REVIEW ARTICLE

Asparaginase-associated hyperammonemia

Raheel Altaf Raja,[1] Bodil Als-Nielsen,[1] Allan M. Lund,[1,2] Hendrik Vilstrup,[3] Kim Peder Dalhoff[2,4] and Kjeld Schmiegelow[1,2]

[1]Department of Pediatrics and Adolescent Medicine, Rigshospitalet, University of Copenhagen, Copenhagen; [2]Department of Clinical Medicine, Faculty of Medicine, University of Copenhagen, Copenhagen; [3]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus and [4]Clinical Pharmacology, Bispebjerg Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark

Correspondence: R.A. Raja
raheel.altaf.raja@regionh.dk

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Abstract

Asparaginase is an essential drug in the treatment of acute lymphoblastic leukemia, and discontinuation of asparaginase therapy due to clinical toxicity or silent inactivation may lead to reduced event-free survival. Common toxicities include hypersensitivity reactions, acute pancreatitis, thrombosis, hepatotoxicity, and hyperlipidemia. In addition, several small case series have described asparaginase-associated hyperammonemia, the true frequency and clinical importance of which, both short- and long-term, remain unclear. Descriptions vary from asymptomatic patients to those with severe, acute encephalopathy leading to withdrawal of asparaginase therapy. The cause and management of the problem remain elusive. This review summarizes current knowledge on asparaginase-associated hyperammonemia, including its pathogenesis, clinical presentation, and possible interventions.

Introduction

Asparaginase is an essential drug in the treatment of acute lymphoblastic leukemia (ALL) in children. Discontinuation of asparaginase therapy may result in a decrease in event-free survival. The main cause of asparaginase discontinuation is asparaginase-associated toxicity, e.g., allergic reactions or silent inactivation, acute pancreatitis, and thromboembolism.[1-6]

Asparaginase-associated hyperammonemia (AAH) is a known, but infrequently reported, adverse reaction in patients receiving asparaginase. Ammonia is a by-product of the deamidation of both asparagine and glutamine.[7-12] In most patients AAH is transient and generally asymptomatic. However, it has been reported that some patients may experience severe encephalopathy. Although hyperammonemia is a known cause of cognitive impairment in patients with urea cycle deficiency, the impact on the intelligence quotient of significant and extended exposure to hyperammonemia secondary to asparaginase treatment has not been thoroughly studied, even though the ammonia levels seen in ALL patients are comparable to those in patients with inborn urea cycle deficiencies.[13]

There is no consensus as to which interventions should be applied to reduce symptomatic ammonia levels during asparaginase therapy, including whether to reduce dose, prolong infusion time, switch to a different asparaginase formulation, or discontinue asparaginase therapy.

This review summarizes current knowledge on AAH, including its pathogenesis, clinical presentation, potential deleterious effects, and possible interventions. A clinical case is presented early to illustrate the challenges of AAH management

An illustrative case of asparaginase-associated hyperammonemia

A 10-year-old boy was admitted with a late, isolated extramedullary relapse confined to the central nervous system four years after completing therapy for B-cell precursor acute lymphoblastic leukemia. He had been initially treated according to the NOPHO ALL2008 protocol. During his primary treatment, he experienced a hypersensitivity reaction to PEG-asparaginase, prompting a switch to Eryaspase® (asparaginase encapsulated in erythrocytes) as part of the NOR-GRASPALL 2016 trial (NCT03267030).[14]

At relapse, the patient received induction therapy according to the IntReALL SR 2010 arm A protocol (ClinicalTrials.gov ID: NCT01802814), comprising dexamethasone, methotrexate, high-dose cytarabine, vincristine, asparaginase, and intrathecal therapy with methotrexate, prednisolone, and

cytarabine. Due to his prior hypersensitivity, PEG-asparaginase was replaced with Erwinase. Seven courses of 20,000 IU/m^2 Erwinase were scheduled to replace one course of PEG-asparaginase, with a total of 28 doses planned for induction and consolidation.

Twenty-four hours after receiving the sixth dose of Erwinase during induction, the boy became lethargic and briefly unconscious. Electroencephalography revealed signs of encephalopathy without seizures, and imaging ruled out cerebral sinus venous thrombosis. Despite these findings, Erwinase dosing was initially continued. Ammonia levels, which had been mildly elevated (>100 μmol/L) throughout Erwinase treatment, were found to exceed 300 μmol/L. The patient was diagnosed with encephalopathy (Common Terminology Criteria for Adverse Events [CTCAE] grade 2-3), likely due to hyperammonemia.

