Adult-Onset Type II Citrullinemia: Clinical Pictures before and after Liver Transplantation

Akihiro Kawata, Minami Suda and Hitoshi Tanabe

In a 25-year-old man with adult-onset type II citrullinemia, liver transplantation resulted in elimination of hyperammonemia and amino acid abnormalities associated with the disease. Postoperatively, a high intensity area in the right cingulate gyrus on a T2-weighted brain magnetic resonance imaging (MRI) also disappeared, suggesting that it reflected an early reversible lesion due to the hyperammonemia. Moreover, the serum level of pancreatic secretory trypsin inhibitor (PSTI), which had been elevated, was normalized. Since the levels of PSTI mRNA and PSTI have been reported to be increased in the livers of type II citrullinemia patients, measurement of serum PSTI levels could aid in the diagnosis of this disease.

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Key words: hyperammonemia, amino acid abnormalities, brain magnetic resonance imaging (MRI), encephalopathy, pancreatic secretory trypsin inhibitor

Introduction

Citrullinemia is an autosomal recessive disease caused by deficiency of argininosuccinate synthetase (ASS; E.C. 6.3.4.5). Saheki et al analyzed the enzyme abnormalities in Japanese citrullinemia patients and classified them into three types (types I, II and III) (1). The classic neonatal and/or infantile form was assigned to type I (abnormal kinetics of the enzyme) and type III (undetectable or extremely low levels of the enzyme). The enzyme defects in types I and III are found in all tissues and/or cells where ASS is expressed. Type II citrullinemia is caused by a decreased level of ASS with normal kinetic properties in the liver but normal ASS levels in other tissues, such as the kidney and brain, and fibroblasts (1-4). Type II is clinically characterized by a sudden onset of consciousness disturbance, a high serum citrulline concentration, a slightly increased serum arginine concentration, and hyperammonemia. Most Japanese patients with adult-onset citrullinemia are affected by type II citrullinemia. Although no effective treatments for type II citrullinemia have been available, orthotopic liver transplantation was recently performed on two Japanese patients and proved to be effective in elimination of hyperammononemia and plasma amino acid abnormalities (5, 6; Kawamoto et al., manuscript in preparation). We report here a 25-year-old man with adult-onset type II citrullinemia who also underwent liver transplantation. The treatment resulted in elimination of the metabolic abnormalities associated with citrullinemia. Moreover, it resulted in normalization of an abnormal intensity area in the right cingulate gyrus on a brain magnetic resonance imaging (MRI) and of the serum levels of some tumor markers, the association of neither of which with this disease has been previously reported.

Case Report

A 25-year-old man was the second child of healthy second-cousin parents. His elder brother died of pneumonia at age 9; his sister has rigid spine syndrome which requires nocturnal ventilatory support (7). The patient had scarlet fever at age 3 and a propensity for cheese since childhood. He was healthy and worked for a company until finger tremor and several episodes of temporary spatial disorientation, restlessness, and sleeplessness occurred 4 months before admission.

On April 4, 1995, he was admitted to the Tokyo Metropolitan Neurological Hospital. Physical examination revealed that the patient was of short stature (162.7 cm, 58.5 kg) and was suffering from hepatomegaly (palpable 4 cm below the costal margin). Neurologically, he was alert and intelligent but sometimes showed temporal and spatial disorientation. Prominent positional and flapping tremor of the four limbs was present. Otherwise he was neurologically normal.

Blood tests revealed hyperammonemia (221.5 nmol/ml,
Table 1. Amino Acid Profiles and Ammonia Levels of the Body Fluid before and after Liver Transplantation

<table>
<thead>
<tr>
<th>Body fluid</th>
<th>Amino acids</th>
<th>before LT (4/13/95)</th>
<th>after LT (9/8/95)</th>
<th>(3/18/96)</th>
<th>(7/1/96)</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>Citrulline</td>
<td>782.2</td>
<td>60.5</td>
<td>55.8</td>
<td>36.4</td>
<td>10.8–36.5</td>
</tr>
<tr>
<td></td>
<td>Arginine</td>
<td>279.1</td>
<td>152.2</td>
<td>139.3</td>
<td>135.4</td>
<td>39.6–138.4</td>
</tr>
<tr>
<td></td>
<td>Glutamine</td>
<td>873.3</td>
<td>697.3</td>
<td>695.6</td>
<td>697.0</td>
<td>396.0–729.8</td>
</tr>
<tr>
<td></td>
<td>Ammonia</td>
<td>221.5</td>
<td>118.7</td>
<td>36.3</td>
<td>58.2</td>
<td>41.2–123.5</td>
</tr>
<tr>
<td>Urine</td>
<td>Citrulline</td>
<td>269.6</td>
<td>76.3</td>
<td>41.2</td>
<td>20.9</td>
<td>9.7–36.0</td>
</tr>
<tr>
<td>CSF</td>
<td>Citrulline</td>
<td>102.7</td>
<td>N.E.</td>
<td>1.7</td>
<td>1.7</td>
<td>2.1±0.8f</td>
</tr>
<tr>
<td></td>
<td>Glutamine</td>
<td>1,538.1</td>
<td>N.E.</td>
<td>539.0</td>
<td>443.8</td>
<td>602.1±118.6f</td>
</tr>
<tr>
<td></td>
<td>Ammonia</td>
<td>192.2</td>
<td>N.E.</td>
<td>38.5</td>
<td>23.8</td>
<td>20.0±7.0^</td>
</tr>
</tbody>
</table>

