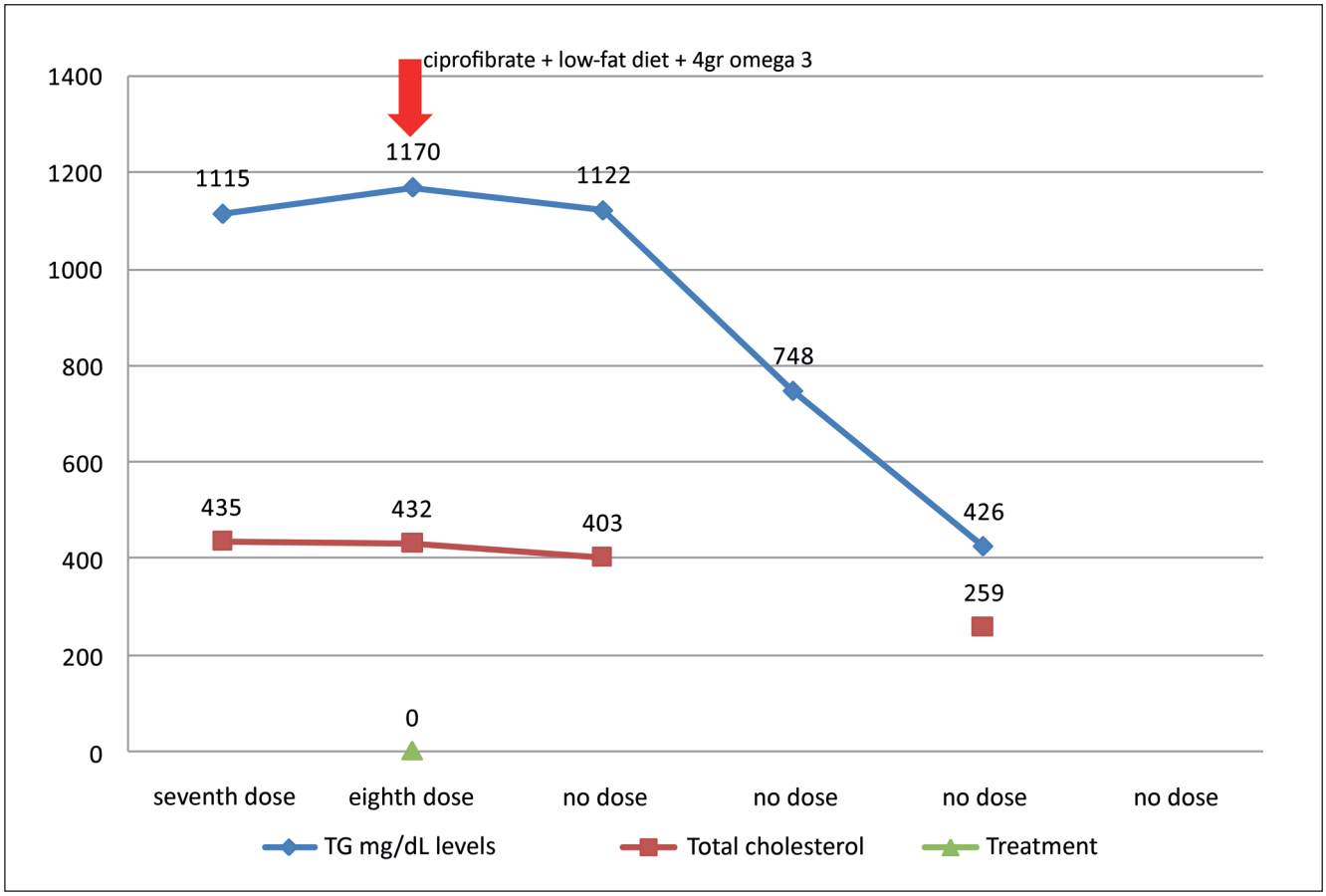

Figure 1. Relationship between triglyceride (TG) levels and the administration of L-asparaginase (E.coli) during Induction, Phase I/A for Lymphoblastic Lymphoma. Cumulative dose at RAM 105,000 IU (seventh dose).

demia is not fully elucidated. However, the probable cause has been raised in observational studies. Glucocorticoids increase triglyceride synthesis, causing fatty acid mobilization and activating lipoprotein lipase, an enzyme necessary for triglyceride hydrolysis. In contrast, L-asp inhibits lipoprotein lipase, by globally decreasing hepatic protein synthesis. This enzyme is responsible for the hydrolysis of triglycerides from lipoproteins. Concomitant administration of L-asp and glucocorticoids can induce high levels of chylomicrons and enhance the synthesis of very low-density lipoproteins while decreasing the clearance of triglyceride-rich lipoproteins. Therefore, when glucocorticoids and L-asp are administered together, transient elevations in triglyceride levels occur rapidly, being more frequently described when patients receive high doses of L-asp and glucocorticoids[7].

