Transient Hyperammonemic Encephalopathy in a Child with Relapsed Acute Lymphoblastic Leukemia and Severe Tumor Lysis Syndrome

Ilja Dubinski[1] Tobias Feuchtinger[2] Esther Maier[3] Moritz Tacke[4] Florian Hoffmann[1]

[1] Department for Pediatric Critical Care Medicine, Ludwig Maximilians University Munich, Dr. von Hauner Children's Hospital, Munich, Germany
[2] Department for Pediatric Oncology, Hematology and Hemostaseology and Stem Cell Transplantation, Ludwig Maximilians University Munich, Dr. von Hauner Children's Hospital, Munich, Germany
[3] Department for Inborn Errors of Metabolism, Ludwig Maximilians University Munich, Dr. von Hauner Children's Hospital, Munich, Germany
[4] Department for Pediatric Neurology, Ludwig Maximilians University Munich, Dr. von Hauner Children's Hospital, Munich, Germany

Address for correspondence Ilja Dubinski, MD, Department for Pediatric Critical Care Medicine, Ludwig Maximilians University Munich, Dr. von Hauner Children's Hospital, Lindwurmstrasse 4, D-80337 Munich, Bavaria, Germany
(e-mail: ilja.dubinski@med.uni-muenchen.de).

Abstract

Keywords
► hyperammonemia
► hyperammonemic encephalopathy
► common acute lymphoblastic leukemia

Idiopathic hyperammonemia (IHA) is a severe condition, which has been reported in intensive chemotherapy and bone marrow transplantation. This case elucidates the diagnostic dilemma in children undergoing initiation of chemotherapy and developing severe disorders of qualitative and quantitative consciousness in the presence of hyperammonemia (HA) and lactic acidosis. The role of mitoxantrone as a causative agent for IHA in children is elusive. Children undergoing chemotherapy are often in a poor general condition, and the clinical presentation of HA is heterogeneous. This case should be a reminder for clinicians to check for HA in children with tumor lysis syndrome and acute neurological deterioration.

Introduction

Hyperammonemia (HA) is defined as an elevation of plasma ammonia concentrations above the normal range. There are several well-known risk factors in childhood, such as chemotherapy, septic shock, gastrointestinal bleeding, renal diseases, severe muscle exertion, heavy exercise, inborn errors of metabolism (e.g., urea cycle disorders), acute liver failure due to hepatotropic infectious diseases or liver autoimmune diseases, Reye syndrome, parenteral nutrition, urinary tract infection, and drug-related toxicity (e.g., valproate or barbiturates).[1–4] The clinical presentation is heterogeneous ranging from mild symptoms like nausea to acute life-threatening conditions with encephalopathy, cerebral edema, and coma.[1] Since the 1980s, there have been reports on HA following intensive chemotherapy and bone marrow transplantation. The term idiopathic hyperammonemia (IHA) has been suggested to describe this condition.[2,3] IHA is defined as elevated concentration of ammonia in serum with normal test results for liver enzymes, and no evidence for inborn errors of metabolism or other identifiable causes.[2,3] The underlying pathophysiological mechanism of this often fatal condition is not yet fully understood and is very likely to be multifactorial.[3–10] There are several available treatment options for HA. Many of them were adopted from the management of inborn

errors of metabolism with HA, such as arginine (-improvement/stimulation of nitrogen excretion by the Krebs–Henseleit cycle). The main goals are the removal of nitrogen by enhancing nitrogen excretion by hemodialysis and ammonia-trapping therapy (alternate pathway therapy with sodium benzoate, sodium phenylacetate or sodium phenylbutyrate) and the reduction of exogenous nitrogen load (optimization of enteral/parenteral nutrition). To reduce the intestinal source of ammonium lactulosis and neomycin/rifaximin are used. Treatment should be started early and be regularly reevaluated.[4]

We describe a unique clinical phenotype of IHA associated with marked tumor lysis syndrome (TLS) after the administration of dexamethasone and mitoxantrone. The role of mitoxantrone as a causative agent for IHA in children is elusive.

