Plasma exchange for hyperammonemia-induced reduced consciousness after PEG-asparaginase in an adult patient with acute lymphoblastic leukemia

We present the case of a 19-year-old female patient diagnosed with cortical T-cell acute lymphoblastic leukemia (T-ALL) in the summer of 2024, classified as NOS (not otherwise specified) according to the 2022 World Health Organization criteria[1] and the 2022 International Consensus Classification.[2] This retrospective data collection was performed in accordance with local legal requirements (Hamburger Krankenhausgesetz, HmbKHG). Treatment was initiated according to national therapy guidelines of the German Multicenter ALL Study Group for Adult ALL (GMALL),[3] representing a pediatric-based therapy protocol. Prephase and induction therapy consisted of chemotherapy, with the administration of 2,000 U/m^2 pegylated (PEG)-asparaginase (Oncaspar™) at the end of the first induction cycle (day 22 after therapy initiation). Induction therapy also includes the application of dexamethasone (10 mg/m^2) on days 1, 2, and 8-11, vincristine (2 mg) on days 1 and 8, daunorubicine (45 mg/m^2) on days 1, 2, 7, and 8, and intrathecal prophylaxis with methotrexate (15 mg) on day 5. Before PEG-asparaginase administration, pre-existing hepatic diseases had been ruled out by medical history, laboratory evaluations (bilirubin, aspartate-aminotransferase [AST], alanine-aminotransferase [ALT], gamma-glutamyltransferase [GGT], glutamate-dehydrogenase [GLDH], albumin and alkaline phosphatase [ALP]), and an ultrasound of the abdominal organs. She was not on any regular medication and only a non-severe asthma was reported in the medical history. Her body mass index (BMI) was normal (22 kg/m^2). Leukemic meningitis was ruled out during the prephase of the GMALL protocol.

Six days after the administration of PEG-asparaginase (2,000 U/m^2 body surface area), the patient developed increasing fatigue. Over the next seven days, her condition deteriorated to the point where she became barely responsive, requiring transfer to the intensive care unit (ICU) at day 35 after the start of initial prephase treatment. At that time, cranial magnetic resonance imaging was performed as part of the diagnostic workup for her decrease in alertness, which showed no signs of sinus venous thrombosis or ischemia. Additionally, a cranial computed tomography scan revealed no critical intracranial mass effect and intracranial bleeding was excluded. Lumbar puncture ruled out an infectious cause of her symptoms (negative polymerase chain reaction tests for herpes simplex virus, cytomegalovirus, varicella zoster virus, toxoplasma, human herpes virus 6 (HHV6) and 8 (HHV8), as well as leukemic meningitis (cytomorphology, fluorescence-activated cell sorting [FACS]). The neurological status was described as Glasgow Coma Scale (GCS) 10: motor response, 4 points (normal flexion); verbal response, 2 points (sounds); eye opening, 4 points [spontaneous]) with psychomotor slowing, no gaze palsy was noted, the pupils were isocoric, there were no visual field deficits, and no facial palsy was observed. There was no paresis in the arm-holding or leg-holding tests, and no ataxia was detected in the head-holding or finger-nose tests. No sensory deficits were found. The patient showed no signs of aphasia, apraxia, dysarthria, or neglect. Reflexes were normal, and there were no signs of meningism. Upon admission to the ICU, laboratory findings revealed hyperammonemia (129 µmol/L, which is 2.5 x upper laboratory normal; normal range: 16-53 µmol/L) and a slightly decreased cholinesterase (CHE), while other liver function parameters were almost normal and showed little dynamic change (e.g., bilirubin, AST/ALT, GGT, GLDH, AP) (Figure 1). Sputum cultures taken upon ICU admission detected *Ureaplasma parvum*, but blood cultures remained sterile, and the patient had no symptoms of pulmonary infection. In line with literature recommendations, treatment with lactulose was initiated due to hyperammonemia for stool regulation, followed by glycerol phenylbutyrate as no clinical improvement was observed. Additionally, an empirical anti-infective regimen with ciprofloxacin and doxycycline was given for seven days due to detection of *Ureaplasma parvum*.

