Reversibility of Serum \( \text{NH}_3 \) Level in a Case of Sudden Onset and Rapidly Progressive Case of Type 2 Citrullinemia

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Abstract

A 48-year-old male presented with an acute change in mental status due to a marked elevation of plasma \( \text{NH}_3 \) and was diagnosed with citrullinemia with amino acid analysis of blood. Hemodialysis and hemodiafiltration were performed, but serum chemical analysis did not show any improvement which led us to terminate dialysis following intensive care for 3 days. Surprisingly, \( \text{NH}_3 \) level had decreased by 6 days after admission, coinciding with normalization of the size of the pupils. Since spontaneous remission had never been discussed, we discuss this relatively rare, but clinically significant entity with regard to its acute phase management and its potential reversibility.

(Key words: hemodialysis, hemodiafiltration, argininosuccinate synthetase, brain edema, citrin)

Introduction

Citrullinemia (CTLN) is a rare metabolic disorder, in which the impaired function of argininosuccinate synthetase (ASS) predisposes afflicted individuals to elevations of serum \( \text{NH}_3 \), citrulline, and arginine. ASS is one of 6 enzymes controlling the 'urea cycle'. Each of the enzymes can be impaired congenitally, and citrullinemia is the second most common urea cycle disorder next to ornithine carbamoyl transferase (OCT) deficiency. Adult onset type II citrullinemia (CTLN2) is characterized by a liver specific ASS deficiency with no abnormalities in hepatic ASS mRNA or the gene ASS (1-14). CTLN2 differs from classical citrullinemia (CTLN1) in that CTLN1 is neonatal or infantile in onset, with ASS enzyme defect in all tissues arising from a mutation in the ASS gene itself (15-18). Recently, Kobayashi et al identified the novel gene, citrin, which appears to be a calcium-dependent mitochondrial solute transporter with a role in urea cycle function (19). Mutations were also identified in the citrin gene as the cause of CTLN2 (19).

Though the exact mechanism of onset of CTLN2 has not been clearly demonstrated, this clinical entity is considered to be induced by certain stresses, including pregnancy, infection, drugs such as valproate and acetaminophen, alcohol, and liver dysfunction (20-24). Once the disease appears, disturbances in consciousness rapidly worsen and the plasma \( \text{NH}_3 \) level becomes markedly elevated, resulting in death in many cases.

Considering the generally unfavorable clinical course of the disease, liver transplantation has recently been initiated, and is an effective therapy for correction of the metabolic abnormalities associated with citrullinemia (24-26). In the present case, plasma ammonia levels had been normalized without dialytic support, accompanied by the improvement of neurological signs. We investigate this relatively rare clinical entity further, both in terms of treatment and the reversibility of plasma \( \text{NH}_3 \) levels.

Case Report

A 48-year-old male was admitted to the intensive care unit of our hospital while completely unconscious on December 4, 1997. The patient had been physically well until he suffered from pneumonia one month before the admission. Antibiotic treatment for 2 weeks seemed to be effective and a chest X-ray showed almost complete recovery from the bout of pneumonia in spite of mild elevation of aminotransferase activity (AST: 38 U/l, ALT: 51 U/l). Disorientation to time and place appeared 2 weeks after the treatment had been initiated (a week before the admission to our hospital). Serum chemical screening examinations revealed the elevation of \( \text{NH}_3 \) (122 \( \mu \)g/dl) and a moderate elevation of aminotransferase activity (AST: 94 U/l, ALT: 306 U/l) without the evidence of hepatic virus infection. Intravenous administration of branched chain amino acid (aminoleban) or glycerol made no improvement. Therefore,
the patient was transferred to our hospital for further examination and treatment.

Upon admission, the patient had no reaction to any stimuli, with very weak spontaneous breathing. Appropriate respiratory management was initiated immediately after the admission. He had an interesting life history of an extraordinary preference for eating beans. Although the precise reason that patients with CTN prefer to eat beans is unknown, the fact that the beans are rich in arginine may be important (27). It is noteworthy that the elder brother of the patient, with the same eating habit, experienced a severe consciousness disturbance following an operation for a duodenal ulcer at the age of 45, though the operation itself had no technical complications. The elder brother did recover from this semi-comatose state after 7 days, spontaneously and without any specific medical support. The other family members denied a preference for eating beans.