Supportive interventions were introduced, including a protein-restricted diet, 10% glucose infusion, and sodium benzoate infusion (250 mg/kg). While lethargy improved, ammonia levels remained elevated, prompting a reduction in the Erwinase dose to 15,000 IU/m^2 and an extension of infusion time to 2 hours. Asparaginase activity was closely monitored to ensure therapeutic levels (>100 IU/L). Following these adjustments, the patient's symptoms resolved, and Erwinase treatment continued without further encephalopathy (*Online Supplementary Figure S1*).

Asparaginase

Asparaginase depletes systemic and cerebrospinal asparagine through deamidation of asparagine to aspartic acid and ammonia, leading to apoptosis in malignant lymphoblasts, due to their limited asparagine synthetase activity.[15-19] Different formulations of asparaginase are available, including *Escherichia coli* (*E. coli*)-derived ones (native L-asparaginase, and the longer acting pegylated versions, including Calaspargase Pegol) and *Erwinia chrysanthemi*-derived ones (Erwinase and recombinant Rylaze®). Pegylation extends the half-life and reduces immunogenicity.[15-23]

Asparaginase also exhibits glutaminase activity, deamidating glutamine to glutamate and ammonia, potentially contributing to the toxicity of L-asparaginase.[24,25] Glutamine is the most abundant amino acid in the human body, and the glutaminase activity of asparaginase is not sufficient to deplete glutamine.[26] Erwinase and Rylaze® have the highest glutaminase activity, approximately five times higher than the *E. coli*-derived asparaginase formulations.[24,25,27]

Pegylated *E.Coli*-derived asparaginase is the most commonly used formulation. Asparaginase-directed antibodies influence the efficacy and toxicity of L-asparaginase, with up to 20% of patients developing allergies. Erwinase/Rylaze® is given to patients who are allergic to *E. coli*-derived asparaginase.[2,28,29] In cases of silent inactivation most collaborative study groups switch patients to an *Erwinia*-based asparaginase.[30,31]

Monitoring asparaginase activity ensures that enzyme activity remains above 100 IU/L, the therapeutic target,[32,33] though reductions in asparagine levels occur at enzyme activity levels above 50 IU/L.[32-35] It has been shown that it is possible to reduce doses of PEG-asparaginase while maintaining adequate asparaginase depletion through monitoring of PEG-asparaginase activity. The same has not been demonstrated in patients receiving Erwinase.[33]

Ammonia levels have been suggested as a surrogate marker when asparaginase activity measurement is unavailable or not possible, but large clinical studies to validate this are lacking.[36]

Major adverse events include allergic reactions, allergy-like reactions, silent inactivation, pancreatitis, hepatotoxicity, thrombosis, severe hyperlipidemia and non-ketotic hyperglycemia.[1,34,37] Apart from allergy-like reactions, these toxicities are not dose-related, although associations have been shown with osteonecrosis and pancreatitis.[33,38] Toxicities frequently lead to dose reductions or discontinuation, which can lead to a decrease in event-free survival.[39-41]

Asparaginase-associated hyperammonemia

AAH is rarely reported, most likely due to the lack of clinical recognition. AAH definitions differ with respect to ammonia levels above the upper normal limit with or without symptoms in patients who are treated with L-asparaginase at the time of onset of hyperammonemia (Table 1).[7-12] It has been shown in animal models that multiple asparaginase infusions cause stepwise increments of hyperammonemia,[42] but the same pattern has not been sufficiently explored and reported in children and young adults treated with asparaginase.

Higher ammonia levels, probably due to increased glutaminase activity, are mainly observed with Erwinase administration compared to the *E.coli*-derived asparaginase formulations, as seen in the case described in this review.[24,25,27]

Ammonia is a by-product of amino acid metabolism and of gut bacterial hydrolysis of urea. Major organ contributors are the intestines and the kidneys. Ammonia is toxic to several cellular functions and is effectively scavenged from the blood stream by a clearance rate close to cardiac output. This happens primarily by amidation of glutamic acid to glutamine by glutamine synthetases, and also by the action of transaminases converting carbon skeletons to amino acids. Final elimination from the body is by hepatic transfer of amide- and amino-nitrogen into the urea cycle, which has a very large capacity, followed by urinary excretion of urea (*Online Supplementary Figure S2*).

