



Recurrent Cerebral Venous Sinus Thrombosis Occurred in an Acute Lymphoblastic Leukemia Child with Mutated Lipoprotein Lipase Gene during Asparaginase Therapy

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Abstract

Keywords

- acute lymphoblastic leukemia
- gene mutation
- L-Asparaginase
- cerebral venous sinus thrombosis

Cerebral venous sinus thrombosis (CVST) and hyperlipidemia are severe complications of L-Asparaginase (L-Asp) during the treatment of B-cell acute lymphoblastic leukemia (B-ALL). Herein, we reported a 9-year-old B-ALL boy who underwent abnormal hypertriglyceridemia and CVST presenting as seizures and disturbance of consciousness twice during the induction therapy. Fortunately, he survived treatment with anticoagulant and lipid-lowering therapy. No thrombophilia-related gene mutation was detected, but a heterozygous mutation in lipoprotein lipase (LPL) gene was identified. His neurological symptoms were managed with short-term anticoagulant therapy and long-term lipid-lowering therapy. This case illustrated the manifestation and potential pathogenesis of CVST and highlighted the essentiality of screening baseline lipid profile and dyslipidemia- and thrombophilia-related gene mutation.

Introduction

Acute lymphoblastic leukemia (ALL) is the most prevalent childhood malignancy and constitutes approximately 25% of cancer diagnoses among children,^{1,2} and the long-term overall survival and event-free survival rate of pediatric ALL has exceeded 90 and 85%.^{1,3} L-Asparaginase (L-Asp) is a basic component of chemotherapy in pediatric ALL but comes with numerous side effects, including affecting lipid metabolism and inciting thrombosis.⁴ Cerebral venous sinus thrombosis (CVST)

is a rare complication during the treatment of ALL, presenting as seizures, hemiplegia, severe headaches, and coma.

Case Report

A 9-year-old boy (weight: 35 kg, height: 150 cm) was admitted to our hospital and diagnosed as intermediate-risk B-cell ALL based on his morphology, immunophenotypic, and genetic features. According to the Chinese Children Cancer Group study ALL-2020 (CCCG-ALL-2020) protocol (referred to the 20-protocol; this study was registered at the Chinese Clinical

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Trial Registry [registration number: ChiCTR2000035264]), he began remission induction therapy (vincristine, daunorubicin, prednisone, and pegasparginase [PEG-Asp]) on March 20, 2023. Unfortunately, the patient failed to achieve minimal residual disease (MRD)-negative complete remission (CR) on day 19 of induction, with a significant percentage of lymphoblasts (13.19%) in cerebrospinal fluid, thus reclassified as having a high-risk disease with central nervous system (CNS) involved. The patient experienced persistent coagulation dysfunction and hypofibrinogenemia following the application of PEG-Asp, but the baseline lipid and triglycerides (TG) levels were not assessed at that time. On day 30 of induction, the child suffered a 3-minute-long nighttime seizure, manifesting as disturbance of consciousness, diplopia, cyanosis of the lips, ptialism, and tremors in the extremities, with no other neurological deficits. Then, these symptoms were promptly alleviated with an intramuscular injection of phenobarbital 0.1 g. An immediate brain computed tomography (CT) scan was performed, which could not rule out venous sinus thrombosis. Subsequent brain magnetic resonance venography (MRV) revealed frontal-parietal superior sagittal sinus, part of the cortical veins, and sigmoid sinus thrombosis. The patient continued with mannitol, phenobarbital, fibrinogen, and other symptomatic supportive treatments from days 30 to 33. Because of his stable condition and mild symptoms, anticoagulant therapy has not been initiated.

