

# Liver transplantation for late-onset ornithine transcarbamylase deficiency: A case report

*By Xiao-Hui Fu*

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**Liver transplantation for late-onset ornithine transcarbamylase deficiency: A case report**

3

Fu XH et al. Liver transplantation for late-onset ornithine transcarbamylase deficiency

Xiao-Hui Fu, Yu-Hui Hu, Jian-Xiang Liao, Li Chen, Zhan-Qi Hu, Jia-Lun Wen, Shu-Li Chen

**Abstract****BACKGROUND**

Ornithine transcarbamylase deficiency (OTCD) is an X-linked inherited disorder and characterized by marked elevation of blood ammonia. The goal of treatment is to minimize the neurological damage caused by hyperammonemia. OTCD can be cured by liver transplantation (LT). Post-transplant patients can discontinue anti-hyperammonemia agents and, consume a regular diet without the risk of developing hyperammonemia. The neurological damage caused by hyperammonemia is almost irreversible.

**CASE SUMMARY**

An 11.7-year-old boy presented with headache, vomiting, and altered consciousness. The patient was diagnosed with late-onset OTCD. After nitrogen scavenging treatment and protein-free diet, ammonia levels were reduced to normal on the third day of admission. Nevertheless, the patient remained in a moderate coma. After discussion, LT was performed. After LT, the patient's blood ammonia and biochemical indicators stabilized in the normal range, he regained consciousness, and his nervous system function significantly recovered. Two months after LT, blood amino acids and urine organic acids were normal, and brain magnetic resonance imaging showed a decrease in subcortical lesions.

**CONCLUSION**

LT can significantly improve partial neurological impairment caused by late-onset OTCD hyperammonemic encephalopathy, and LT can be actively considered when early drug therapy is ineffective.

**Key Words:** Ornithine transcarbamylase deficiency, Urea cycle disorder, Hyperammonemic encephalopathy, Liver transplantation, Case report

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**Core Tip:** There are differing views on the timing of OTCD liver transplantation and whether it makes sense to perform LT in a patient with severe neurological impairment. We report a case of late-onset OTCD with severe neurological impairment, whose nervous system function recovered after LT, for late-onset OTCD patients with severe neurological impairment, LT can be considered.

## INTRODUCTION

<sup>7</sup>  
Ornithine transcarbamylase deficiency (OTCD) is the most common urea cycle disorder, with an incidence of approximately 1/56500 to 1/80000 reported in the literature<sup>[1-4]</sup>. The 2019 Urea Cycle Disorders Diagnosis and Management Recommendations guidelines recommend liver transplantation (LT) for patients with severe urea cycle disorders who do not have severe neurological impairment and have stable metabolic status<sup>[5]</sup>. Opinions regarding LT for children with pre-existing severe brain damage differ because LT does not restore pre-existing neurological damage and because of the high risk of LT in children with acute encephalopathy; there is no experience regarding the extent to which neurological damage can be restored after surgery<sup>[5]</sup>. We report a patient with late-onset OTCD patient with good neurological recovery after LT.

## CASE PRESENTATION

### *Chief complaints*

<sup>11</sup>  
An 11.7-year-old boy was admitted to our hospital because of headache , vomiting and altered mental status.

### *History of present illness*

Two days before admission, the patient complained of a headache without obvious inducement, accompanied by vomiting 25 times. The headache did not improve with cold medicine. He became unconscious 12 h before admission, and relevant tests were completed at a referring hospital. His blood ammonia was  $>500\mu\text{mol/L}$ . He was referred to our hospital for further treatment.

### *History of past illness*

The patient was the product of a G1P1 (first pregnancy and first birth) mother, delivered by cesarean section at term with a birth weight of 3.0 kg. His perinatal condition was unremarkable, with no history of asphyxia. He was generally healthy and developed normally for a child of the same age. Prior to this episode, the family was not aware that the patient had OTCD.

### *Personal and family history*

The patient had no significant family history. No patients in the family had OTCD and symptoms associated with the disease.

### *Physical examination*

On physical examination, he was in a moderate comatose state (Glasgow score 6) and was unresponsive to sound. Eyes could not be closed, the pupils were equally large and round, about 3 mm in diameter, and the light reflex was delayed. There were no significant abnormalities on cardiopulmonary or abdominal examinations. Muscle strength of the limbs could not be tested, muscle tone was normal, and all pathological signs were negative.

### *Laboratory examinations*

Laboratory tests showed a significantly elevated blood ammonia level (Table 1). Liver functions and coagulation times were abnormal. Blood tandem mass spectrometry showed moderately elevated glutamine. Citrulline and arginine were in the normal

range. Urine organic acid gas phase mass spectrometry showed uracil and orotic acid levels were elevated. Blood ammonia levels during the first week of admission are shown below(Figure 1). During the remainder rest of the hospital stay, levels were in the normal range.