Glutamine is the most abundant amino acid in the body. The enzyme glutaminase catalyzes release of the amide nitrogen to ammonia and is present in all organs. The dynamics

Table 1. Studies assessing asparaginase-associated hyperammonemia.

Study	Study type	N of pts	Age, years	Sex	ALL subtype	Type of asparaginase	Definition of hyperammonemia	Ammonia levels	Symptoms	Interventions
Steiner *et al.* 2007[7]	Prospective	10	1.1-16.9	7 M 3 F	3 BCP 7 Common ALL	L-asparaginase	NA	Median 1 day prior to asparaginase: 91 mg/dL. Median 1 day after asparaginase: 190 mg/dL	Anorexia Irritability Lethargy Vomiting	NA
Jörck *et al.* 2011[8]	Retrospective	4/54 46 ALL 8 NHL	6-15	1 M 3 F	1 BCP 2 Common ALL 1 NHL	PEG asparaginase & native *E. coli* asparaginase	>100 μmol/L for children >1 year >80 μmol/L for neonates	260-700 μmol/L	Headache Dizziness Vomiting	10% glucose Sodium Benzoate Protein restriction
Heitink-Polle *et al.* 2012[9]	Prospective	8	3-12	3 M 5 F	4 BCP 4 Common ALL	PEG-asparaginase	Hyperammonemia: ammonia >50 μmol/L Clinically significant hyperammonaemia: ammonia >100 μmol/L	89-400 μmol/L	Headache Lethargy Nausea, Vomiting Dizziness Neurological symptoms	Protein restriction Lactulose Omission of PEG-asparaginase
Nussbaum *et al.* 2016[10]	Retrospective case report	4	12-20	3 M 1 F	2 BCP 1 T ALL 1 T-cell lymphoma	PEG-asparaginase Erwinase	Elevated: ammonia >40 μmol/L	140-366 μmol/L	Lethargy Difficulty awakening Eye deviation Fatigue Hallucination Paranoia Tingling Light-headedness Blurry vision Loss of consciousness	Lactulose
Gossai *et al.* 2018[11]	Retrospective	7/45	2-23	3 M 4 F	6 BCP 1 T-ALL	Erwinase	ammonia >50 μmol/L	17-358 μmol/L	Refractory nausea Vomiting Profound fatigue Malaise Coma	NA
Lee *et al.* 2023[12]	Retrospective	5	2-20	2 M 3 F	1 BCP 4 T-ALL	RCP (N=4) Erwinase (N=1)	NA	15-309 μmol/L	Fatigue Vomiting Weakness Headache Mood swings Confusion	Phenyl butyrate Dextrose Lactulose Sodium benzoate Rifamixin Sodium phenylacetate

N: number; pts: patients; ALL: acute lymphoblastic leukemia; M: male; F: female; BCP: B-cell precursor; NA: not available; NHL: non-Hodgkin lymphoma; T-ALL: T-cell acute lymphoblastic leukemia; SD: standard deviation; RCP: recombinant crisantaspase.

of ammonia turnover thus involves the balance between glutamine synthetase/glutaminase and the capacity of urea synthesis in the urea cycle. Hyperammonemia occurs when ammonia production is increased beyond the elimination rate or elimination is decreased. Thus, increased production may result both from increased glutaminase activity and decreased elimination from compromised urea synthesis.[43-45] Ammonia passes freely across the blood-brain barrier in amounts parallel to the blood concentration, and astrocytic glutamine synthase subsequently increases glutamine concentration. The osmotic action of glutamine results in astrocytic swelling that may be discrete or, in cases with very high ammonia, be associated with brain edema. The metabolic consequence of the increased glutamine includes disturbances between excitatory glutaminergic/glutamatergic neurotransmission and neurotransmission via the strong inhibitory neurotransmitter gamma-amino-butyric acid (GABA) which suppresses neuronal energy consumption. The cerebral symptoms of hyperammonemia can, therefore, be related to different degrees of brain edema and/or to psychomotor neurodepression, as detailed below.[44,46,47]

