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Recurrent hyperammonemia in an 80-year-old woman with congenital urea cycle abnormality

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Abstract

An 80-year-old woman was brought to our hospital with disturbance of consciousness. The only relevant abnormality detected by laboratory investigations was hyperammonemia, but the cause of her hyperammonemia could not be identified. There were no evidences of uremia, cirrhosis, gastrointestinal hemorrhage, severe constipation, infection by urea-producing bacteria, or portosystemic shunt. Her vital signs and ammonia level significantly improved after the initiation of a high-calorie, low-protein diet and administration of sodium benzoate and lactulose. Genetic diagnosis was not performed. However, she had a history of maintaining a low protein intake since she was young and had frequent headaches and nausea. A congenital abnormality of the urea cycle was strongly suspected.

Keywords

hyperammonemia; urea cycle disorder; disturbance of consciousness

Introduction

Hyperammonemia is a well-known cause of disturbance of consciousness. The main conditions leading to hyperammonemia include uremia, cirrhosis, gastrointestinal hemorrhage, severe constipation, infection by urea-producing bacteria, and portosystemic shunt. However, there are some rare cases that are not applicable to these conditions. Congenital urea cycle abnormalities are generally presented in childhood, especially in the neonatal period, but partial enzyme deficiency has been reported to present in late childhood or in adulthood [1]. We report here a rare case of elderly patient with highly suspected urea cycle abnormality.

Case Report

In October 2014, an 80-year-old woman was brought to our hospital with disturbance of consciousness. The patient lived in a retirement home. She was escorted to the toilet on the night before admission, after which nobody checked on her until the next morning. There was no response when a staff member called her name. Therefore, a staff member called an ambulance and she was transported to our hospital.

On arrival, the Glasgow Coma Scale was E1V 1M5. ECG revealed sinus rhythm with a terminal

inverted T wave in leads II, III, and aVF as well as inverted T waves in leads V1–6. No significant valvular disease was found at echocardiography and there was no evidence of left ventricular hypertrophy. No brain lesions other than ventricular dilatation were seen in head computed tomography (CT) and magnetic resonance imaging (MRI), and there was little difference from scans taken two years ago (fig.1). The possibility of non-convulsive epileptic seizures was considered, but administration of diazepam under oxygen support did not produce an improvement in the level of consciousness. The blood test revealed the kidney dysfunction, which she was already known to have. In addition to that, elevated level of ammonia was found.

Her past history included type 2 diabetes, dyslipidemia, glaucoma, and dementia. The dementia was so advanced that she could not recognize her own children and had difficulty answering questions, making it difficult to evaluate her mental status using the Mini Mental State Examination(MMSE) or Hasegawa Dementia Scale(HDS).

The patient had previously presented to another facility with disturbance of consciousness in July 2014. At that time, there were no new lesions on MRI and her condition improved rapidly, so further tests were not performed and she was only kept under observation.

She had also been admitted to our hospital 2 years ago for disturbance of consciousness, and hyperammonemia had been found at that time. Since the patient was taking valproic acid, hyperammonemia was considered to be secondary to the medication, and she improved after valproic acid was discontinued.

We also found hyperammonemia at the current admission, but she was no longer taking valproic acid. In addition, there was no evidence of uremia, cirrhosis, gastrointestinal hemorrhage, severe constipation, or infection by urea-producing bacteria. We did not perform contrast enhanced CT because of her chronic renal failure, but evidence of aportal-systemic shunt was not observed on abdominal ultrasound.

Because of the disturbance of consciousness, she could not take food orally. Therefore, a stomach tube was inserted and a normal protein diet was given, but high ammonia levels and disturbance of consciousness persisted. After switching to a low-protein diet, ammonia began to decrease and improvement of the level of consciousness was observed. We then switched the patient to a low-protein oral diet. However, her food intake decreased and the blood ammonia level increased again, making oral feeding difficult due to impairment of consciousness. The resultant insufficient calorie intake led to further catabolization and exacerbation of the increase in ammonia. Therefore, we gradually switched to oral intake of a high-calorie and low-protein diet. Ammonia decreased to within the normal range and her level of consciousness improved when administration of lactulose and sodium benzoate was commenced. After beginning the high-calorie and low-protein diet, no significant abnormalities of amino acid breakdown were found. Because we were able to control the patient with a high-calorie, low-protein diet plus lactulose and sodium benzoate, she was discharged from hospital and returned to the retirement home. The details of clinical course and plasma ammonia level are described in fig.2. There have been no subsequent episodes of disturbance of consciousness.