Case Presentation

Our patient, an 8-year-old male, presented with common lymphoblastic leukemia (central nervous system [CNS] not involved) and received chemotherapy according to the CoALL-08/09 protocol (German Co-operative Study Group for Treatment of Acute Lymphoblastic Leukemia 08–09, Low-Risk group) from March 2017 to October 2017. From October 2017 to February 2018, he was on oral maintenance chemotherapy with methotrexate and 6-mercaptopurine. In February 2018, our patient presented with progressive fatigue and reduced general condition. Laboratory analysis revealed anemia (7.5 g/dL, reference range (RR): 11.8–14.8), thrombocytopenia (7.0 G/L, RR: 195–464), and leukopenia (2.73 G/L, RR: 3.50–14.00). The diagnostic workup revealed a relapse of common acute lymphoblastic leukemia. The treatment was started according to the IntReALL-HR protocol (International Study for Treatment of High Risk Childhood Relapsed Acute Lymphoblastic Leukemia 2010, High-Risk group) with dexamethasone (20 mg/m², intravenously, twice a day) from therapy day 0 to 5 and mitoxantrone (10 mg/m², intravenously, once a day) on therapy day 0. Furthermore, he received a concomitant intravenous hydration therapy (4,000 mL/m² per day). He developed severe TLS with hyperuricemia (9.2 mg/dL, RR: 1.9–5.0), hyperphosphatemia (7.4 mg/dL, RR: 3.0–5.4), hyperkalemia (6.6 mmol/L, RR: 3.3–4.7), and lactic acidosis (pH = 7.22, RR: 7.35–7.43, lactate = 13.3 mmol/L, RR: 0.5–2.2, base excess: −14.6 mmol/L, RR: −1.5 to 3.0). The coagulation parameters were slightly abnormal (international normalized ratio: 1.5, RR: 0.8–1.2, and partial thromboplastin time: 45 seconds, RR: 25–42). The liver function studies were normal (total bilirubin, alanine-aminotransferase, and γ-glutamyltransferase). There was no evidence for acute kidney injury. Repeated blood cultures remained sterile. On therapy day 1, he developed a qualitative and quantitative disorder of consciousness in an undulating manner with confusion, agitation, disorientation, anxiousness, and somnolence, respectively. An electroencephalography revealed a generalized slowing, consistent with metabolic encephalopathy (►**Fig. 1**). A computed tomography of the brain showed
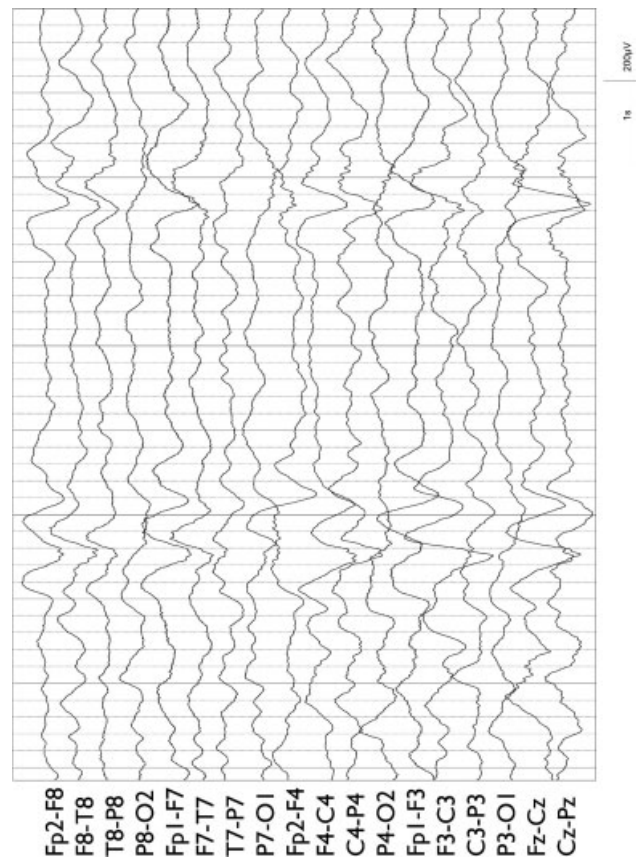