On day 33, the boy experienced another seizure lasting nearly 1 minute, characterized by unresponsiveness, tremors in the extremities, and extension of both lower limbs. Phenobarbital 0.1 g was administered immediately, alleviating these symptoms gradually. An urgent brain CT revealed intracranial thrombosis combined with hemorrhage, and MRV indicated that thrombosis in the superior sagittal sinus, cortical veins, and sinus confluence (–Fig. 1). He was transferred to the intensive care unit for further treatment. Immediate anticoagulation therapy was initiated with heparin at a dose of 0.2 mL every 12 hours (q12h). Additionally, intermittent transfusions of fibrinogen and fresh-frozen plasma were administered to rectify coagulation dysfunction. After 15 consecutive days of heparin administration, his neurological symptoms were relieved significantly, and MRV scans showed that the thrombus and hemorrhage had resolved with no other noticeable abnormalities. The patient was then transferred back to the general ward later.

He continued with the remaining remission induction and consolidation therapy based on the 20-protocol but failed to achieve MRD-negative CR throughout. From August 23, 2023, blinatumomab (17.5 µg/d; days 1–28) was administered, continuing with subsequent continuation therapy with high-dose methotrexate and triple intrathecal therapy every other week and daily mercaptopurine for four courses, and he eventually obtained MRD-negative CR. During the course of treatment, coagulation dysfunction and hypofibrinogenemia recurred but normalized after fibrinogen and plasma supplementation.

On December 5, 2023, the boy was readmitted due to wandering pain in the lumbar, back, and hip. Brain CT scan identified multiple thromboses in the left transverse and

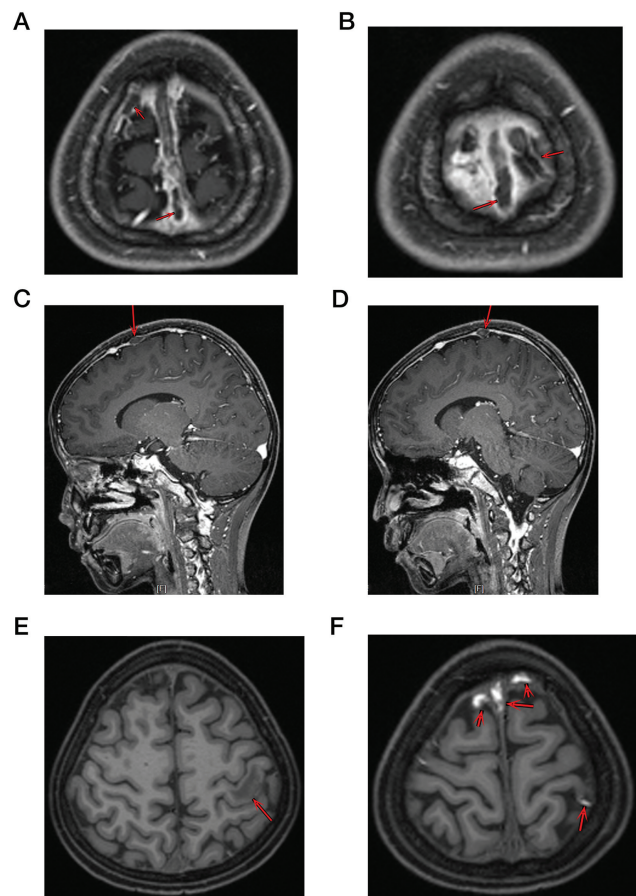


Fig. 1 Radiographic data of first thromboses. (A) Right superior sagittal sinus thromboses in magnetic resonance venography (MRV) axial view. (B) Left superior sagittal sinus thromboses in MRV axial view. (C) Right superficial cutaneous vein thromboses in MRV sagittal view. (D) Left superficial cutaneous vein thromboses in MRV sagittal view. (E) Left postcentral gyrus ischemic focus in magnetic resonance imaging (MRI) analysis. (F) Superior sagittal sinus and superficial cutaneous vein thromboses in MRI analysis. The red arrows show where the thromboses are.

