

## Hyperammonemia Associated Encephalopathy in Two Cases with Hematological Malignancy

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### Abstract

Hyperammonemia syndrome is one of the causes of metabolic encephalopathy that is rarely observed after high dose chemotherapy for the treatment of hematologic malignancies. Two cases, who developed neurologic symptoms and coma due to hyperammonemia subsequent to chemotherapy for Burkitt's lymphoma and acute myeloid leukemia, respectively are being presented in this report. In case respiratory alkalosis, unexplained neurological symptoms and mental status changes develop after intensive chemotherapy, hyperammonemia should come into mind, and the serum ammonium level should be measured to implement ammonium-lowering therapy.

**Keywords:** Hyperammonemia; Hematological malignancy; Acute leukemia; Burkitt's lymphoma

### Introduction

The ammonium is a form of nitrogen that originates from proteins metabolized by bacteria in the intestine. The liver converts ammonia to urea that is excreted by the kidney. If the liver cannot convert ammonium to urea, hyperammonemia leads to metabolic disorders and organ dysfunction. Progressively worsening mental status, confusion, sleepiness, tremors in hands, respiratory alkalosis and coma are hyperammonemia associated signs and symptoms. Rarely, high protein and caloric diet (intravenous nutrition) may cause hyperammonemia as well. Hyperammonemia syndrome is one of the causes of metabolic encephalopathy that is rarely observed after high-dose chemotherapy for the treatment of hematologic malignancies. It may rarely lead to death [1]. Two cases, who developed neurologic symptoms and coma due to hyperammonemia subsequent to chemotherapy for Burkitt's lymphoma and acute myeloid leukemia, respectively are being presented in this report.

### Case 1

A 67-year-old female patient with a diagnosis of Burkitt's lymphoma received hyper CVAD 1A and 1B, and then 2A and 2B. Fever and signs of infection developed one week after hyper CVAD 2B. Cultures were performed and then antibiotic therapy was started. Confusion, lethargy, and coma developed. Metabolic parameters (i.e. blood sodium, calcium, and urea) showed no abnormality except for serum alkaline phosphatase (ALP) and gamma glutamyltransferase (GGT) values that indicate bile duct damage. Serum ALP values fluctuated between 300-400 U/L and serum GGT values fluctuated between 500-1500 U/L. The findings were normal by abdomen ultrasonography. Those signs were thought to develop due to the toxicity of chemotherapy. Blood ammonia values were measured between 350-500 mmol/L (normal upper limit of 35 mmol/L) in different times. The blood glucose level was measured every six hours and insulin therapy was set to be over 150 mg/dL, as the patient has diabetes mellitus. Neurological examinations and brain imaging methods (cranial computed tomography (CT), magnetic resonance imagination (MRI)) did not reveal any pathology. There were no findings suggestive of liver dysfunction; so that AST and ALT, albumin levels, and homeostasis were normal. Meanwhile, patient received parenteral nutrition solutions by

nasogastric tube. About 15 days later, loss of consciousness and neurologic symptoms recovered steadily. The patient was discharged as healthy.

### Case 2

A 46-year-old male patient diagnosed with AML M3 received remission-induction therapy (ATRA and idarubicin), and then first consolidation therapy. Fever was 39°C about 10-12 days after chemotherapy and he received antibiotic therapy. Confusion developed and his consciousness gradually closed down within 3 days. The patient was transferred to the intensive care unit and followed up for 15 days. The patient whom loss of consciousness had partially recovered was admitted to hematology ward from intensive care unit. Serum ALP values fluctuated between 300-400 U/L and serum GGT values fluctuated between 600-2000 U/L during follow-up at ward. Other laboratory tests and radiology modalities revealed normal findings. We thought that drug toxicity is more likely to cause increased serum ALP and GGT values. All metabolic parameters were within normal ranges in further investigations except for high blood ammonia. Blood ammonia levels were measured between 400 to 600 mmol/ L (normal upper limit of 35 mmol/ L) in different times. Liver dysfunction was not examined. Neurological examination with cranium imaging tests (CT and MRI) was within normal limits. Cerebro-spinal fluid examination was normal. The nonspecific electrical potentials, which are observed in metabolic disorders and deep coma, were captured in EEG. Clinical and laboratory findings of patient have recovered after one month of second admission.

