CASE REPORT

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Hyperammonemia-Associated Delirium Mimics Dementia: A Case Report

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ABSTRACT

Ammonia is considered to be a neurotoxin that affects various physiological pathways, including energy metabolism, mitochondria function, and inflammatory response. Dysfunctions of these pathways contribute to the development of cognitive and executive function impairments. A case of a 67-year-old female patient who presented with unusual features of delirium after spine surgery was reported in this study. The patient initially developed acute hepatitis, and 3 weeks later, liver functions gradually improved. However, the acute onset of cognitive impairment and mild hyperammonemia was found. The patient mainly presented with cognitive deficits and impairment of executive functions without a fluctuating course. Her cognitive impairment was resolved when the serum ammonia level returned to the normal range. Consequently, we considered the diagnosis for this patient was delirium rather than a major neurocognitive disorder (dementia). Thus, the clinical diagnosis for delirium and etiologies are discussed.

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INTRODUCTION

The possible effects of high ammonia concentration include dysregulations of cellular energy metabolism, mitochondrial functions, inflammatory response modulation, and neurotransmission in neurons. Moreover, hyperammonemia can cause damage to the central nervous system, including changes in the blood–brain barrier morphology, modifications in astrocyte and neuron morphologies, and hepatic encephalopathy.[1,2] Serum ammonia level has been traditionally used to evaluate the severity and determine the resolution of patients with hepatic encephalopathy.[3]

Delirium is characterized by the acute onset of deficits in attention, awareness, and cognition that fluctuate in severity over time. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),[4] it develops over a short period, and the clinical course tends to fluctuate in severity during a day. Aside from the DSM-5, the Confusion Assessment Method (CAM)[5] is one of the tools widely utilized for assessing delirium in clinical practice. It includes acute onset, fluctuating course of symptoms, inattention, disorganized thinking, and altered level of consciousness (decreased level of arousal or hyperarousal) in the diagnostic algorithm. Moreover, multiple factors could interact and cause dysfunction of the neuronal networks in the brain, leading to acute cognitive impairment and delirium. Hyperammonemia is one of the significant factors that synergistically act with inflammation to develop cognitive dysfunction. Inflammation and neuroinflammation play roles in cognitive dysfunction in various conditions (e.g., postoperative cognitive impairment, aging, and mental (like schizophrenia) and neurodegenerative diseases).[6,7]

Herein, a patient who fit the diagnostic criteria for delirium but did not represent the fluctuating symptom course, altered consciousness level, and disorganized thinking was reported in this study. The patient's symptoms were mainly cognitive and executive deficits instead of fluctuations in consciousness and changes in awareness. However, the cognitive dysfunction and delirium of the patient improved in 2 weeks after the hyperammonemia was managed.

CASE PRESENTATION

The 67-year-old female patient had received psychiatric treatment for many years due to dysthymic disorder. The patient had underlying diseases including hepatitis B virus infection and chronic liver disease. Moreover, she visited the neurosurgery department for assessment because of right lower limb numbness. Thoracic lumbar

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kyphosis, right fifth lumbar, and first sacral spine foraminal stenosis were diagnosed, and the patient received posterior-lateral fusion, osteotomy, and transforaminal lumbar interbody fusion. Duloxetine was discontinued after she was hospitalized. The day after surgery, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels increased from 42 and 55 U/L (before surgery) to 435 U/L (reference range, 15-37) and 542 U/L (reference range, 14-47), respectively. Five days later, the AST and ALT serum levels reached 211 and 1440 U/L, respectively. Liver ultrasonography showed mild coarse liver parenchyma, decreased size, blunted angle, and moderate irregular liver surface compatible with chronic liver disease. Hepatitis B surface antigen was 5740.11 IU/mL, and hepatitis C virus antibody was nonreactive. Acute loss of daily functions in 1 day was noticed in the patient 3 weeks later. The patient would suddenly become confused and forget what to do. She forgot the procedure for using the lumbar bracket, did not remember to take medicine, and forgot how to open the lid of the washing machine and operate the machine. Furthermore, she did not know how to turn on the television, urinate/defecate in the toilet, cook, and wash dishes. Slow movement and gait difficulties with shuffling and unsteadiness were noted. The patient presented in the clinic with disorientation to time and persons, except for her husband and son. She was easily distracted and had difficulty keeping track of what was being said and asked by the physician. However, neither delusions nor hallucinations were observed. Furthermore, no progressive course, loss of consciousness, fluctuating consciousness, convulsion, fever, photophobia, nausea, and headache were noted. Additionally, the patient had no history of diabetes, hypertension, hyperlipidemia, chronic kidney disease, and drug allergy. A dementia-like presentation was found, and 30 mg of duloxetine daily was prescribed again as before. Consequently, she was followed up at the outpatient department. One week later, her mental status did not improve and cognitive impairment was noted. Serum ammonia level was 60 μg/dL (reference range, 19-54 μg/dL), and serum AST and ALT levels were 29 and 55 U/L, respectively. Other laboratory data, including hemoglobin, total white blood cell count, differential neutrophil count, lymphocyte count, serum glucose, renal function, thyroid stimulation hormone, C-reactive protein level, serum sodium, serum potassium, serum vitamin B12, folate, and rapid plasma reagin, were all within normal limits. A brain electroencephalogram revealed generalized cortical dysfunction. No obvious epileptiform discharge was recorded. The magnetic resonance imaging of the brain showed mild aged brain with brain atrophy and small vessel ischemic disease. Furthermore, no evidence of acute infarction with cytotoxic edema existed. Under the impression that delirium and chronic liver disease with hyperammonemia were present, a laxative and lactulose solution (667 mg/mL) 30 mL thrice daily was prescribed for reducing serum ammonia levels by decreasing the intestinal production and absorption of ammonia. Three days later, she concentrated better and was oriented. Serum ammonia decreased to 28 μg/dL. The basic activities of daily living improved 14 days later. One month later, the abilities of daily living (e.g., washing clothes, turning on the television, and cooking) were recovered. Informed consent for this case report was obtained from the patient.