So far only one patient with AAH with a urea cycle deficiency has been reported,[12] and no AAH patients have been reported with liver failure at the time of hyperammonemia.[7-12] Thus, AAH likely results primarily from increased production of ammonia by the exogenous glutaminase activity, overwhelming the capacity of the glutamine synthases and other amino acid transfers of ammonia. This compromises the primary high ammonia scavenger clearance, and thus prevents ammonia-derived nitrogen from reaching final elimination by urea synthesis. Normally, urea synthesis, with its very large capacity,[43] can effortlessly cope with ammonia production, provided ammonia-derived nitrogen is appropriately transferred to the urea cycle by amino acid bound nitrogen.[43] Since asparaginase can indiscriminately inhibit protein synthesis this is likely the mechanism of the cases of acute liver failure reported.[48] Likewise, it is conceivable that asparaginase may inhibit protein expression from the urea cycle genes and thus reduce urea synthesis capacity. If so, the hyperammonemia will further aggravate, persist for a longer time, and be more difficult to counteract.

Differential diagnoses

AAH requires consideration of differential diagnoses, including liver failure, infections with urease-producing organisms (e.g., *Proteus mirabilis*, *Escherichia coli*, and *Klebsiella*),[49] hepatotoxic drugs (e.g., valproic acid, acetylsalicylic acid, and carbamazepine),[50,51] and rarely other urea cycle disorders with late onset, including late-onset ornithine transcarbamylase deficiency.[52]

Clinical signs and symptoms

Patients with AAH are usually asymptomatic even with high ammonia levels. However, in younger children, moderate neurotoxic symptoms such as fatigue and nausea may fail to be diagnosed. Common symptoms reported are vomiting and nausea refractory to conventional anti-nausea medication, weight loss secondary to nausea and vomiting, and neurotoxicity with lethargy, fatigue and malaise[7-12] (Table 1). These symptoms may be difficult to distinguish from other common toxicities related to chemotherapy.

Symptoms associated with development of severe encephalopathy include dizziness, irritability, eye-deviation, hallucinations, seizures, altered mental status, and coma.[53] On examination patients may exhibit difficulty cooperating with examination, including verbal communication. If encephalopathy is severe, patients may present with hypertonia, hyperreflexia, nystagmus, fatigue, and a decreased Glasgow coma score.[53]

Some patients with AAH may be classified as having allergy-like reactions. Patients with allergy-like reactions exhibit no inactivation of asparaginase activity, which is the case in patients with true hypersensitivity. The symptoms of patients with an allergic reaction or allergy-like reaction and symptoms of AAH may resemble one another, with vomiting, nausea, rashes and edema.[54] It has been shown that some patients with allergy-like reactions have drastic elevations of ammonia levels.[55] Importantly, as opposed to patients with allergic reactions, patients with allergy-like reactions can continue asparaginase therapy.[54] In instances in which ammonia levels are not monitored, AAH may be misinterpreted as allergy-like reactions, and lead to an unnecessary shift to *Erwinia chrysanthemi*-derived asparaginases, which may increase the risk of hyperammonemia. Studies regarding differences in ammonia levels with the different asparaginase formulations are lacking.

In patients with inherited urea cycle deficiencies, even ammonia levels only two times above the upper limit of normal may cause long-term cognitive impairment.[13,56-58]

It is important that ammonia is sampled and handled correctly. The sample should be transported in an ice bath and serum should be separated no later than 15 minutes after collection in order to avoid asparaginase activity in the sample with the risk of false high values.[59]

Treatment options

The management of AAH depends on the severity of the hyperammonemia and associated symptoms. The primary goal is to reduce ammonia levels while maintaining effective asparaginase therapy whenever possible. Early recognition of symptoms, such as lethargy, vomiting, and encephalopathy, is critical to prevent severe complications such as cerebral herniation.[53]

In patients with hyperammonemia due to causes other than asparaginase treatment, such as inborn errors of metabolism, liver failure or sepsis, the therapy for hyperammonemia encompasses: (i) reduced protein intake, (ii) interventions that can reduce ammonia absorption from the gut, (iii) ammonia-scavengers using metabolic interventions and (iv) increasing the function/activity of the urea cycle

with arginine and carglumic acid[60] (*Online Supplementary Figure S2*). Similar approaches have been used in patients receiving asparaginase, including reducing the asparaginase doses preferably while monitoring asparaginase activity or by extending the infusion time of Erwinase and withdrawal of asparaginase. The latter however should be avoided[7-12] (Table 1).