Interesting in this case is the cumulative dose of L-asp (105,000 IU) at the time hypertriglyceridemia occurs, which may suggest a dose-dependent effect, which has not been described so far compared with other adverse effects frequently described for L-asp, such as allergies where they associated the number of doses received until the presentation of the dermatological ADR, under 80,000 IU with the start of the reinduction phase according to the acute lymphatic leukemia protocol[8,11]. Other studies report a lack of linearity between the cumulative dose (135,000 IU/m^2) and the occurrence of pancreatic complications associated with L-asp. However, likely, the first intense dose received in the first month of treatment (45,000 IU/m^2/month) and the prolonged duration of treatment would be related to an increased incidence of pancreatitis[9].

In a randomized comparison of native *E. coli* L-asp versus pegylated-asp (PEG-asp), grade 4 hypertriglyceridemia, defined under the Common Terminology Criteria for Adverse Events (CTCAE) by the National Cancer Institute (NCI): >1000 mg/dL; was 8% versus 4% with PEG-asp (10,11).

Parson et al.[12] determined in a prospective observational study lipid abnormalities associated with L-asp with an incidence of hypertriglyceridemia of 67% after 30 weeks of L-asp treatment, without detecting an association between hypertriglyceridemia and acute L-asp toxicity, particularly pancreatitis. This observation suggests that modifications of L-asp therapy are not necessary in the case of hypertriglyceridemia, with two important considerations: if triglyceride value is < 1,000 mg/dL, maintain L-Asp; If > 1,000 mgdL, (CTCAE) discontinue and resume once triglyceride levels normalize, with mandatory close monitoring of clinical signs and symptoms[12].

A case-control study with 37 patients with ALL showed hyperlipidemia in 27% of cases after the fourth to sixth dose of L-asp. In severe cases, the levels decreased to less than 1000 mg/dL after 10 days of drug discontinuation but rose again after reinitiation of the drug[13].

In the clinical case presented, the suspected drugs (L-asp/glucocorticoids) were not withdrawn, and hypertriglyceridemia improved after 14 days, with normalization of triglyceride values by symptomatic treatment with diet, fibrates (ciprofibrate), and omega-3. The role of discontinuation of L-asp treatment when ADR occurs is still unclear since it is reversible, transitory, and can be prevented with a low-fat diet, omega-3, and the addition of fibrates if necessary[14,15].

The evolution of ADR in this case, both hyponatremia and hypertriglyceridemia were transitory because triglyceride values were normalized through diet, fibrates, omega-3, and prednisone and L-asp were suspended at the end of the indication, according to the PINDA protocol.

Regarding corticosteroids, they appear as a contributing factor to ADR[16]. In this case, no other alternative causes were found to explain the causal association between hypertriglyceridemia and baseline disease or other pathological conditions (diabetes, obesity, familial hypertriglyceridemia).

Causality was assigned for each of the suspected drugs, L-asp and glucocorticoids as definitive ADR (+8), as there is a validating laboratory measure[5].

The literature on the adverse effect profile of native L-asp comes primarily from the pediatric population, with few cases reported in adults. However, it should be noted that toxicity differs between children and adults: in the former, hypersensitivity is the most frequent serious adverse effect, and, in adults, hepatic, pancreatic, and thrombotic adverse effects. Prevention of complications is an important part of management. Patients with high-risk factors such as obesity or diabetes should be carefully evaluated for the occurrence of hypertriglyceridemia. Re-exposure with L-asp has shown to be well tolerated, but this decision should be made on a case-by-case basis, and when triglycerides have normalized[17,18].

To ensure optimal treatment, it is necessary to be prepared to make the necessary adjustments in treatment by minimizing the number of long-term adverse effects possibly through personalized treatment regimens. In this report, there was no measurement of asparaginase levels, so this may be a key component in guiding treatment decisions for patients employing different available formulations of L-asp[19,20] (table 1).

Conclusions

Pseudohyponatremia secondary to L-asparaginase hypertriglyceridemia is an underdiagnosed, dose-

Table 1. Recommendations on the management of hypertriglyceridemia due to L-asp *E. coli*[19]

- Consider a basal level of triglycerides: prior to starting use of the drug and before receiving any formulation of L-asp, it should be considered in clinical practice.
- Elevated triglyceride values Grade 4; >1000mg/dL: suspect and look for when taking between the sixth and eighth dose of L-asp or with accumulated doses (ninety thousand international units): you can maintain L-asp and evaluate liver and pancreatic functions.
- Interventions such as administration of fibrates, omega 3 reduce hypertriglyceridemia associated with L-asp.
- In case of hypertriglyceridemia with risk factors, evaluate adjustments or suspension of L-asparaginase.

dependent, definite, benign, and transient ADR that should be considered in the differential diagnosis especially when associated with glucocorticoids. Its early detection can prevent complications such as hypercoagulable states and pancreatitis. Its knowledge about prognosis and management allows for maintaining treatment continuity and patient survival.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors state that the information has been obtained anonymously from previous data, therefore, Research Ethics Committee, in its discretion, has exempted from obtaining an informed consent, which is recorded in the respective form.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Acknowledgments

To Dr. Lily Quiroz, pediatric nephrologist, for reviewing the manuscript.