Fig. 1 Electroencephalography with generalized slowing and periodic pattern well consistent with metabolic encephalopathy.

no apparent morphological involvement of the CNS. A magnetic resonance imaging on the following day confirmed the results. A sonography of the abdomen revealed a hepatosplenomegaly and diffuse leukemic infiltration of liver, spleen, gut, and kidneys. There was no evidence for hepatic veno-occlusive disease. With a lumbar puncture, malignant cells and a CNS infection could be excluded. Strikingly, the concentration of ammonia in serum was significantly elevated (213 µmol/L, RR: 16–53). Sampling was performed by using a triple-lumen Hickman catheter. The sample was transported refrigerated. The measurement was performed immediately upon arrival at the laboratory. Additionally, analysis of organic acids in urine, amino acids, and carnitine/acylcarnitine in plasma did not indicate an inborn error of metabolism associated with HA. Moreover, a comprehensive workup for hepatotropic infectious diseases and autoimmune liver diseases showed no significant findings.

The TLS could be managed sufficiently with hydration, rasburicase, and forced diuresis. The patient received crystalloid fluids only. Our management of HA comprised lactulosis three times a day (3 × 3.3 g) and rifaximin twice a day (2 × 200 mg) via nasogastral tube to reduce the intestinal source of ammonium and sodium benzoate (100 mg per kg per day, continuously) intravenously for ammonia-trapping therapy. After a subsequent plateau phase with slightly elevated and fluctuating results for the concentration of
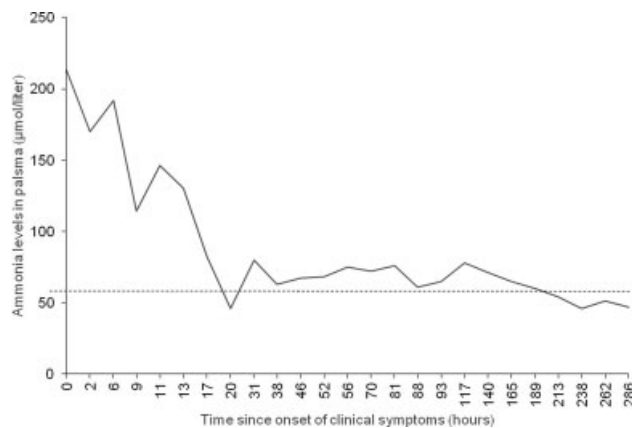
Fig. 2 Plasmatic concentration of ammonia versus hours since onset of clinical symptoms. The dashed line indicates the threshold (= 53 μmol/L) of pathological concentration of ammonia in serum.

ammonia in serum (with a range from 54 to 80 μmol/L), they returned to normal after 165 hours (►**Fig. 2**).

Discussion

IHA is generally regarded as a diagnosis of exclusion. Since we do not have any identifiable causes for HA in our patient, we suspect a case of IHA. IHA was previously described in the literature in the context of high-dose chemotherapy for hematological malignancies,[3-7] chemotherapy in solid tumors,[11] bone marrow transplantation for malignant,[2,3,8-10] and nonmalignant diseases (Hurler syndrome) and solid organ transplants (lung transplant).[12,13] IHA is a rare, but frequently lethal complication, despite ammonia-trapping therapy and hemofiltration.[5,6] Thus, we hypothesize a mild and unusually early-onset form of IHA in our patient, who received dexamethasone and mitoxantrone on the first therapy day.

The occurrence of IHA during initiation of chemotherapy for leukemia is highly unusual and was described in a pediatric population only twice: once on day 15 in a 15-year-old male with newly diagnosed acute lymphoblastic leukemia and initiation of chemotherapy with steroids only[14] and another time in a case of a 13-month-old male with a lethal IHA on day 35 after induction therapy with seven different chemotherapeutic drugs.[6]

The only report of IHA in combination with mitoxantrone described the case of a 59-year-old woman who received a polychemotherapy including mitoxantrone.[15] However, mitoxantrone was linked to mitochondrial cardio toxicity in a dose-dependent manner during long-term use in a mouse model.[16] An acute adverse reaction to mitoxantrone cannot be ruled out in our patient. Yet, a study in de novo diagnosed lymphoblastic leukemia could not show a higher toxicity for mitoxantrone compared with daunorubicin.[17]