In asymptomatic patients (CTCAE grade 1) elevated ammonia levels do not require treatment. In patients with mild neurotoxicity, a protein-reduced or protein-free diet may reduce intestinal ammonia production. The role of restricting protein intake has been questioned. Protein restriction may offer limited benefit for patients with AAH, as most ammonia derives from asparaginase's glutaminase activity rather than dietary protein. It is not recommended in patients with hepatic encephalopathy because it results in catabolism with increased muscle ammonia production, and sarcopenia in which the reduced muscle mass reduces clearance of ammonia. Additionally, administration of 10% glucose infusions to reduce protein catabolism is commonly used.[61,62]

In patients with moderate encephalopathy (CTCAE grade 1 or 2) we recommend ammonia-reducing therapies such as sodium benzoate and lactulose, antibiotics, glucose 10% infusion and a reduction in asparaginase dose.

Sodium benzoate is routinely used in children with inborn urea cycle deficiencies to reduce ammonia levels.[63] Sodium benzoate conjugates with glycine in the liver to form hippuric acid, which is water soluble and can be easily excreted in urine. As hippuric acid contains one nitrogen molecule per hippuric acid molecule, it provides an alternative pathway for excretion of nitrogen.[64] AAH patients benefit from intervention with sodium benzoate as the reduction in available nitrogen limits ammonia elevations and sodium benzoate is a treatment option in patients with AAH and moderate encephalopathy (CTCAE grade 2) (Figure 1).

The primary highly efficacious intervention for hepatic encephalopathy is oral lactulose, which causes gut overgrowth of *Lactobacillus* species without high urease activity and production of short chain fatty acids that lead to acidification of colonic pH which can push diffusible ammonia into ammonium ions, thus reducing uptake of ammonia. It is important to monitor hydration status and sodium levels during lactulose therapy.[65] There are no reports on the effect of lactulose in AAH.

Secondary treatment for hepatic encephalopathy is oral, heavily absorbed antibiotics including rifaximin and neomycin. Rifaximin is widely used. It can reduce colonization with ammonia-producing gut bacteria and has a favorable low toxicity profile. Neomycin can inhibit mucosal glutaminase in the intestine resulting in reduced ammonia production.[65]