Screening exams on admission revealed a moderate elevation of aminotransferases (AST: 123 U/l, ALT: 191 U/l) and marked elevation of NH₃ (826 µg/dl) (Fig. 1), whereas coagulation tests and serum cholesterol levels were normal. These findings argued against the presence of hepatic failure. Brain CT showed marked brain edema (Fig. 2A), whereas abdominal CT showed no significant abnormalities including liver by the imaging of the liver. Plasma amino acid analysis showed a marked elevation of citrulline, 518 nmol/l (22.4–33.0 nmol/l) (reference value) accompanied with increased arginine, 152 nmol/l (61–118 nmol/l) and threonine/serine ratio, 3.87 (1.17 ± 0.13) (Table 1). We diagnosed this point as CTN2 based on the clinical aspects and the biochemical findings, although we could not measure ASS activity in a liver biopsy due to his poor condition.

Since the severe disturbances in consciousness are thought to be caused by the marked elevation of NH₃ in CTN, hemodialysis (HD) was initiated in order to reduce NH₃ immediately after the admission. Additionally, betamethasone, mannitol, and glycerol had been administered intravenously for reducing NH₃ in plasma, from 829 µg/dl to 247 µg/dl in 6 hours (Fig. 1). The only concern about this treatment, the possibility of worsening the brain edema, forced us to change from hemodialysis to continuous hemodiafiltration (CHDF). Four hours after the alteration of dialysis technique, the patient’s presenting partial convulsion localized mainly around the face had progressed to epileptic status resistant to diazepam. The NH₃ level at that time was again elevated up to 700 µg/dl (Fig. 1), resulting in apnea during the night of hospital day 1. Marked elevation of aminotransferases (AST: 901 U/l, ALT: 733 U/l) was observed on day 2. Brain edema had been markedly aggravated in the first 24 hours as shown in Fig. 2B. CHDF and intensive treatment for brain edema were continuously executed for 72 hours until the morning of day 4, but had resulted in no improvement of clinical symptoms nor laboratory data, and with exacerbation of brain edema. Therefore, we decided to terminate the dialysis on day 4.

Despite this discontinuation of dialysis, on the 6th day after the admission he showed remarkable changes. The size of the pupils had decreased from 8 mm to 4 mm, bilaterally. This incident prompted us to immediately check the plasma NH₃ level, which also had markedly improved from >1,000 µg/dl to 164 µg/dl (Fig. 1). Liver damage had also improved, and the levels of AST and ALT were 442 U/l and 356 U/l, respectively. The only remaining problem was the progressive deterioration of renal function due to acute renal failure since the termination of dialysis, leading to marked elevation of serum creatinine and oliguria. The patient died of renal failure on day 7, and no autopsy was performed. Plasma amino acid analysis on day 7 showed elevation of citrulline, 728 nmol/l (22.4–33.0

![Figure 1. Clinical course of NH₃ (closed square), alanine aminotransferase (ALT) (open square), creatinine (open circle), and BUN (closed circle). HD, hemodialysis; CHDF, continuous hemodiafiltration. The data of NH₃ indicated as 1,000 µg/dl (from day 2 to day 5) mean more than 1,000 µg/dl.](image-url)
Figure 2. Brain CT showing brain edema on admission (A), which had markedly progressed during the first twenty hours (B).

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Day 1 (nmol/ml)</th>
<th>Day 7 (nmol/ml)</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrulin</td>
<td>518.5</td>
<td>728.1</td>
<td>22.4–33.0</td>
</tr>
<tr>
<td>Urea</td>
<td>2,973.0</td>
<td>29,665.2</td>
<td>3,395–6,019</td>
</tr>
<tr>
<td>Arginine</td>
<td>152.4</td>
<td>160.0</td>
<td>61.4–118.3</td>
</tr>
<tr>
<td>Ornithine</td>
<td>29.4</td>
<td>37.7</td>
<td>66.8–104.6</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>13.0</td>
<td>57.4</td>
<td>23.9–51.9</td>
</tr>
<tr>
<td>Glutamine</td>
<td>602.9</td>
<td>1,021.3</td>
<td>482.9–619.6</td>
</tr>
<tr>
<td>Asparaginic acid</td>
<td>2.6</td>
<td>ND</td>
<td>3.6–9.7</td>
</tr>
<tr>
<td>Valine</td>
<td>100.4</td>
<td>138.1</td>
<td>197.2–310.2</td>
</tr>
<tr>
<td>Leucine</td>
<td>57.4</td>
<td>95.1</td>
<td>100.2–179.8</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>25.7</td>
<td>44.1</td>
<td>55.8–100.3</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>39.3</td>
<td>11.6</td>
<td>54.2–88.1</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>54.5</td>
<td>357.0</td>
<td>48.8–71.6</td>
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<tr>
<td>Tryptophan</td>
<td>72.2</td>
<td>46.2</td>
<td>51.9–72.1</td>
</tr>
<tr>
<td>Methionine</td>
<td>18.2</td>
<td>50.1</td>
<td>22.8–36.0</td>
</tr>
<tr>
<td>Threonine/serine Ratio</td>
<td>3.86</td>
<td>1.69</td>
<td>1.17–0.13</td>
</tr>
</tbody>
</table>

ND: not detected.