Discussion

The main causes of hyperammonemia include uremia, cirrhosis, gastrointestinal hemorrhage, severe constipation, infection by urea-producing bacteria, and portosystemic shunt [2,3].The present case was atypical because none of the above causes were found. Other possible causes of hyperammonemia include various congenital abnormalities of the urea cycle. These urea cycle abnormalities generally present in childhood, especially in the neonatal period. However, in persons with partial deficiency of an enzyme, presentation later in childhood or in adulthood has also been reported [1]. In patients with partial enzyme deficiency, hyperammonemia may be chronic or may only occur in response to metabolic decompensation associated with severe catabolic stress, such as during a viral illness. Congenital urea cycle abnormalities that are known to cause hyperammonemia include carbamoylphosphate synthetase 1 deficiency, N-acetyl glutamate synthetase deficiency, ornithine transcarbamylase deficiency, type 1 citrullinemia, type 2 citrullinemia, argininosuccinate lyase deficiency, and arginase deficiency [4](Fig.3). Among these urea cycle abnormalities, a high-protein diet is known to be effective for type 2 citrullinemia, while a low-protein and high calorie diet is effective for the other abnormalities [5,6]. In addition to dietary modification, treatment can include hemodialysis or the administration of sodium benzoate, phenylbutyric acid, lactulose, arginine,or citrulline. In severe cases, liver transplantation should be considered [7,8]. In all of these conditions except for type 2 citrullinemia, patients tend to avoid high protein foods because of neurological manifestations and digestive symptoms. We found out the episodes from the daughter that our patient had previously avoided high-protein foods such as meat and fish because they caused headaches and nausea. In recent years, her dementia had become severe and she had been fed a standard high-protein diet at the retirement home.

Genetic testing for type 2 citrullinemia is available in Japan. Since the treatment of this condition from that of the other congenital urea cycle abnormalities, we obtained permission from the family to test for type 2 citrullinemia, but the results were negative. This finding was consistent with the improvement of our patient on a low-protein, high-calorie diet plus sodium benzoate and lactulose.

In this case, no clear abnormalities of amino acid breakdown were found. Although this is not consistent with congenital urea cycle abnormalities, testing was done after she started the low-protein, high-calorie diet, so it is difficult to interpret the findings.

Prolonged hyperammonemia causes atrophy of the cerebral cortex and saccular changes of the white matter, with cerebral atrophy being obvious in our patient [9], (Fig.1). Neurologic abnormalities and cognitive impairment are significantly correlated with the duration of hyperammonemia and encephalopathy [10,11]. Therefore, there is a high possibility that our patient's severe dementia was due to recurrent hyperammonemia.

Although a genetic diagnosis was not confirmed, based on the history, laboratory results and response to treatment at our hospital, we strongly suspected this patient as having a congenital abnormality of the urea cycle involving partial enzyme deficiency.

During the hospital stay, we repeatedly discussed about the patient's condition not only with her family but also with her care manger. Her care manager played an important role in transferring the

the patient's condition to the retirement home and in offering nearly the same condition as in the hospital after discharge. Offering low-protein, high-calorie diet is not so easy in a retirement home, but her care manager made it possible by reporting the detail content of the meals during hospitalization to the retirement home, though it is not completely the same as in the hospital. Moreover, her care manager helped offering the medicine, which is rarely used in daily medical practice, by consulting the pharmacy nearby the retirement home. It is already reported that the collaboration of physicians, care managers and patients showed positive impact on patient health and self-management and also attributed the outcomes to the strong partnership between physicians, care managers and patients [12]. In this case, owing to the help of her care manager, there have been no subsequent episodes of disturbance of consciousness after discharge.

Conclusion

In conclusion, we reported an 80-year-old woman who probably had a congenital urea cycle disorder. She responded well to a high-calorie, low-protein diet plus lactulose and sodium benzoate. When hyperammonemia occurs in middle-aged to elderly persons without a common cause, we should take into consideration the congenital urea cycle disorder due to partial enzyme deficiency. Obtaining a dietary history is the key to suspecting this disease, and early treatment should be initiated [13,14].