Creat.: creatinine, CSF: cerebrospinal fluid, LT: liver transplantation, N.E.: not examined. Amino acids were measured by an automated amino acid analyzer according to the nonhydrin-coloring method. Ammonia was measured by the direct colorimetric method. Normal levels of amino acids and ammonia in CSF are expressed as mean±SD and cited from references (24, 25).

Table 2. Urea Cycle Enzymes in the Liver of the Patient and Control Adults

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Patient (% of control)</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboxylphosphate synthetase</td>
<td>0.029 (81%)</td>
<td>0.03±0.03 (n=18)</td>
</tr>
<tr>
<td>Ornithine transcarbamylase</td>
<td>1.10 (125%)</td>
<td>0.8±0.35 (n=16)</td>
</tr>
<tr>
<td>Argininosuccinate synthetase</td>
<td>0.0018 (5.5%)</td>
<td>0.03±0.012 (n=16)</td>
</tr>
<tr>
<td>Argininosuccinate lyase</td>
<td>0.047 (90%)</td>
<td>0.05±0.025 (n=25)</td>
</tr>
<tr>
<td>Arginase</td>
<td>8.5 (54%)</td>
<td>15.8±3.1 (n=20)</td>
</tr>
</tbody>
</table>

The activities of the 5 urea cycle enzymes in the liver were measured by the methods of Schimke et al (26), Pierson et al (27), Su et al (28), and Rüegg and Russell (29) in the Department of Biochemistry of Kagoshima University, Kagoshima, Japan. The results of control are expressed as mean±SD with the number of control samples in parenthesis.

On diagnosis of type II citrullinemia with associated hyperammonemia and metabolic encephalopathy, he was first treated with dietary protein restriction and administration of electron microscopic examinations showed no specific changes of cell organella including mitochondria. A computed tomography (CT) scan (Fig. 1B) revealed an enlarged liver as a diffuse low-density area, which was compatible with the microscopic findings. A T2-weighted brain MRI revealed a localized high-intensity area in the right cingulate gyrus (Fig. 2A). Electroencephalography (EEG) showed diffuse slowing with θ waves and an occasional triphasic wave.

On diagnosis of type II citrullinemia with associated hyperammonemia and metabolic encephalopathy, he was first treated with dietary protein restriction and administration of.
lactulose, vancomycin, and sodium benzoate. This somewhat alleviated the hyperammonemia and improved his consciousness disturbance. However, considering his severe fatty liver and the poor prognosis with such conservative therapies, he was finally treated with partial liver transplantation at Shinshu University Hospital on June 20, 1995. The patient’s whole liver was removed and part of his father’s liver (the left lobe) was transplanted. The details of the operative procedure and subsequent immunosuppression therapy was reported by Yazaki et al (10). We have continued postoperative follow-up of the patient for one year. Soon after surgery, the fluctuating consciousness disturbance and flapping tremor completely disappeared, accompanied by normalization of the abnormal EEG findings. The high-intensity area in the cingulate gyrus on the T2-weighted MRI disappeared by September 1995 (Fig. 2B). The blood ammonia level normalized (118.7 nmol/ml, Table 1) and serum levels of the tumor markers except for CA 19-9 also normalized (PSTI 16.5 ng/ml, ferritin 18.8 ng/ml, IAP 474 μg/ml, CA 19-9 59.5 U/ml) within 2.5 months after the surgery. The plasma and urine citrulline levels gradually decreased and were in the physiological range one year after the surgery (Table 1). He returned to his previous employment 10 months postoperatively.

Figure 1. A) Histopathological findings of the patient’s liver, showing severe fatty change (HE stain, bar = 100 μm). B) Abdominal CT scan before liver transplantation (April 10, 1995). It revealed diffuse low density in the liver, suggestive of fatty liver.