Many chemotherapeutic agents have been linked to IHA: vinciristine, busulfan, cyclophosphamid, etoposide, methotrexate, cytarabain, daunomycin, and amsacrine.[4,5,18] However, some chemotherapeutic agents seem to cause less

devastating outcomes when it comes to HA, as for instance asparaginase and 5-Fluorouracil.[4] Some reports suggest specific adverse drug effects in these cases. For instance, treatment with asparaginase for acute leukemia has been linked to transient HA.[19-21] Asparaginase hydrolyses asparagine in aspartic acid and ammonia as a mechanism of action. Measuring plasma concentrations of ammonia was previously suggested to be used as a parameter for drug efficacy and toxicity.[22-24] The intermediate product of 5-Fluorouracil, fluoracetate, is regarded as a direct inhibitor of the urea cycle, thus leading to elevated plasmatic ammonia concentrations.[4,25]

For a functioning homeostasis of ammonia a functioning Krebs–Henseleit cycle and a balanced ratio of protein anabolism and catabolism are crucial.[26] The capacity of the Krebs–Henseleit cycle varies in humans without clinical relevance.[19,27] However, when HA is combined with a previously unknown latent ornithine transcarbamylase deficiency, a defect of the urea cycle, lethal outcomes have been reported.[23] Since we do not have evidence for underlying enzymatic defects in the Krebs-Henseleit cycle in our patient and no chemotherapeutic agents with known transient HA as a side-effect were used, we hypothesize that our patient had a mild form of IHA. A transient form of HA due to massive acute protein breakdown in TLS should be considered as a differential diagnosis. In addition, liver infiltration with leukemia blasts may have exaggerated the metabolic decompensation.

Conclusion

Children undergoing chemotherapy are often temporarily in a poor general condition and the clinical presentation of HA is heterogeneous. This could be one explanation for HA being potentially under-recognized and thus under-diagnosed in TLS.

This case report should be a reminder for pediatric intensive care doctors to check for HA in children with TLS and acute neurological deterioration. Routine measurements of plasma ammonia concentrations in high-risk patients could lead to earlier diagnosis.

In addition, latent metabolic disorders and drug-induced HA should be taken into consideration.

To conclude, in children with acute alterations in consciousness of unknown origin during chemotherapy and especially with TLS, HA should be considered and closely monitored.

References

1 Auron A, Brophy PD. Hyperammonemia in review: pathophysiology, diagnosis, and treatment. Pediatr Nephrol 2012;27(02): 207–222

2 Davies SM, Szabo E, Wagner JE, Ramsay NK, Weisdorf DJ. Idiopathic hyperammonemia: a frequently lethal complication of bone marrow transplantation. Bone Marrow Transplant 1996; 17(06):1119–1125

3 Leonard JV, Kay JD. Acute encephalopathy and hyperammonaemia complicating treatment of acute lymphoblastic leukaemia with asparaginase. Lancet 1986;1(8473):162–163

4 Nott L, Price TJ, Pittman K, Patterson K, Fletcher J. Hyperammonemia encephalopathy: an important cause of neurological deterioration following chemotherapy. Leuk Lymphoma 2007;48(09): 1702–1711

5 Mitchell RB, Wagner JE, Karp JE, et al. Syndrome of idiopathic hyperammonemia after high-dose chemotherapy: review of nine cases. Am J Med 1988;85(05):662–667

6 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

7 Watson AJ, Chambers T, Karp JE, Risch VR, Walker WG, Brusilow SW. Transient idiopathic hyperammonemia in adults. Lancet 1985;2(8467):1271–1274

8 Espinós J, Rifón J, Pérez-Calvo J, Nieto Y. Idiopathic hyperammonemia following high-dose chemotherapy. Bone Marrow Transplant 2006;37(09):899–899