sigmoid sinuses, and magnetic resonance imaging and MRV revealed multiple thrombi in the left internal jugular vein, sigmoid sinus, transverse sinus, and sinus confluence (–Fig. 2). Immediate anticoagulation therapy with heparin 0.2 mL every 12 hours was administered. Additionally, a thrombophilia workup was performed to evaluate the acute thrombosis of unknown origin. The fibrinogen concentration was 0.98 g/L (normal range: 2–4 g/L), and lipid level was elevated, with TG 49.73 mmol/L, nearly 30 times above normal (range: 0–1.7 mmol/L), cholesterol 20.34 mmol/L, 5 times higher (range: 3.0–5.7 mmol/L), and low-density lipoprotein 0.63 mmol/L, 3 times higher (range: 1.89–4.21 mmol/L). Given the patients' young age and healthy lifestyle, genetic testing was performed to investigate potential thrombophilia-related and dyslipidemia-related genetic disorders as causes of abnormal hyperlipidemia and CVST. No thrombophilia-related gene mutation was detected, but a heterozygous mutation in lipoprotein lipase (LPL) gene (c.547G > A) was identified (–Fig. 3A, B), which is associated with autosomal recessive inheritable LPL deficiency, indicating a high likelihood of hyperlipidemia. Considering the lack

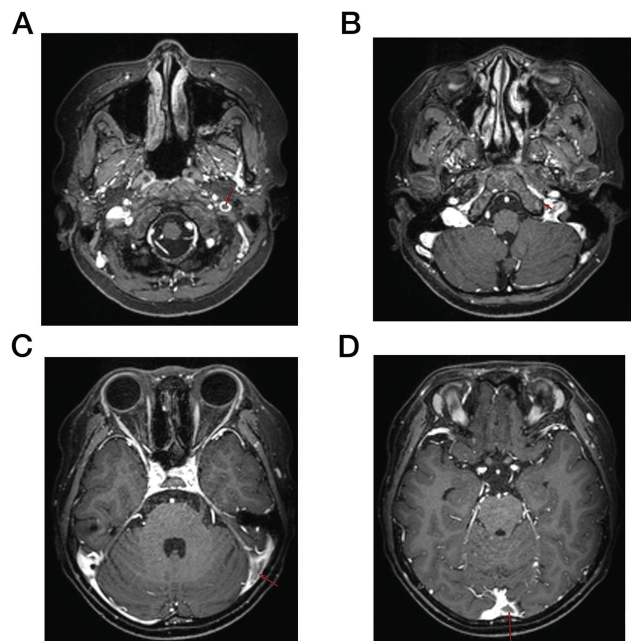


Fig. 2 Radiographic data of second thromboses. (A) Thrombi in the left internal jugular vein in magnetic resonance venography (MRV) analysis. (B) Thrombi in the left sigmoid sinus in MRV analysis. (C) Thrombi in the left transverse sinus in MRV analysis. (D) Thrombi in sinus confluence in MRV analysis. The red arrows shows where the thromboses are.

of guidelines for the use of fibrates–lipid-lowering drugs in children, atorvastatin 10 mg was initiated for lipid-lowering treatment. Despite this intervention, the TG level remained significantly elevated, approximately 15 times higher than normal. Consequently, atorvastatin was discontinued, and fenofibrate 0.1 g was introduced, resulting in a substantial decrease in TG level. Continuation therapy was commenced on December 21, 2023, and PEG-Asp was temporarily suspended due to persistently high TG levels. Given the genetic predisposition, relevant genetic and lipid examination was conducted on his parents as well, and his father was found to have the same LPL gene mutation and hyperlipidemia (→Fig. 3C). To safeguard his health, we recommended the father immediately adopt initiate lipid-lowering treatment and adopt lifestyle modifications.