Acknowledgments

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Figures

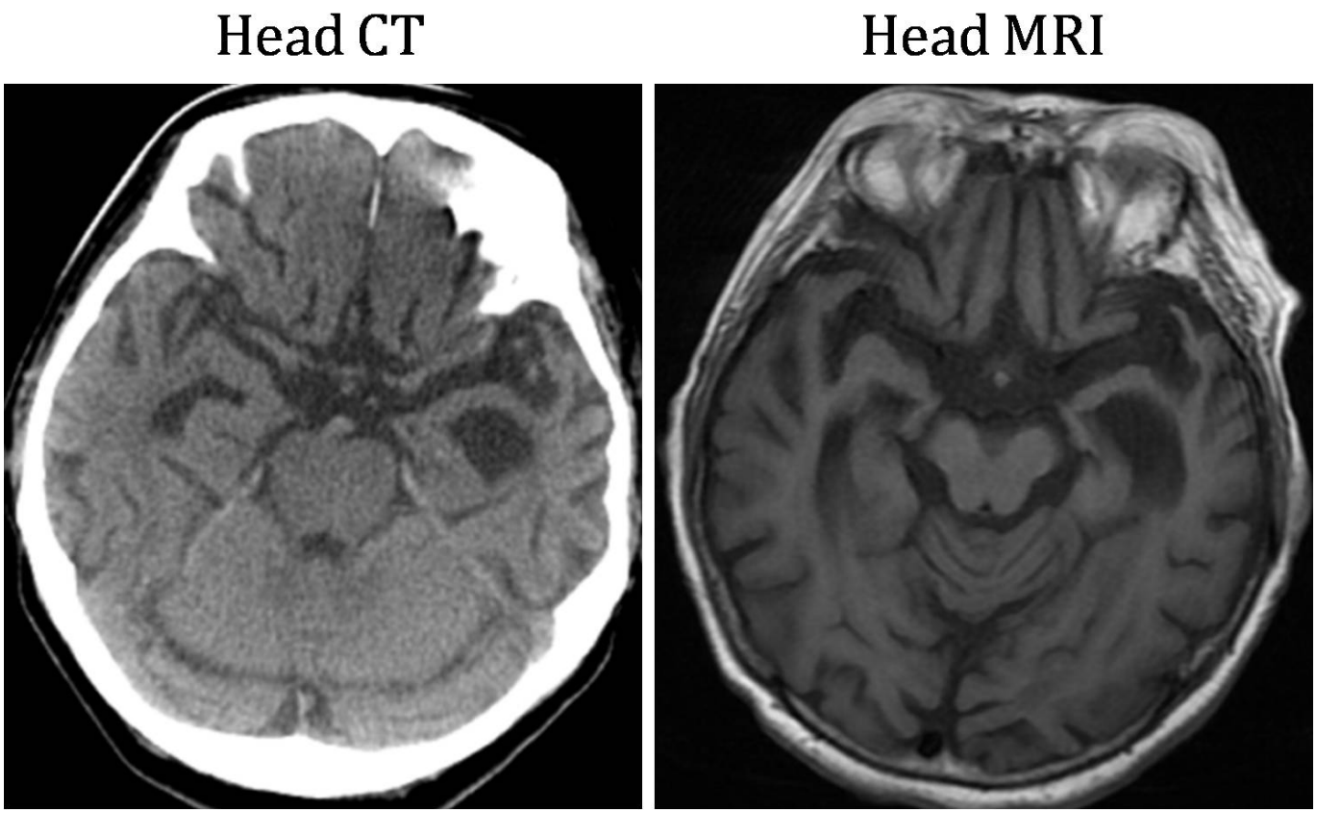
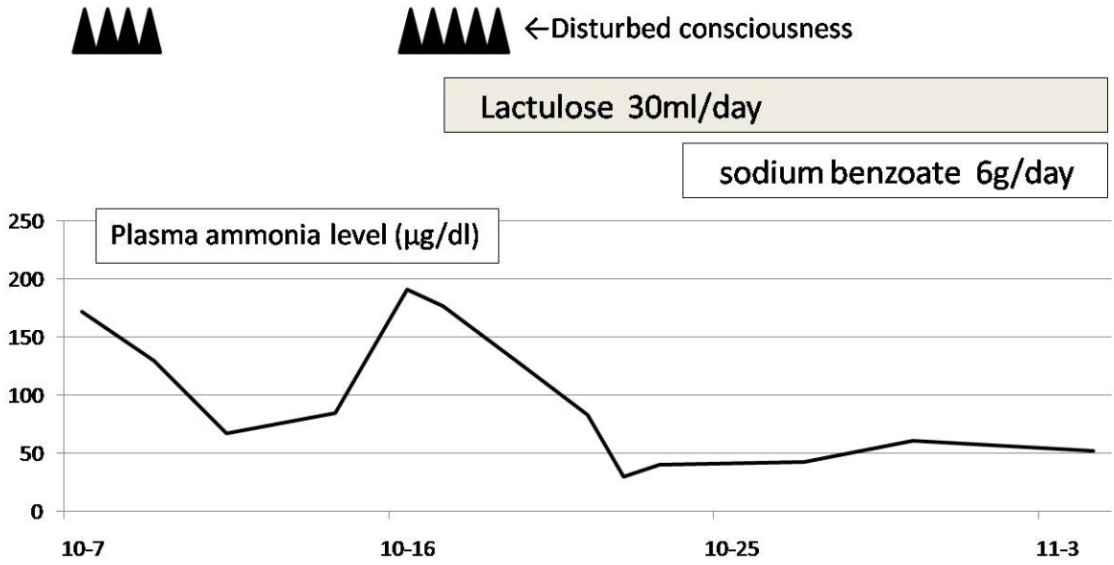


Figure 1: Head CT and MRI showing bilateral ventricular dilatation which was dominant in the left.



