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Hyperammonemic Encephalopathy Case Report in Multiple Myeloma

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Abstract

Background: Hyperammonemic encephalopathy is a rare cause of altered level of consciousness in patients. When investigating encephalopathy, common causes are ischaemic, metabolic, toxic, inflammation, demyelinating, degenerative, and hereditary and infection. In this case reports, we present a rare case of encephalopathy in a patient with hyperammonaemia on a background of multiple myeloma.

Case presentation: A 67 year old Caucasian male with a background history of monoclonal gammopathy of undetermined significance, presented with confusion, asterixis and recurrent falls. As part of the work up he was found to have a high ammonia level at 123 umol/L (normal 0-50 umol/L). The patient also had a bone biopsy as he had mild pancytopenia and hyperproteinemia and was diagnosed with multiple myeloma, likely a progression from his paraproteinemia disorder. The patient significantly improved to his baseline with normalisation of ammonia level once he was commenced with Velcade based chemotherapy as well an adjunctive treatment with lactulose.

Conclusion: Hyperammonemia in multiple myeloma is a rare but an important differential in patients with encephalopathy. The diagnosis of this is important so that an appropriate treatment can be provided.

Keywords: Multiple Myeloma • Hyperammonemia • Encephalopathy

Introduction

Hyperammonemic encephalopathy is an uncommon cause of altered level of consciousness in multiple myeloma patients. To date, there are few case reports and retrospective studies about this condition, only one of which is Australian [1]. We will present a case of hyperammonemic encephalopathy in a patient with multiple myeloma, and briefly discuss the current research to date regarding the pathophysiology and the management for this condition.

Case Presentation

A 67 year old male with a background history of monoclonal gammopathy of undetermined significance, rheumatic fever as a child, prostate cancer, gastroesophageal reflux disease, depression, obstructive sleep apnea and osteoarthritis, presented with a worsening confusion and recurrent falls worsening over one week. He appeared encephalopathic with evidence of asterixis, without hepatosplenomegaly or ascites. He was mildly fluid overloaded with peripheral edema, bibasilar pulmonary crackles, and his heart sounds were dual with no added sounds. Investigation revealed mild pancytopenia with a neutrophil count of 1.1 × 109/L, hemoglobin of 129 g/L, and platelets of 95 × 109/L. He had a mild hypoalbuminemia at 29 g/L, with otherwise a normal corrected Calcium level of 2.54 mmol/L and serum creatinine of 65 umol/L. He also has a normal liver function test and total bilirubin level. Echocardiography did not reveal any evidence of cardiac failure. He went on to have further investigation to exclude liver pathology as a cause of encephalopathy and asterixis, including liver biopsy and ultrasound which were normal and gastroscopy which found no varices, but he did have a peptic ulcer. As part of the liver work up, he was found to have high ammonia level at 104 umol/L (normal 0-50 umol/L) on D1 of admission and 123 umol/L on repeat level on D9 of admission. In addition, his serum protein electrophoresis showed a raised total beta-globulin region of 23 g/L and immunofixation further revealed an IgA kappa monoclonal protein with a serum kappa free light chain of 117 mg/L and a serum kappa/lambda ratio of 16.7. He went on to have a bone marrow biopsy which found 10% to 20% of clonal plasma cells on immunophenotyping indicating a diagnosis of multiple myeloma.

He was initially managed with rigorous lactulose with improvement in his ammonia level from 124 to 82 umol/L and his symptoms of asterixis. However, he remained lethargic, disorientated and paranoid. Once the diagnosis of myeloma was confirmed, he went on to have a chemotherapy with a combination of velcade (bortezomib), cyclophophamide and dexamethasone, as his Eastern Cooperative Oncology Group score was 3, and therefore was not eligible for stem cell transplant. Lactulose was ceased whilst on chemotherapy. After completing chemotherapy, the ammonia level decreased to 44 umol/L suggesting the multiple myeloma was the cause of the hyperammonemia. Furthermore more, his confusion and paranoia also resolved suggesting the encephalopathy was secondary to hyperammonemia (Figure 1).

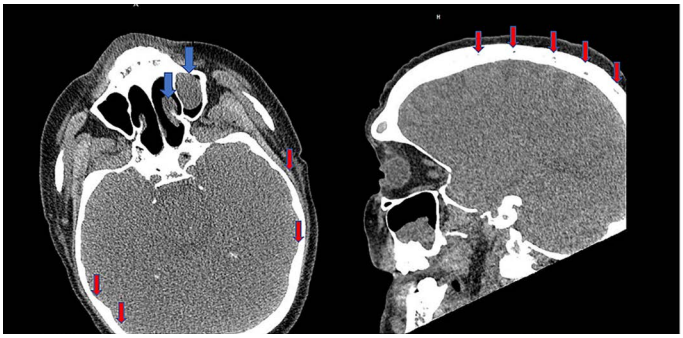

Figure 1. Hyperammonemic encephalopathy.