Figure 2. A) MRI T2-weighted coronal image (TR 2,000 ms/TE 100 ms, 0.5 T) of the cerebrum (April 6, 1995). A high intense area was observed in the right cingulate gyrus (arrow). B) Postoperatively, on September 28, 1995, the high-intensity area had disappeared (TR 2,000 ms/TE 100 ms, 0.5 T).
patients tested (21). In specimens of the livers of these patients, Internal Medicine Vol. 36, No. 6 (June 1997)
our patient's liver were not measured, the serum levels of PSTI
Although the levels of PSTI mRNA, PSTI and CRP mRNA in
level of CRP mRNA, which is another major acute phase
measurement of CSF glutamine and ammonia levels may be
encephalopathy due to the hyperammonemia and partly due to the imbalance of amino acid levels in the body fluids. Regarding brain CT findings related to such metabolic encephalopathy, previous reports mentioned brain edema occurring chiefly in the early stage of the disease (6, 11–13), and brain atrophy in patients who had a relatively long clinical course (6, 14, 15). In the present patient, the localized lesion in the cingulate gyrus on the brain MRI disappeared after the surgery, suggesting that it reflected an early reversible disease process which would have extended to other brain regions if left untreated. Based on an experimental model of hyperammonemic coma in primates, it is inferred that the swelling of astrocytes is the primary response to hyperammonemia (16, 17). Astrocytes are considered to be the sites of incorporation of ammonium into glutamine, resulting in an increase in their endogenous osmolarity and swelling (17). In addition, a strong relationship between hyperammonemia, neurologic dysfunction, and a high cerebrospinal fluid glutamine concentration has been detected in hepatic encephalopathy (18). Therefore, the high CSF ammonia and glutamine levels in this patient and previously reported cases of adult-onset type II citrullinemia (9, 19) might indicate disruption of the compensative astrocyte function for hyperammonemia. EEG, brain magnetic resonance imaging and measurement of CSF glutamine and ammonia levels may be helpful in detection of early brain dysfunction in this disease.
Another remarkable finding in the present case was the high concentrations of so-called tumor markers in the serum. Among these markers, PSTI showed the most prominent serum concentration increase. Concerning the molecular basis of adult-onset type II citrullinemia, causative abnormalities within the ASS gene remain to be identified (20). Recently, however, Kobayashi et al reported detecting overexpression of PSTI mRNA and a high concentration of PSTI in the liver of 9 type II citrullinemia patients tested (21). In specimens of the livers of these patients, no malignant histological changes were observed. Although PSTI is known to be an acute phase reactant, the expression level of CRP mRNA, which is another major acute phase reactant, was not increased in the liver of these patients. Although the levels of PSTI mRNA, PSTI and CRP mRNA in our patient’s liver were not measured, the serum levels of PSTI and CRP were completely consistent with their expression patterns in the livers of Kobayashi et al’s type II citrullinemia patients (21). In addition, the fact that the serum PSTI level normalized after the liver transplantation suggests that the excess serum PSTI originated from the liver. It also indicates that the putative factors which regulate the expression of PSTI and most likely ASS in the liver are present in the liver itself and not in extrahepatic tissues or other organs. Furthermore, our results suggest a possible relationship between PSTI and the primary defect of adult-onset type II citrullinemia. In addition to serum PSTI, the other markers such as serum ferritin and serum IAP could be useful for diagnosing citrullinemia.
Regarding therapy for adult-onset type II citrullinemia, patients have been treated for hyperammonemia with such therapies as a low protein diet, hypertonic glucose transfusion, dietary arginine supplementation, sodium citrate or sodium benzoate administration, lactulose administration, nonabsorbed antibiotic administration, peritoneal dialysis, and plasmapheresis. Transfusion of branched chain amino acids has also been performed but a subsequent decrease in consciousness level and exacerbation of hyperammonemia were noted in one patient (12). These conservative therapies result in temporary alleviation of hyperammonemia and/or consciousness disturbance. However, the long-term prognosis is poor, with coma and a status epilepticus occurring, followed by death due to brain swelling usually within two years of onset of encephalopathy (11, 12, 19, 22, 23). If the patient survives longer than two years, severe organic brain damage is inevitable (14, 15). Recently two Japanese patients were treated with orthotopic liver transplantation (5, 6; Kawamoto et al, manuscript in preparation). In these patients, hyperammonemia and abnormalities in plasma amino acids were alleviated to an extent not achieved by the above conservative treatments. In addition, the patients are not only alive at 7.5 and 2 years, respectively, after the surgery, but also live normal lives. The present condition of the present patient also indicates that liver transplantation is an effective therapy for correction of the metabolic abnormalities associated with citrullinemia. Furthermore, it suggests that liver transplantation in the early stage of the disease could prevent development in the brain of organic lesions due to the metabolic abnormalities. Since the original metabolic disturbance of adult-onset type II citrullinemia is localized in the liver, development of the disease seems to be a good indication for liver transplantation. Moreover, the transplant should be performed as soon as possible after onset of the disease before irreversible brain damage occurs.

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References