Energy(kcal)	0	300	800	700	600		700	1101		450
Protein(g)	0	13.2	8	25	6	+	25	30.2	+	0
Fat(g)	0	6.75	22.4	20	16.8		20	34.7		0
Carbohydrate(g)	0	46.8	147.2	105	11.4		105	173.2		112.5
Way		tubal	tubal	oral	tubal	+	oral	oral		

Figure 2: Clinical course, plasma ammonia level and the types of the diet. Plasma ammonia level got worse when we changed tubal low-protein diet to oral low-protein diet, because of the insufficient intake. We changed to both tubal and oral low-protein diet, and we adjunctively used high calorie jerry for patients with renal failure when we changed oral low-protein diet only.

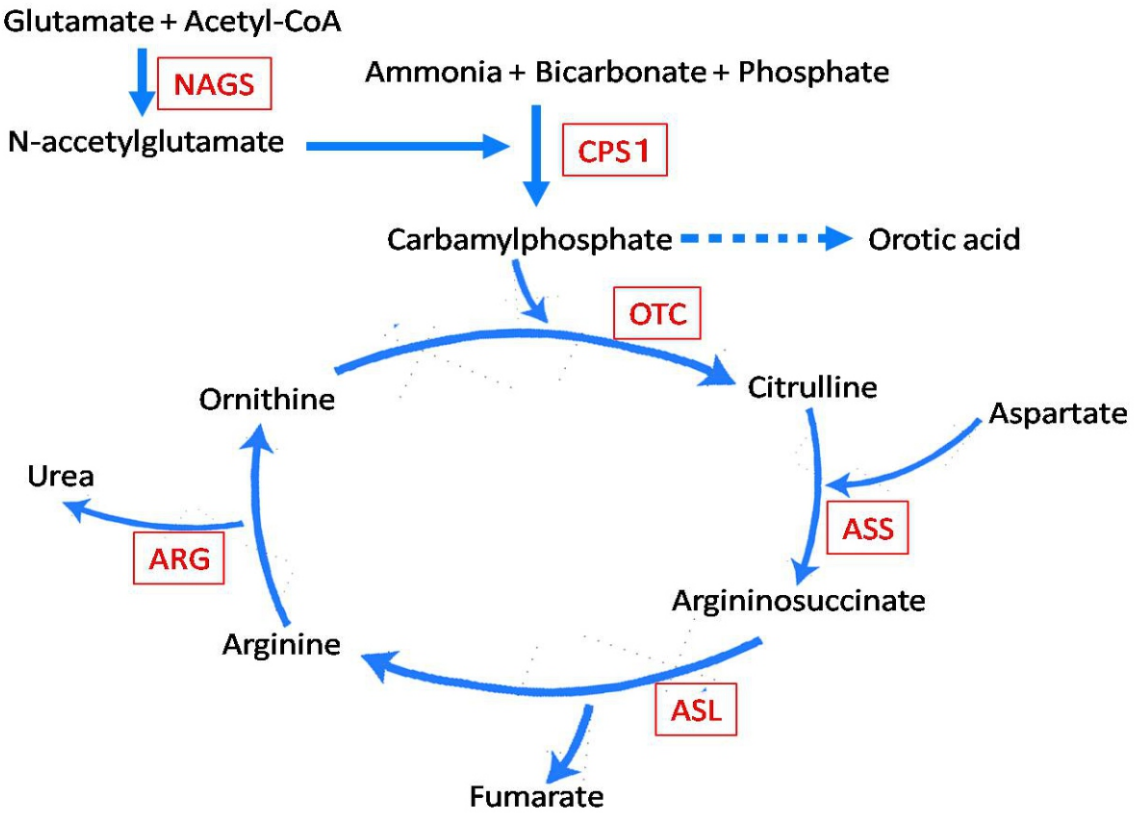


Figure 3: The urea cycle and associated pathways. Abbreviations are follows: NAGS, N-acetyl glutamate synthetase; OTC, ornithine transcarbamylase; ASS, argininosuccinate synthetase; ASL, argininosuccinate lyase; ARG, arginase.

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