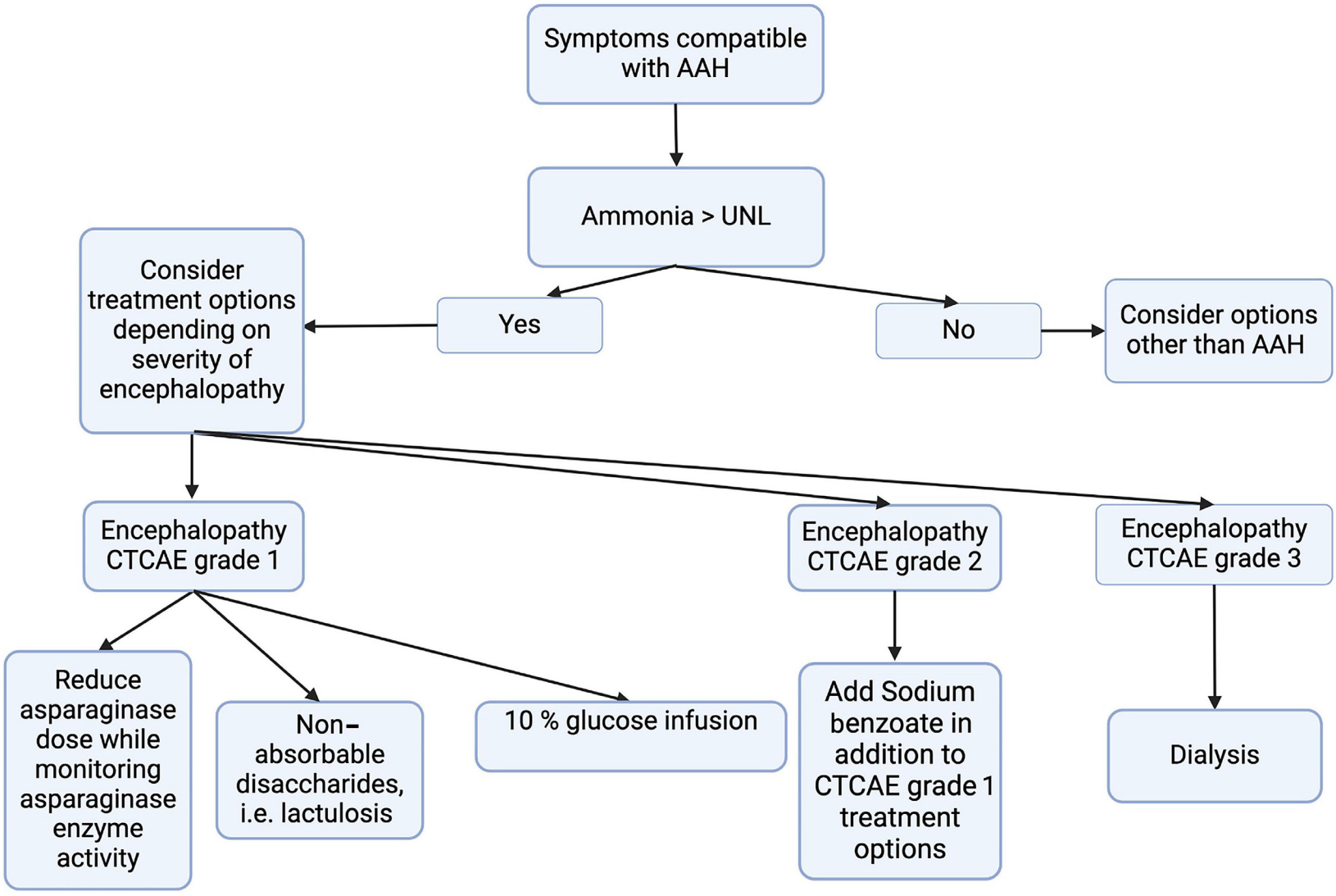

Figure 1. Possible interventions according to Common Terminology Criteria for Adverse Events grade of encephalopathy. AAH: asparaginase-associated hyperammonemia; UNL: upper normal level; CTCAE: Common Terminology Criteria for Adverse Events.

Neomycin is, however, very rarely used due the drug's dismal toxicity profile. There are no reports of the effects of use of antibiotics to reduce ammonia in patients with AAH. Another intervention option in grade 1 encephalopathy is intravenous infusion of 10% glucose, which is known to reduce protein catabolism.

We recommend reducing asparaginase doses with concomitant monitoring of asparaginase enzyme activity to ensure levels >100 IU. The reduced amount of available asparaginase will result in a decrease of glutaminase activity and reduced levels of ammonia (Figure 1).

In patients with severe encephalopathy and high ammonia levels (≥ CTCAE grade 3) dialysis or plasmapheresis is considered an option in the intensive care setting, especially for patients with acute liver failure[66] (Figure 1).

Currently, there are no guidelines on how to manage AAH. Based on our experience we propose treating only symptomatic patients. The choice of treatment options depends on the severity, according to CTCAE grade, of any encephalopathy (Figure 1).

Conclusion

AAH is an underrecognized but significant complication of asparaginase therapy. Effective management requires early recognition, careful monitoring, and tailored interventions to reduce ammonia levels while preserving therapeutic efficacy. The case presented here highlights the challenges and potential solutions in managing AAH, underscoring the importance of individualized care. Further research is needed to establish standardized treatment protocols, evaluate the long-term impacts of AAH, and optimize asparaginase formulations to minimize toxicity. Addressing these gaps will ensure better outcomes for pediatric patients with acute lymphoblastic leukemia.

Disclosures

KS has been a speaker for or received honoraria for advisory board participation from Illumina (2021), Jazz Pharmaceuticals (2020, 2021, 2023) and Servier (2020, 2021, 2023); has received speaker's fees from Amgen (2020, 2021) and Medscape (2020, 2021); has received educational grants from Servier (2020, 2021, 2023); has received research grants from the Novo Nordisk Foundation (2020,2022); and holds stocks in Novo Nordisk. All the other authors have no conflicts of interest to disclose.

Contributions

RAR and KS conceived the manuscript. RAR wrote the manuscript. RAR, BA-N, AML, HV, KPD and KS all contributed to the manuscript, and critically revised and approved it.

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