Later, he returned regularly for continuation therapy. Coagulation function and lipid profile were within normal range, but MRV results suggested left jugular vein, sigmoid sinus, transverse sinus, and sinus confluence thrombosis. Rivaroxaban 15 mg was administered orally for anticoagulation, along with fenofibrate for lipid-lowering treatment. Due to the potential negative impact of PEG-Asp on coagulation function and lipid levels, the long-acting PEG-Asp was replaced with short-acting Erwinia L-asparaginase (Erwinia-Asp). After the third term of Erwinia-Asp, lipid testing results revealed a recurrence of severe hypertriglyceridemia (HTG), with TG levels of nearly 13.09 mmol/L. Consequently, Asp was promptly discontinued.

The patient is now in long-term lipid-lowering therapy with fenofibrate, and intermittent TG levels are within normal range. Scheduled bone marrow assessments have

been carried out to monitor the remission status of the primary disease status, and he remains in an MRD-negative CR state currently.

Discussion

A previous meta-analysis of 17 prospective studies calculated the thrombosis rate in pediatric ALL patients to be 5.2%, with most thromboses occurring during induction therapy.^{5–7} The overall rate of cerebral thrombosis was found to be 2.9%.⁸ During the course of ALL treatment, hyperlipidemia tends to occur at two main time points: weeks 4 to 6 and months 5 to 7 of induction, typically following the administration of L-Asp. In the case of the study, the patient developed hyperlipidemia and CVST during L-Asp treatment, with a dyslipidemia-related but no thrombophilia-related genetic mutation detected. neurological symptoms were managed with short-term anticoagulant therapy and long-term lipid-lowering therapy.

Hyperlipidemia is associated with thrombosis and other severe complications, but no standard recommendations are provided for screening or monitoring of hyperlipidemia in the treatment of L-Asp.^{6,9–14} While the elevated TG levels in pediatric ALL patients are generally transient and rarely necessitate the suspension of therapy, significant increases in TG levels are thought to be attributed partially to genetic predisposition,¹⁵ as evidenced by the child in this case who exhibited abnormal TG and LPL gene mutation during L-Asp treatment. LPL gene mutation could affect the enzyme responsible for breaking down TG in chylomicrons and very low-density lipoprotein. Deficiency in lipoprotein lipase could lead to HTG. Accordingly, it is prudent to monitor baseline lipid profile and dyslipidemia-related gene testing at the start of L-Asp treatment and continue periodic monitoring throughout the course of ALL therapy, a limitation we acknowledge in this case. Further studies are essential to identify children who might potentially benefit from increased monitoring of TG levels and relevant gene testing.

CVST often occurs during induction therapy, particularly after L-Asp infusion, and its occurrence appears to be unrelated to CNS leukemia.⁶ The mechanism by which L-Asp induces thrombosis and CVST is complex, and L-asparaginase is believed to disrupt the physiologic balance between the hemostatic and anticoagulation pathways, alongside activating platelets and endothelial cells. Risk factors for venous thromboembolism and CVST included TG > 500 mg/dL, thrombophilia, elevated coagulation factors, high-risk ALL, and chemotherapeutic agents, of which HTG and thrombophilia proved to be independent predictors.^{15–17} Hereditary factors were reported to increase the risk of thrombosis by 8.5 times in pediatric patients treated with L-asparaginase.¹⁷ In the clinical case above, the patient was diagnosed with genetic HTG and concomitant CVST, but no mutations related to thrombophilia were detected. We speculate that dyslipidemia-related gene mutation contributed to HTG, thereby increasing the risk of CVST. This rationale underpins our decision to conduct dyslipidemia- and thrombophilia-related gene testing for the child, as we believe relevant gene