References

1. Ministerio de Salud. Departamento de Epidemiología. Primer Informe del Registro Nacional de Cáncer Infantil de Chile (menores de 15 años), RENCI. Quinquenio 2007-2011. Chile 2018. Disponible en: http://epi.minsal.cl.
2. Campbell M. Desarrollo de la Oncología Pediátrica en Chile. Rev Ped Elec. 2005;2(2):1-4.
3. Hijiya N, Van der Sluis IM. Asparaginase-associated toxicity in children with acute lymphoblastic leukemia. Leuk Linfoma. 2016;57;4:748-57. doi: 10.3109/10428194.2015.1101098. PMID: 26457414
4. BC Cancer Agency Cancer Drug Manual© Monograph Asparaginase (acceso 27 de noviembre 2023). Disponible en: http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual/drug-index#a-content
5. Karch F, Lasagna L. Toward the Operational Identification of Adverse Drug Reaction. En Clin Pharmacol and Ther. 1997;21:247-54.
6. Hinson A, Newbern D, Linardic CM. Asparaginase-Induced Hypertriglyceridemia Presenting as Pseudohyponatremia during Leukemia Treatment. Case Rep Pediatr. 2014:e635740. Published 2014 Oct 27. doi: 10.1155/2014/635740. PMID: 25405049
7. Finch ER, Smith CA, Yang W, et al. Asparaginase formulation impacts hypertriglyceridemia during therapy for acute lymphoblastic leukemia. Pediatr Blood Cancer. 2020;67(1):e28040. doi: 10.1002/pbc.28040. PMID: 31612640
8. Cohen H, et al. Treatment of L- Asparaginase-Associated Lipid Abnormalities in Children With Acute Lymphoblastic Leukemia. Pediatr Blood Cancer. 2010;54:703-706. doi: 10.1002/pbc.22305. PMID: 20063421.
9. Chen CB, Chang HH, Chou SW, et al. Acute pancreatitis in children with acute lymphoblastic leukemia correlates with L-asparaginase dose intensity. Pediatr Res. 2022;92:459-65. doi: 10.1038/s41390-021-01796-w. PMID: 34718353.
10. National Cancer Institute Common Terminology Criteria for Adverse Events (acceso 2 de noviembre 2022). Disponibleen:https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40. 6 14, 2010.
11. Schmidt MP, Ivanov AV, Coriu D, et al. L-Asparaginase Toxicity in the Treatment of Children and Adolescents with Acute Lymphoblastic Leukemia. J Clin Med. 2021;10(19):4419. doi: 10.3390/jcm10194419. PMID: 34640436.
12. Parsons SK, Skapek SX, Neufeld EJ, et al. Asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. Blood. 1997;89(6):1886-95. PMID: 9058708.
13. Nesheli HM, Tamaddoni A, Nesheli MM, et al. L-asparaginase induced hyperlipidaemia in acute lymphoblastic leukaemia. JPMA. 2013;63(3):324-6. PMID: 23914630.
14. Bhojwani D, Darbandi R, Pei D,

et al. Severe hypertriglyceridaemia during therapy for childhood acute lymphoblastic leukaemia. Eur J Cancer. 2014;50(15):2685-94. doi: 10.1016/j.ejca.2014.06.023. PMID: 25087182.

15. Mayerhofer C, Speckmann C, Kapp F, et al. Lipid Apheresis to Manage Severe Hypertriglyceridemia during Induction Therapy in a Child with Acute Lymphoblastic Leukemia. Pediatr Hematol Oncol. 2020;37(6):530-8. doi: 10.1080/08880018.2020.1756999. PMID: 32374222.
16. Persson L, Harila-Saari A, Hed Myrberg I, et al. Hypertriglyceridemia during asparaginase treatment in children with acute lymphoblastic leukemia correlates with antithrombin activity in adolescents. Pediatr Blood Cancer. 2017;64(10):e26559. Published 2017 Apr 25. doi: 10.1002/pbc.26559. PMID: 28440015.
17. Lau KM, Saunders IM, Goodman A. Pegaspargase-induced hypertriglyceridemia in a patient with acute lymphoblastic leukemia. J Oncol Pharm Pract. 2020;26(1):193-9. doi: 10.1177/1078155219833438. PMID: 30823860.
18. Lashkari HP, Lancaster D, Atra A, et al. Symptomatic severe hypertriglyceridaemia with asparaginase therapy in acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma: is rechallenging safe? Int J Hematol. 2011;94(6):571-5. doi: 10.1007/s12185-011-0966-9. PMID: 22057510.
19. Stock W, et al. Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. Leuk Lymphoma. 2011;52:2237-53. doi: 10.3109/10428194.2011.596963. PMID: 21827361.
20. Kloos RQH, Pieters R, Jumelet FMV, et al. Individualized Asparaginase Dosing in Childhood Acute Lymphoblastic Leukemia. J Clin Oncol. 2020;38(7):715-24. doi: 10.1200/JCO.19.02292. PMID: 31922920.