After further clinical deterioration and a decrease in the GCS, we opted for plasma exchange (PE). A total of three sessions of PE were performed on consecutive days using a Plasauto™ device and a Plasmaflo OP-05 (0.5 m^2) membrane. The total plasma exchange volume was 21,160 mL. After the first session, the patient's clinical condition improved significantly, and she became responsive again. Upon completion of the three PE sessions, the patient was transferred back to a general ward (day 41 after the start of the initial prephase). Further investigating laboratory findings showed a recovery of antithrombin activity and fibrinogen after eliminating PEG-asparaginase with plasma exchange (Table 2). For an additional 15 days, the patient reported psychomotor disturbances, primarily in the form of hallucinations, which gradually lessened in intensity. Subsequently, these symptoms completely resolved, and the patient was able to continue with the second cycle of induction therapy.

According to the GMALL protocol, it is recommended to measure PEG-asparaginase activity in serum on days 7 and

14 post administration of the first dose to rule out early inactivation and to ensure an activity level of at least 100 U/L on day 14, indicating sufficient asparagine depletion. These measurements were also performed in our patient, showing a high 7- and 14-day activity of 568 U/L and 405 U/L, respectively. Following a single session of PE, the activity decreased to 74 U/L. Three days after completing the PE sessions, PEG-asparaginase activity was undetectable (Figure 1). The elevated serum ammonia levels normalized during the PE treatment.