### Discussion

Hyperammonemic encephalopathy has been reported to develop especially secondary to high dose chemotherapy [1]. High levels of ammonia after chemotherapy were reported in the literature in patients with acute leukemia (AML and acute lymphoblastic leukemia (ALL)). Hyperammonemic encephalopathy most commonly occurs in patients with multiple myeloma (MM). Liver function tests and abdomen computed tomography are not suggestive of hepatic dysfunction and in those patients without taking salicylates [2]. Aforementioned two cases that received chemotherapy due to hematological malignancy and developed neurological symptoms, lethargy and coma with elevated

blood ALP, GGT and ammonia levels were more likely to be related to hyperammonemia secondary to chemotherapy. The exact cause and treatment of this syndrome are not known, although some reasons were suggested [1]. In such cases, blood ammonia level should be measured and then ammonium lowering-therapy which was reported to improve survival should be implemented [1]. In a study investigating plasma ammonium level of 43 patients with acute leukemia before and after chemotherapy, plasma ammonium levels were measured as  $38.8 \pm 16.6$   $\mu\text{mol/L}$  and  $39.21 \pm 26.2$   $\mu\text{mol/L}$  in patients and healthy controls, respectively [3]. After chemotherapy, plasma ammonia levels (PASI) were high in 40 patients and very high in six patients. Dizziness, lethargy, confusion, coma, respiratory alkalosis, and mental changes were identified in varying degrees in patients with very high plasma ammonia levels. Ammonia lowering therapies cured five of the six patients, while one patient had died [3].

Asparaginase, which is used for treatment of ALL in children, was reported to cause hyperammonemia as a side effect. As reported in that study, pegylated Asparaginase (PEG-Asparaginase) caused hyperammonemia ( $>50$   $\text{mmol/L}$ ) in all eight children who received it due to ALL, and very high plasma ammonia level ( $>100$   $\text{mmol/L}$ ) was measured in seven patients. The maximum concentration of ammonium reached to 400  $\text{mmol/L}$  [4]. Aforementioned clinical symptoms, i.e. vomiting, dizziness, lethargy developed in patients. Hydrolysis of glutamine and asparagine was suggested to be because of increased ammonium in patients without urea cycle dysfunction. Measurement of patient's asparagine and asparaginase to determine the optimal dose is recommended to prevent hyperammonemia [4]. Idiopathic hyperammonemic encephalopathy, which includes acutely conscious change, increase blood ammonia without liver disease, coma, and death are rare but fatal complications of chemotherapy. It often develops during the period of neutropenia after chemotherapy in patients with hematological malignancies. Early initiation of lowering ammonemia therapy should come into mind to prevent a fatal outcome [5]. Hyperammonemia, which is not related to hypercalcemia, hyperviscosity and increased urea can be fatal in patients with MM in case immediate diagnosis and treatment are not initiated, was reported. It may be observed in the treatment of aggressive and treatment-refractory forms of MM. Hyperammonemia (more than 47  $\text{mmol/L}$ ) leads to increased brain pressure and can cause death. The incidence of hyperammonemic encephalopathy was found 0.72% in patients with MM. Normally the blood glycine/tyrosine ratio is high, this ratio was found low in patients with hyperammonemia because of cirrhosis or chemotherapy for acute leukemia. Dialysis, which is eliminating precursors and increase the clearance of ammonium, should be initiated. Carnitine stimulates the

synthesis of urea and increase renal clearance of sodium benzoate and sodium phenyl acetate. Flumazenil, a low protein diet (providing enough calories), intestinal decontamination with antibiotics, enemas, and use of laxatives may reduce excessive ammonia production [2].

It was reported that hyperammonemia may develop without chemotherapy in patients with hematological malignancies, and after treatment of malignancy, plasma ammonium level decreases. A 43-year age patient with plasmacytoma had undergone to dialysis due to increased blood ammonia levels. After treatment of cyclophosphamide (2 grams/day for two days), size of plasmacytoma and plasma ammonium level ( $<10$   $\mu\text{mol/L}$ ) reduced five days after. The patient's consciousness recovered. That reduction was suggested to reveal a relationship between malignancy and hyperammonemia [6].

## Conclusion

In case respiratory alkalosis, unexplained neurological symptoms and mental status changes develop after intensive chemotherapy, hyperammonemia should come into mind, and the serum ammonium level should be measured to implement ammonium-lowering therapy. Early lowering therapy improves survival [3].

## References

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