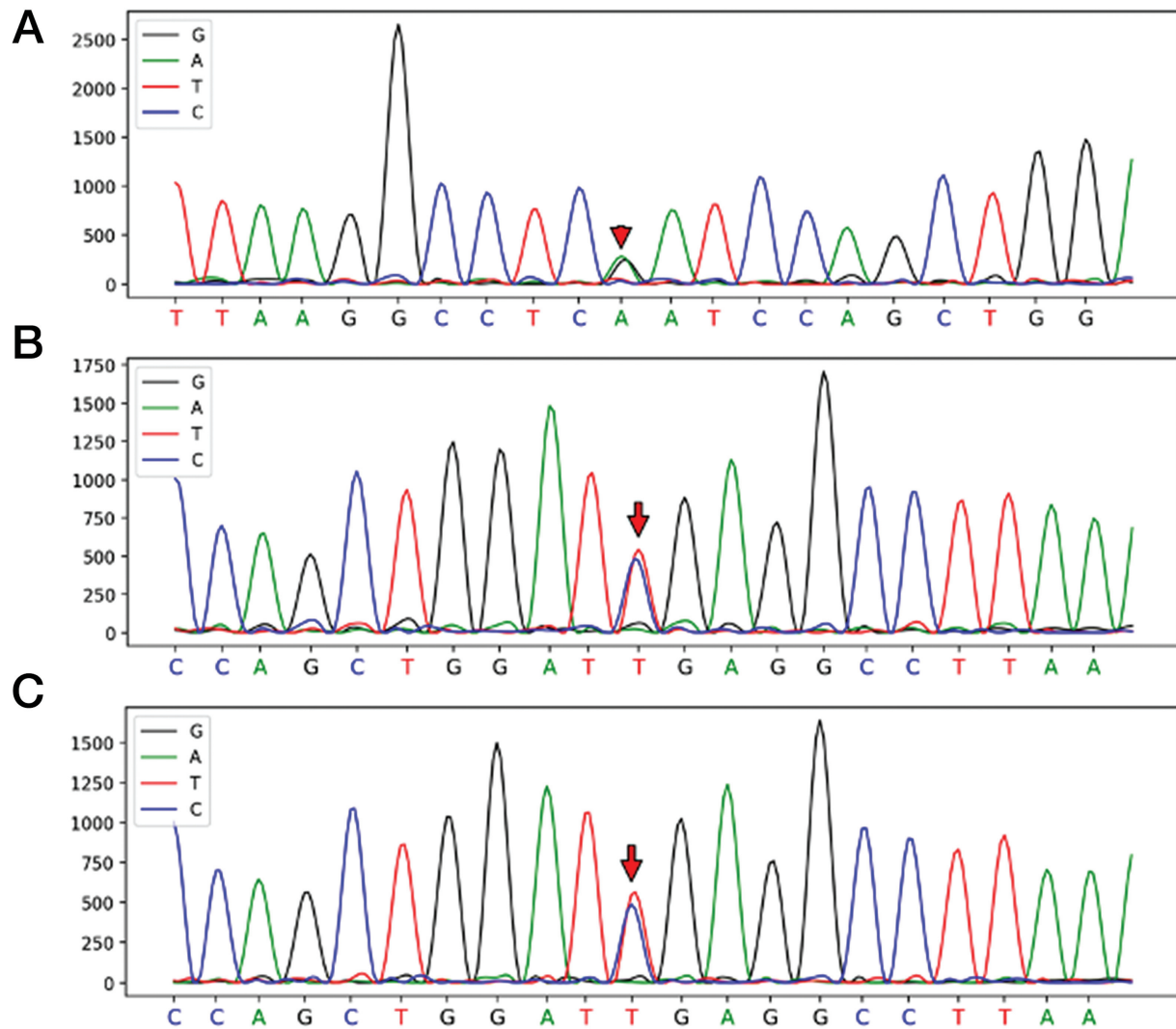


Fig. 3 Gene mutation data. (A, B) The sequencing information of the patient. (C) The sequencing information of his father. The red arrows shows where the mutation are.

screening throughout the treatment to be valuable. Based on these findings, we suspected that it is crucial to conduct not only thrombophilia-related gene testing but also dyslipidemia-related gene testing when administering drugs with a high risk of intriguing hyperlipidemia and CVST.