Whole exome gene testing revealed the *OTC* gene exon2 hemizygote variant c.119G > A (p.R40H), inherited from his mother. The missense mutation is located in the well-studied exon functional domain without benign variation(PM1). The frequencies of all normal population databases (dsSNP, 1000 genomes) were less than 0.0005(PM2). This is a variant with different amino acid changes at the same locus reported in the literature as pathogenic variants (PM5). Pathogenic missense mutations of this gene are common, and benign missense mutations are rare (PP2). The literature reported the variant to cause impaired gene function *in vitro* functional assays (PS3). In summary, according to American College of Medical Genetics (ACMG) guidelines, this variant is likely pathogenic (PM1+PM2+PM5+PP2+PS3).

### ***Imaging examinations***

Brain magnetic resonance imaging(MRI) revealed that large patches of symmetrical high signal shadows T2 weighted imaging(T2WI) and fluid attenuated inversion recovery (FLAIR) in the cerebral hemispheres, and diffusion weighted imaging(DWI) revealed a significantly high signal, more pronounced in the bilateral dorsal thalamus, caudate nucleus, lenticular nucleus, insula, cingulate gyrus and frontal lobe into the cortex at the falx.

### **FINAL DIAGNOSIS**

Hyperammonic encephalopathy, ornithine transcarbamylase deficiency.

### **TREATMENT**

After admission, the patient underwent continuous hemodiafiltration (Disposable hemodialysate filter and supporting pipeline, Prismaflex M100 set, Gambro Industries,

blood flow velocity 150-300mL/min, replacement velocity 1000-2500 mL/ h, dialysis velocity 1500-5000 mL/h) to lower the blood ammonia level. The impairment of consciousness worsened, and the repeat blood ammonia level was 511.72  $\mu\text{mol/L}$ . Within a few hours, he fell into a severe coma (Glasgow score 3) and developed central respiratory failure. We immediately gave ventilation, reduce intracranial pressure (mannitol and sodium hypertonic), nitrogen scavengers agents include sodium benzoate and arginine, antibiotics to inhibit ammonia production by intestinal bacteria, along with multiple nutritional support treatments.

On day 3, blood ammonia decreased to normal and was maintained in the normal range for the remainder of the hospital stay. The continuous hemodiafiltration parameters (blood flow velocity 120mL /min, replacement velocity 500 mL/h, dialysis velocity 2500 mL/h) were gradually adjusted downwards. On day 6, the patient discontinued hemodiafiltration. On day 7, the patient's consciousness changed from deep coma to moderate coma. On day 12, the patient was weaned from the ventilator; however, the patient remained in a moderate coma.

On day 31, modified piggyback orthotopic liver transplantation<sup>5</sup>(anastomosis of the donor inferior vena cava to the recipient inferior vena cava) was performed, the donor is deceased. Postoperatively, he was treated with tacrolimus, sodium mescaline, and methylprednisolone. On day 35 (day 4 after surgery), the patient became conscious (open eyes autonomously, obey commands, Verbal response is "T"). A repeat brain MRI more than 2 mo after transplantation showed that the previous subcortical lesions had largely disappeared; however, hydrocephalus was worse (Figure 2). He was discharged after 3 mo and underwent abdominal ventricular drainage at another hospital.

### **OUTCOME AND FOLLOW-UP**

At follow-up after discharge, six months after surgery, he could sit, squat, and walk smoothly on his own. He could say simple superlatives, and his command execution



rate was about 30%. He showed poor emotional control and a greater temper to his parents; however, he was gentler to strangers and his brother.

## DISCUSSION

<sup>10</sup>Ornithine transcarbamylase deficiency (OTCD) can develop at any age. Depending on <sup>1</sup>the time of onset, OTCD can be divided into the neonatal-onset type and the late-onset type (age of onset > 28d)<sup>[6]</sup>. Patients with neonatal onset usually present in the first few hours and days after birth with severe disease and high mortality. The clinical presentation of late-onset disease varies widely, with no specific clinical manifestations before initial onset. Acute onset of late-onset OTCD can be induced by infection, prolonged fasting, or fatigue. The outcome for conservative treatment is poor in patients with hyperammonemia crisis, 5-year survival is approximately 45% <sup>[7]</sup>.

Outcomes in urea cycle disorders are related to blood ammonia levels and the duration of the coma. According to a European questionnaire, <sup>2</sup>patients with blood ammonia levels > 300  $\mu\text{mol/L}$  or <sup>2</sup>peak blood ammonia levels > 480  $\mu\text{mol/L}$  at the first episode suffered neurological dysfunction<sup>[8]</sup>. Although patients with late-onset OTCD generally have better outcomes than those neonatal onset, there is a higher incidence of residual neurological damage, and the mortality rate for late-onset OTCD with coma on the first episode is high. In a follow-up study that included 90 OTCD cases, 18 patients had coma as their first presentation and 6 of them died <sup>[9]</sup>. Among 16 genetically confirmed cases of late-onset OTCD reported in the Chinese literature<sup>[10]</sup>, nine died shortly after hospital admission, suggesting the disease's aggressive nature at acute onset. In our case, the patient was physically fit and had normal development before the presentation. Headache and vomiting were the primary manifestations; these symptoms were not taken seriously until the onset of unconsciousness, which delayed the treatment. Although blood ammonia levels reduced to normal range after aggressive treatment, the neurological damage did not improve with the normalization of blood ammonia. The patient was in a moderate coma before LT.