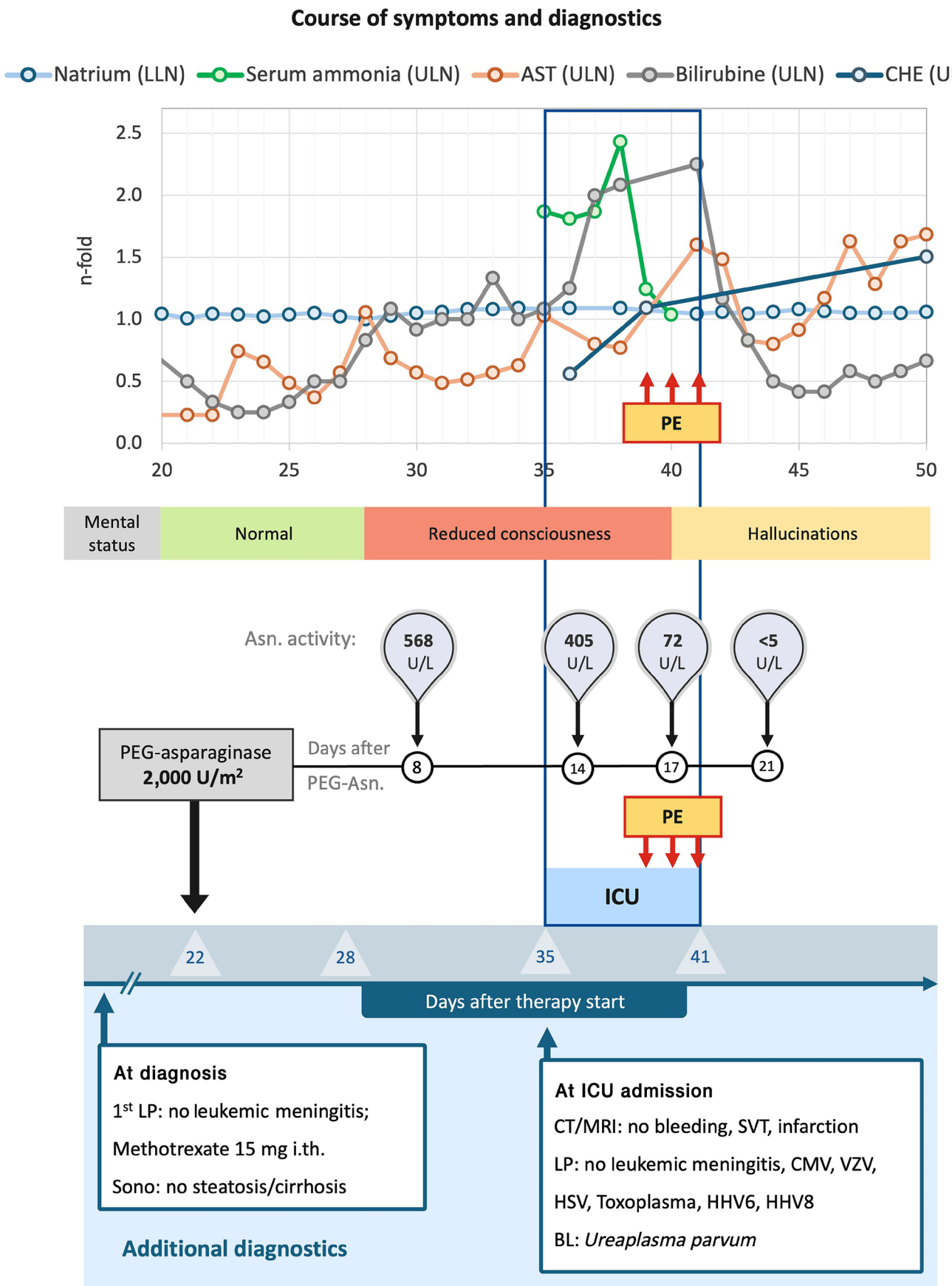

Figure 1. Treatment history of a 19-year-old patient with hyperammonemia-induced reduced consciousness. Laboratory test results are presented as n-fold of upper laboratory normal (ULN) or lower laboratory normal (LLN) as appropriate. Leukemic meningitis was ruled out by cytomorphology and fluorescence-activated cell sorting (FACS). Infectious diseases of the central nervous system (CNS) were ruled out by polymerase chain reaction (PCR) and serology (cytomegalovirus [CMV], varicella zoster virus [VZV], herpes simplex virus [HSV]) or by serology only (Toxoplasma) or by PCR only (human herpes virus 6 [HHV6] and 8 [HHV8]), Asn.: asparaginase; AST: aspartate aminotransferase; BL: bronchial system; CHE: cholinesterase; CT: computed tomography; ICU: intensive care unit; i.th.: intrathecal; LP: lumbar puncture; MRI: magnet resonance imaging; PE: plasma exchange; PEG-asn.: PEG-asparaginase; Sono: sonography; SVT: sinus venous thrombosis.

For the treatment of ALL patients, asparaginase is an important component of standard chemotherapy protocols. In the GMALL protocol, PEG-asparaginase is used as a standard with a prolonged half-life of 5-8 days. Hyperammonemia can occur after asparaginase administration due to the enzyme's mechanism of action, which metabolizes asparagine into aspartic acid and ammonia, and also converts glutamine into glutamate and ammonia.[4] After checking for interactions between chemotherapeutic drugs in this specific induction regimen, no interactions are known in the context of hyperammonemia. In the literature, several case reports and case series describe hyperammonemia following the administration of PEG-asparaginase, mainly in pediatric ALL patients,[5-11] while nearly no cases have been described in adults.[6] Ammonia levels in pediatric ALL patients treated with PEG-asparaginase suffering from encephalopathy differed widely in range but reports exceeding 200 μmol/L are common.[6] However, in adult patients, it is unclear whether ammonia levels correlate with clinical severity of encephalopathy. Treatment of patients with asparaginase-induced hyperammonemia varied from lactulose administration to promote enteral ammonia excretion, and reduced protein residence time, or the administration of glycerol phenylbutyrate or sodium phenylbutyrate, or a combination of both. The use of plasma exchange to eliminate ammonia and PEG-asparaginase, a 140 kDa protein, presents another therapeutic option; however, clinical evidence is limited with only three publications addressing this treatment.[12-14] The cause of hyperammonemia in our patient is most likely related to asparagine depletion due to PEG-asparaginase, with ammonia being produced as a byproduct. Additionally, the accompanying *Ureaplasma parvum* infection could have contributed to elevated ammonia levels, as *Ureaplasma* species are known to produce ammonia as a metabolic byproduct.[15] During adequate conservative medication treatment (lactulose, glycerol phenylbutyrate, doxycycline and ciprofloxacin), ammonia levels did not decrease and the patient's status did not improve. Although plasma exchange ultimately led to a rapid improvement in symptoms, it is noteworthy that after one session of plasma exchange asparaginase activity was significantly reduced but remained detectable. It was only after three sessions of plasma exchange and a total exchange volume of approximately 21 L of plasma that no asparaginase activity was detectable. We conclude that although symptomatic hyperammonemia following PEG-asparaginase application is rare in adults,

Table 1. Overview of the previously published cases of adult acute lymphoblastic leukemia patients undergoing plasmaphereses due to PEG-asparaginase-induced toxicities..

Case report study	Sex and age of patient	Indication for plasmapheresis	N of plasmaphereses	Symptoms resolved
Tölle *et al.* 2024[12]	Male, 57 years	Liver toxicity, high PEG-asparagine level at day 27 after administration	3	Yes
Bilgir *et al.* 2013[13]	Female, 48 years	Encephalopathy (no ammoniac level indicated)	4	Yes
Göpel *et al.* 2016[14]	Male, 44 years	Liver toxicity/reduced liver synthesis capacity	3	Yes

Table 2. Selected laboratory test results at various relevant time points.