9 Ho AY, Mijovic A, Pagliuca A, Mufti GJ. Idiopathic hyperammonemia syndrome following allogeneic peripheral blood progenitor cell transplantation (allo-PBPCT). Bone Marrow Transplant 1997; 20(11):1007–1008

10 Tse N, Cederbaum S, Glaspy JA. Hyperammonemia following allogeneic bone marrow transplantation. Am J Hematol 1991; 38(02):140–141

11 Thomas SA, Tomeh N, Theard S. Fluorouracil-induced hyperammonemia in a patient with colorectal cancer. Anticancer Res 2015;35(12):6761–6763

12 Snyder MJ, Bradford WD, Kishnani PS, Hale LP. Idiopathic hyperammonemia following an unrelated cord blood transplant for mucopolysaccharidosis I. Pediatr Dev Pathol 2003;6(01): 78–83

13 Lichtenstein GR, Yang Y-X, Nunes FA, et al. Fatal hyperammonemia after orthotopic lung transplantation. Ann Intern Med 2000;132 (04):283–287

14 Kobayashi S, Ito M, Sano H, et al. Idiopathic hyperammonemia that developed during initial treatment with steroid in a patient with newly diagnosed leukemia. J Pediatr Hematol Oncol 2015;37 (06):e361–e363

15 Metzeler KH, Boeck S, Christ B, et al. Idiopathic hyperammonemia (IHA) after dose-dense induction chemotherapy for acute myeloid leukemia: case report and review of the literature. Leuk Res 2009; 33(07):e69–e72

16 Rossato LG, Costa VM, Dallegrave E, et al. Mitochondrial cumulative damage induced by mitoxantrone: late onset cardiac energetic impairment. Cardiovasc Toxicol 2014;14(01):30–40

17 Nickel RS, Keller F, Bergsagel J, et al. Mitoxantrone as a substitute for daunorubicin during induction in newly diagnosed lymphoblastic leukemia and lymphoma. Pediatr Blood Cancer 2014;61 (05):810–814

18 del Rosario M, Werlin SL, Lauer SJ. Hyperammonemic encephalopathy after chemotherapy. Survival after treatment with sodium benzoate and sodium phenylacetate. J Clin Gastroenterol 1997;25(04):682–684

19 Jörck C, Kiess W, Weigel JFW, Mütze U, Bierbach U, Beblo S. Transient hyperammonemia due to L-asparaginase therapy in children with acute lymphoblastic leukemia or non-Hodgkin lymphoma. Pediatr Hematol Oncol 2011;28(01):3–9

20 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. In: Brown G, Morava E, Peters V, Gibson KM, Zschocke J, eds. JIMD Reports: Case and Research Reports, 2012/4. Vol 7. JIMD Reports Springer Berlin Heidelberg; 2012:103–108

21 Steiner M, Attarbaschi A, Kastner U, et al. Distinct fluctuations of ammonia levels during asparaginase therapy for childhood acute leukemia. Pediatr Blood Cancer 2007;49(05):640–642

22 Stock W, Douer D, DeAngelo DJ, et al. Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. Leuk Lymphoma 2011;52(12):2237–2253

23 Peters M, Zee-Cheng J, Kuhl A, Orozco J, Lally E, Schwoerer JS. Pegylated asparaginase as cause of fatal hyperammonemia in patients with latent urea cycle disorder. Pediatr Blood Cancer 2018;65(09):e27239

24 Czogała M, Balwierz W, Sztefko K, Rogatko I. Clinical utility of ammonia concentration as a diagnostic test in monitoring of the treatment with L-asparaginase in children with acute lymphoblastic leukemia. BioMed Res Int 2014;2014:945860

25 Koenig H, Patel A. Biochemical basis for fluorouracil neurotoxicity. The role of Krebs cycle inhibition by fluoroacetate. Arch Neurol 1970;23(02):155–160

26 Cohn RM, Roth KS. Hyperammonemia, bane of the brain. Clin Pediatr (Phila) 2004;43(08):683–689

27 Kohn MC, Tohmaz AS, Giroux KJ, Blumenthal GM, Feezor MD, Millington DS. Robustness of MetaNet graph models: predicting control of urea production in humans. Biosystems 2002;65(01): 61–78