There are currently no standardized guidelines for the management of CVST during ALL treatment. Anticoagulation involving heparin and low molecular weight heparin remains the primary therapeutic approach for CVST, with mechanical thrombectomy and thrombolysis indicated when necessary. While the safety and efficacy of direct oral anticoagulants (DOACs) have been confirmed in adults, there has been no clinical experience in children.¹⁸ Previous studies have recommended prophylactic anticoagulation for patients at high risk of CVST and emphasized immediate initiation of anticoagulation for children and adolescents with CVST, irrespective of the presence of hemorrhage.^{13,19} Therefore, we recommend that pediatric ALL patients who experienced CSVT receive anticoagulation therapy as early as possible. As to prophylactic anticoagulation and the application of DOACs in pediatric ALL patients, further research is required to ascertain its necessity.

Debate continues regarding the safety of L-Asp reexposure, dose adjustment, or permanent discontinuation after CVST.¹⁹ In this case, we restarted L-Asp with short-acting products after the child recovered from neurological symptoms, but permanently discontinued L-Asp due to recurrent HTG and CVST. Decisions about rechallenging with L-Asp who experienced L-Asp-induced HTG and CVST must be made on personalized analysis. Consequently, we emphasize the urgent need for developing management strategies and standard guidelines for patients who developed HTG and CVST during ALL therapy.

Conclusion

In the treatment of childhood ALL, L-Asp is a critical component, playing a crucial role in both the induction and intensification phase, but L-Asp always contributes to several unique and potentially lethal toxicities. Genetic screening for thrombophilia-related mutation before L-Asp treatment, as well as lipid level monitoring during treatment course, and dyslipidemia-related gene mutation when necessary, may be of clinical significance for clinical decisions. Future research

Table 1 The coagulation function and lipids level at key time points

Time	Events	PT	APTT	TT	Fibrinogen	FDP	D-dimer	TG	CHO	HDL	LDL
April 18, 2023	First CVST (first seizure)	13.4	28.1	22.5	0.63	17	4.04	–	–	–	–
April 18, 2023	–	12.7	29.5	20.3	0.98	15.9	4.26	–	–	–	–
April 19, 2023	–	13.2	26.6	20.7	0.88	17.9	4.81	–	–	–	–
April 20, 2023	–	13	27.7	20.5	0.86	13.5	3.68	–	–	–	–
April 21, 2023	First CVST (second seizure)	12.7	29.6	23.2	0.84	10.3	3.58	–	–	–	–
April 21, 2023	–	12.3	28.2	22.6	1.03	11.5	3.47	–	–	–	–
April 22, 2023	–	12.9	31.4	24.9	1.43	12.7	4.00	–	–	–	–
He continued with the remaining remission induction and consolidation therapy, and coagulation dysfunction and hypofibrinogenemia recurred but normalized after fibrinogen and plasma supplementation											
December 7, 2023	Second CVST	11.7	26.7	20.1	2	<2	0.88	–	–	–	–
December 8, 2023	–	12.5	32.8	32.2	1.75	<2	0.65				
December 9, 2023	–	13.1	32.2	24.7	1.74	<2	0.55	49.73	20.34	4.04	0.63
December 12, 2023	–	13.2	29.9	18.7	1.87	<2	0.56	21.49	20.66	4.3	1.03
December 14, 2023	–	13.2	33	20	1.59	<2	0.42	–	–	–	–

Abbreviations: APTT, activated partial thromboplastin time; CHO, cholesterol; CVST, cerebral venous sinus thrombosis; FDP, fibrinogen degradation products; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PT, prothrombin time; TG, triglycerides; TT, thrombin time.

should focus not only on the guidance of managing the complication of L-Asp but also on exploring methods to reduce the side effects of L-Asp.

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Conflict of Interest
None declared.