DISCUSSION

The diagnosis for delirium in DSM-5[4] includes the following: (a) disturbances in attention, awareness, and cognitive functions; (b) the above disturbances develop over a short period (usually hours to days) and tend to fluctuate in severity during the course; (c) the disturbances are not better explained by another neurocognitive disorder; and (d) the disturbances are indicative of a direct physiological consequence of existing medical conditions. This case fit the definition of delirium in the DSM-5 criteria but did not present a wax and wane course in a day. The patient had symptoms of acute onset and poor attention but did not have a fluctuating course, disorganized thinking, and altered consciousness level (decreased or increased arousal) based on the CAM measurement. Alternatively, she mainly manifested a pervasive deficit in cognitive functions and instrumental activities of daily living. Therefore, this patient presented an unusual presentation of delirium. The proportion of unspecified delirium type compared with hyperactive, hypoactive, and mixed type is relatively smaller at around 6.3%-14%.[8]

The etiology of delirium in this patient may be hyperammonemia. Some hypotheses on the connection between ammonia and cognitive impairment exist. Ammonia is a potent neurotoxin that affects various physiological pathways (e.g., dysfunction and dysregulation of energy metabolism, mitochondria, and inflammatory responses). Therefore, dysfunctions of these pathways may contribute to the generation of cognitive and executive function impairments. Higher ammonia concentrations in both astrocytes and neurons can inhibit the decarboxylation of alpha-ketoglutarate in the tricarboxylic acid cycle, which results in the inhibition of pyruvate dehydrogenase.[1] The above physiological changes would further result in the dysregulation of glucose metabolism. Moreover, ammonia is part of the cellular bioenergetics pathways in the mitochondria. Thus, energy metabolism and mitochondrial dysfunction play roles in cognitive dysfunction in patients with dementia.[9] In addition, hyperammonemia-related neuroinflammation

impairs glutamate and gamma-aminobutyric acid (GABA) neurotransmission by altering the membrane expression of glutamate and GABA receptors, resulting in impaired cognitive functions.[2] Neurosteroid metabolism dysfunction could also contribute to cognitive impairment. Although the effects of chronic ammonia exposure have not yet been confirmed, acute exposure to ammonia can promote neurosteroid production through the activation of N-methyl-D-aspartate receptors and inhibit long-term potentiation induction through a GABA-A receptor-mediated effect in the hippocampus.[10]

In this case report, the main symptoms of the patient were acutely impaired cognitive function and instrumental activities of daily living. However, neither fluctuating course nor disorganized thinking was shown. The time of symptom onset was about 3 weeks after surgery when the liver functions of the patient had improved. In this event, clinicians tend to ignore the role of serum ammonia in the etiology of delirium in the patient. Thus, patients with chronic liver disease and abnormal liver function may experience delirium or cognitive impairment, and their serum ammonia levels should be carefully examined. Furthermore, if the patient has liver disease (like hepatitis B or C) with a normal liver function test but suffers from cognitive decline, the serum concentration of ammonia should also be measured to clarify the cause and provide further treatment.

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