Table 1. Amino Acid Analysis

nmol/l) and arginine, 160 nmol/l (61–118 nmol/l) (Table 1).

Discussion

We diagnosed this case as CTLN2 based on the clinical aspects and biochemical findings including elevations of serum NH₃, citrulline, arginine, and increased serum threonine-serine ratio (8, 11, 15), although we could not measure ASS activity in a liver biopsy due to the fulminant clinical course and the poor patient’s condition. Recently, the CTLN2 gene, citrin, was identified, in which its causative mutations were found (19). These findings now allow for carrier and diagnostic screening. Although we could not examine for a mutation of citrin in this case, we will analyze the citrin genes of his family and relatives. Once the symptoms of CTLN2 appear, its clinical course is a fulminant form often resulting in death, however, the spontaneous recovery of CTLN2 has been discussed, although rare. The reversibility of this clinical entity may be a key factor in considering its appropriate management. Two indirect lines of evidence about such reversibility could be obtained from the present case. One involves the family history of the elder brother, who presented with a consciousness disturbance for seven days, before complete recovery, following operative treatment for a duodenal ulcer. This episode suggests that he might also suffer from CTLN2 with spontaneous recovery. The other indirect evidence is the normalization of the pupil size and plasma NH₃ levels without any treatments. The markedly increased level of urea may suggest the recovery and/or increase of ASS activity of other organs, as is compatible with the pathophysiology of this disorder. Yet, the mechanism of the decreasing NH₃ had not been clarified, as deterioration of renal function could explain the increase in the plasma urea level.
The tentatively understood mechanism of disease onset and its spontaneous recovery could allow clinicians to anticipate the possible reversibility of the entity. In this case, there are several clinical characteristic aspects; liver dysfunction occurred before the onset of disturbance of consciousness, a marked elevation of transaminase levels was observed, and spontaneous decrease of plasma NH₃ levels was accompanied by a decrease in transaminase levels (Fig. 1). Osufune et al recently reported a case of atypical citrullinemia probably triggered by alcoholic liver damage (23). Shiohama et al also reported another case of CTLN 2 triggered by acetaminophen with liver damage (21). They also reviewed 28 CTLN2 cases, and mentioned that 3 of them (11%) were triggered by liver dysfunction (21). Taken together, in some cases of CTLN2, hepatic encephalopathy could be provoked and worsen by liver dysfunction (inflammation) on the basis of a congenital abnormality of hepatic ASS activity which may be ordinarily compensated by another citrin-like factor, or may not be enough to induce consciousness disturbance in ordinary life. In turn, the improvement of liver dysfunction (inflammation) might have induced the spontaneous decrease of plasma NH₃ levels in the present case. We can not estimate the incidence of reversibility of this disease from solely the present case: consideration of such reversibility may facilitate in making the correct diagnosis and suitable management of CTLN-related confusion. Without such consideration, a substantial proportion of CTLN2 cases with relatively short periods of consciousness disturbances might possibly be misdiagnosed without the analysis of plasma amino acid.

Following the disease presentation, prevention of NH₃ elevations may play an essential role in treating the acute phase of the disease. The significant difference in efficacy between HD and CHDF can be recognized in the present case and HD can be performed more safely with continuous monitoring of intracranial pressure, occasionally accompanied by isoflurane coma or hypothermia. In addition to HD and CHDF, patients with CTLN2 have been treated for hyperammonemia with a low protein diet, hypertonic glucose transfusion, dietary arginine supplementation, sodium citrate or sodium benzonate administration, lactulose administration, and nonabsorbed antibiotic administration. In combination, early detection of this disease and the prevention of elevations in NH₃ might exert profound effects upon prognosis. Recently, patients with CTLN2 have been successfully treated with liver transplantation (24–26). Since the original metabolic disturbance of CTLN2 is localized in the liver, and since its clinical course is a fulminant form often resulting in death, CTLN2 is a good indication for liver transplantation. The implementation of gene therapy using retrovirus has been also considered (28). The patient unfortunately died of acute renal failure, and yet the present case provides significant insight into this rare clinical entity, especially regarding its reversibility and treatment. Through our investigation and report, we would like to suggest the potential reversibility of the acute phase of this disorder. More generally, we hope that this report and other previous reports concerning CTLN2 will bring about a reconsideration of the optimal management of the adult type of this dangerous disease, especially in regions where orthotopic liver transplantation is not popular yet, and in cases when living related liver transplantation is not indicated.

References

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