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Results and Discussion

A retrospective study on 279 multiple myeloma patients found the incidence of hyperammonemic encephalopathy is as low as 3% [2]. The most common type of multiple myeloma with hyperammonemic encephalopathy are those with IgG and IgA type, followed by light chain and IgD [3,4]. Other studies found that most cases of hyperammonemic encephalopathy occur in patients with chemotherapy resistant multiple myeloma. The average ammonia level in multiple myeloma patients with hyperammonemic encephalopathy is above 100 umol/L although one study reported a level of serum ammonia >47 umol/L to be the cause of the patient's encephalopathy.

The presentation of hyperammonemic encephalopathy in multiple myeloma patients can vary, but include lethargy, confusion and asterixis. Most patients with hyperammonemic encephalopathy may progress rapidly to coma and death due to the delay in treatment and diagnosis [5]. Encephalopathy due to hyperammonemia is thought to be due to ammonia conversion to glutamine in astrocyte, leading to osmotic gradient resulting in cerebral edema and an increase in intracranial pressure leading to encephalopathy.

The pathophysiology of hyperammonemia in multiple myeloma patients is, on the other hand, not well understood. There are multiple theories that have been presented as possible causes of hyperammonemia. One theory is that there is overproduction of ammonia in vitro by myeloma cell lines through mutation in enzymes involved in ammonia synthesis [5,6]. The mutation however, has not been identified. Otsuki et al failed to detect any difference between myeloma cells and other cell lines after examining the RNA expression levels of genes of the enzymes related to ammonia metabolism. Another theory is excess protein synthesis in myeloma cells including the synthesis of immunoglobulin and cytokines such as IL-6 or IL-1β, which induce excess ammonia biosynthesis.

Ikewaki found the presence of myeloma cells in the peripheral blood and suggested that the infiltration of myeloma cells into the liver was the cause of hyperammonaemia [7]. Howman further elaborated on this, theorizing that the hypercoagulable state in myeloma combined with liver infiltration by plasma cells can result in portal hypertension and a portosystemic shunt leading to hyperammonemia. However, this has yet to be identified in studies so far and there are some reported cases of hyperammonemic encephalopathy without peripheral presence of myeloma cells. Lastly, Gaiani suggested there is an alteration in the urea metabolism whereby increased in protein synthesis and catabolism of plasma cell overfill the urea cycle leading to hyperammonaemia [8].

Chemotherapy directed against multiple myeloma has so far been the most effective treatment to reduce ammonia level and improve symptoms of encephalopathy. In Australia, the initial treatment for non-stem cell transplant eligible patient includes the combination of bortezomib/lenalidomide/dexamethasone (VRD), or continuous lenalidomide/dexamethasone (Rd), or bortezomib/melphalan/prednisolone (VMP) with which cyclophosphamide could be substituted for melphalan (VCD).

There are studies that also trialed the use of hemodialysis to remove ammonia which seems to delay the progression of hyperammonemic encephalopathy. In one study, plasma exchange treatment was found to only improve hyper viscosity but without improvement in symptoms. However, the patient's symptoms were improved with lactulose which reduced the ammonia level [9]. Other suggested adjunctive treatment is the use of sodium benzoate and sodium phenylacetate combination which is a proven adjunctive treatment for inborn enzyme deficiency in urea cycle, as it diverts ammonium from urea cycle and increases its renal clearance [10].

Conclusion

In conclusion, hyperammonemic encephalopathy in multiple myeloma is a rare but an important differential in patients with encephalopathy. Stepwise approach in determining the cause of encephalopathy in these patients should include excluding liver disease, uremia, hyper viscosity, and hypercalcemia. If no other causes found, ammonia level should be performed. Although the pathophysiology is not clear and there are no clear diagnostic criteria for hyperammonemic encephalopathy, in suspected cases initiating treatment of multiple myeloma is necessary, and in this case, lactulose treatment was able to be weaned completely. Further research into invitro multiple myeloma cells and hyperammonemia physiology will be beneficial in determining the cause of this condition and therefore may lead to further treatment options in the future.

Acknowledgments

Not applicable.

Ethical Approval and Consent to Participate

Not applicable.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor in Chief of this journal.

Availability of Data and Materials

Not applicable.

Competing Interests

The authors declare that they have no competing interest.

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Author contributions

RZ conducted the review and drafted the manuscript. RB directly involved with the patient care and edited the manuscript. JR adds pertinent information about the management. All authors read and approved the final manuscript.

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