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References

1 Malard F, Mohty M. Acute lymphoblastic leukaemia. *Lancet* 2020; 395(10230):1146–1162

2 Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. *Haematologica* 2020;105(11):2524–2539

3 Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin* 2021;71(01):7–33

4 Parsons SK, Skapek SX, Neufeld EJ, et al. Asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. *Blood* 1997;89(06):1886–1895

5 Greiner J, Schrappe M, Claviez A, et al; THROMBOTECT Study Investigators. THROMBOTECT - a randomized study comparing low molecular weight heparin, antithrombin and unfractionated heparin for thromboprophylaxis during induction therapy of

acute lymphoblastic leukemia in children and adolescents. *Haematologica* 2019;104(04):756–765

6 Couturier MA, Huguet F, Chevallier P, et al. Cerebral venous thrombosis in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma during induction chemotherapy with L-asparaginase: the GRAALL experience. *Am J Hematol* 2015;90(11):986–991

7 Hoogerbrugge N, Jansen H, Hoogerbrugge PM. Transient hyperlipidemia during treatment of ALL with L-asparaginase is related to decreased lipoprotein lipase activity. *Leukemia* 1997;11(08):1377–1379

8 Tozuka M, Yamauchi K, Hidaka H, Nakabayashi T, Okumura N, Katsuyama T. Characterization of hypertriglyceridemia induced by L-asparaginase therapy for acute lymphoblastic leukemia and malignant lymphoma. *Ann Clin Lab Sci* 1997;27(05):351–357

9 Kloos RQH, Pieters R, Jumelet FMV, de Groot-Kruseman HA, van den Bos C, van der Sluis IM. Individualized asparaginase dosing in childhood acute lymphoblastic leukemia. *J Clin Oncol* 2020;38(07):715–724

10 Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium protocol 91-01. *Blood* 2001;97(05):1211–1218

11 Abbott LS, Deevska M, Fernandez CV, et al. The impact of prophylactic fresh-frozen plasma and cryoprecipitate on the incidence of central nervous system thrombosis and hemorrhage in children with acute lymphoblastic leukemia receiving asparaginase. *Blood* 2009;114(25):5146–5151

12 Kawabori M, Kuroda S, Kudo K, et al. Susceptibility-weighted magnetic resonance imaging detects impaired cerebral hemodynamics in the superior sagittal sinus thrombosis—case report. *Neurol Med Chir (Tokyo)* 2009;49(06):248–251

13 Talamo L, Douvas M, Macik BG, Ornan D. Successful treatment with apixaban of sinus venous thrombosis due to pegylated asparaginase in a young adult with T cell acute lymphoblastic leukemia: case report and review of management. *Ann Hematol* 2017;96(04):691–693

- 14 Sui J, Zhang Y, Yang L, et al. Successful treatment with rivaroxaban of cerebral venous thrombosis and bone marrow necrosis induced by pegaspargase: a case report and literature review. *Medicine (Baltimore)* 2017;96(46):e8715
- 15 Parrella A, Iannuzzi A, Annunziata M, et al. Haematological drugs affecting lipid metabolism and vascular health. *Biomedicines* 2022;10(08):1935
- 16 Caruso V, Iacoviello L, Di Castelnuovo A, et al. Thrombotic complications in childhood acute lymphoblastic leukemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients. *Blood* 2006;108(07):2216–2222
- 17 Athale UH, Chan AK. Thrombosis in children with acute lymphoblastic leukemia Part III. Pathogenesis of thrombosis in children with acute lymphoblastic leukemia: effects of host environment. *Thromb Res* 2003;111(06):321–327
- 18 Rank CU, Toft N, Tuckuviene R, et al. Thromboembolism in acute lymphoblastic leukemia: results of NOPHO ALL2008 protocol treatment in patients aged 1 to 45 years. *Blood* 2018;131(22):2475–2484
- 19 Gupta S, Wang C, Raetz EA, et al. Impact of asparaginase discontinuation on outcome in childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group. *J Clin Oncol* 2020;38(17):1897–1905