Therapy phase in days after start of prephase	Albumin, g/dL Ref. values 34.0-50.0	Fibrinogen, Clauss, g/dL Ref. values 1.7-4.2	Antithrombin activity, % Ref. values 79-120	INR
Before start Day -4	38.7	2.71	96	1.1
Before PEG-asn. application Day 22	26.5	5.70	58	1.0
Worsening of consciousness Day 28	28.0	2.14	63	1.1
Before transfer to ICU Day 34	23.8	1.19	48	1.3
After plasma exchange Day 41	31.5	2.72	82	1.1

ICU: intensive care unit; INR: International normalized ratio; PEG-asn.: PEG-asparaginase; Ref.: reference.

it always needs to be considered as a potential cause of neurologic deterioration, even one week or more after PEG-asparaginase application. Besides conservative therapy options, high volume plasma exchange is an efficient treatment option for patients suffering from PEG-asparaginase-induced reduced consciousness that does not respond to other therapies.

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Contributions

FK, AF, LK, SK, FUl and FUd collected the clinical data. FK, AF, LK, SK, FUl, FUd, CK, DK, CB, NG, WF and FM were involved in treating the patient and making treatment decisions. FK, WF and FM summarized all data and drafted the manuscript. FK, WF and FM revised the final version. All authors have read and agreed to the published version of the manuscript.

Data-sharing statement

The data generated for the current study are available from the corresponding authors on reasonable request.

References

1. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-1748.
2. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228.
3. Goekbuget N, Stelljes M, Viardot A, et al. First results of the risk-adapted, MRD-stratified GMALL trial 08/2013 in 705 adults with newly diagnosed acute lymphoblastic leukemia/lymphoma (ALL/LBL). Blood. 2021;138(Suppl 1):362.
4. Asselin B, Rizzari C. Asparaginase pharmacokinetics and implications of therapeutic drug monitoring. Leuk Lymphoma. 2015;56(8):2273-2280.
5. Sudour H, Schmitt C, Contet A, Chastagner P, Feillet F. Acute metabolic encephalopathy in two patients treated with asparaginase and ondasetron. Am J Hematol. 2011;86(3):323-325.
6. Heitink-Pollé KMJ, Prinsen BHCMT, de Koning TJ, van Hasselt PM, Bierings MB. High incidence of symptomatic hyperammonemia in children with acute lymphoblastic leukemia receiving pegylated asparaginase. JIMD Rep.

2012;7:103-108.
7. Gossai N, Richards M, Boman L, et al. Symptomatic hyperammonemia with Erwinia chrysanthemi-derived asparaginase in pediatric leukemia patients. J Pediatr Hematol Oncol. 2018;40(4):312-315.
8. Jaing T-H, Lin J-L, Lin Y-P, Yang S-H, Lin J-J, Hsia S-H. Hyperammonemic encephalopathy after induction chemotherapy for acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2009;31(12):955-956.
9. Nussbaum V, Lubcke N, Findlay R. Hyperammonemia secondary to asparaginase: a case series. J Oncol Pharm Pract. 2016;22(1):161-164.
10. Xu SR, Yao EG, Dong ZR, et al. Plasma ammonia in patients with acute leukemia. Chin Med J (Engl). 1992;105(9):713-716.
11. Lee A, Eldem I, Altintas B, et al. Treatment and outcomes of symptomatic hyperammonemia following asparaginase therapy in children with acute lymphoblastic leukemia. Mol Genet Metab. 2023;139(3):107627.
12. Tölle M, Gökbuget N, Habringer S, Keller U, Schwartz S. Plasmapheresis effectively abrogates severe liver toxicity of pegaspargase in a patient with acute lymphoblastic leukemia. Ann Hematol. 2024;103(8):3269-3271.
13. Bilgir O, Calan M, Bilgir F, Cagliyan G, Arslan O. An experience with plasma exchange treatment of acute lymphoblastic leukemia in a case with fulminant hepatitis related to L-asparaginase. Transfus Apher Sci. 2013;49(2):328-330.
14. Göpel W, Schnetzke U, Hochhaus A, Scholl S. Functional acute liver failure after treatment with pegylated asparaginase in a patient with acute lymphoblastic leukemia: potential impact of plasmapheresis. Ann Hematol. 2016;95(11):1899-1901.
15. Glass JI, Lefkowitz EJ, Glass JS, Heiner CR, Chen EY, Cassell GH. The complete sequence of the mucosal pathogen Ureaplasma urealyticum. Nature. 2000;407(6805):757-762.