OTCD is treated with a low-protein diet and long-term oral ammonia-lowering medications. LT is the radical treatment for OTCD. After LT, patients no longer need to restrict their diet or take nitrogen scavenging agents [5]. Statistics on LT with urea circulation disorders show that the 5-year survival rate of patients after LT can exceed 90%<sup>[11,12]</sup>. There is not yet consensus regarding the indications or timing of LT. It is now believed that LT should be performed in all patients with neonatal onset to prevent neurological damage<sup>[13]</sup>. The indications and timing of LT for late-onset OTCD must be determined by the clinical symptoms, including poor drug efficacy, recurrent episodes of hyperammonemia, growth retardation, and inability to control diet strictly<sup>[14]</sup>. Although post-transplant patients require long-term immunosuppressive drugs, there is evidence that OTCD patients who underwent LT have a better quality of life than those who did not and no longer risked death from sudden-onset hyperammonemia<sup>[11,15]</sup>.

The patient in the present case had an acute onset, a long duration of hyperammonemia, severe brain damage, and was in a moderate coma before LT. Therefore, the optimal time window for LT was missed, and the choice of LT and the extent to which the patient would recover from neurological damage after transplantation were concerns for his physicians and parents. Most LTs for OTCD patients are carried out in the context of stable metabolism, and there are few reports of LT in the context of severe neurological injury. Nevertheless, given the patient's inability to regain consciousness, we performed an LT, and he became conscious 4 days later. After LT, he did not take nitrogen scavenging agents, and the blood ammonia, liver, and kidney function biochemistry were maintained in the normal range at regular follow-up. Kawagishi *et al* reported a patient who underwent LT for recurrent hyperammonemia due to late-onset OTCD, and the blood ammonia was maintained in the normal range without further nitrogen scavenging agents after surgery. Nevertheless, the at 16 mo after surgery showed no change in subcortical lesions<sup>[16]</sup>. The brain MRI of our patient was repeated about 2 mo after surgery, suggesting a significant reduction of abnormal cranial signals compared with the previous one, both suggesting

that LT was effective in the treatment of this patient, However, brain MRI showed that hydrocephalus had progressed and brain atrophy, suggesting that some neurological damage may still not reverse after LT.

Several studies showed that LT could be used as a radical treatment that significantly improves the quality of life<sup>[11,17]</sup>. However, it is not clear whether LT is beneficial for OTCD patients who already have severe neurological damage. This case report suggests LT can be attempted in children with late-onset OTCD, even if a severe neurological impairment is already present. The neurological recovery after LT in this patient was unexpected; the recovery of higher functions such as emotional control and spatial thinking require long-term rehabilitation training and psychotherapy, and its effects need to be observed on follow-up.

### **CONCLUSION**

In summary, patients with late-onset OTCD with acute hyperammonemic encephalopathy are at high risk, and LT can significantly improve the neurological damage caused by this disease. As a radical cure for OTCD, LT should be considered more aggressively.

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3	Naoki Kawagishi, Kazushige Satoh, Yoshitaka Enomoto, Yorihiro Akamatsu et al. "Improved Quality of Life and Unchanged Magnetic Resonance Brain Imaging After Living Donor Liver Transplantation for Late-Onset Ornithine Transcarbamylase Deficiency: Report of a Case", Surgery Today, 2005 Crossref	17 words — 1%
4	Wakiya, T.. "Impact of enzyme activity assay on indication in liver transplantation for ornithine transcarbamylase deficiency", Molecular Genetics and Metabolism, 201203 Crossref	17 words — 1%
5	"Hepatic Transplantation", Elsevier BV, 2018 Crossref	15 words — 1%

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6 Andrea L. Gropman. "Altered neural activation in ornithine transcarbamylase deficiency during executive cognition: An fMRI study", Human Brain Mapping, 2011 13 words — 1%

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9 Denise L. Chan, Joëlle Rudinger-Thirion, Magali Frugier, Lisa G. Riley, Gladys Ho, Kavitha Kothur, Shekeeb S. Mohammad. "A case of QARS1 associated epileptic encephalopathy and review of epilepsy in aminoacyl-tRNA synthetase disorders", Brain and Development, 2021 8 words — < 1%

Crossref

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10 Hiroki Morizono, Chad D. Listrom, B. S. Rajagopal, Mika Aoyagi, Mark T. McCann, Norma M. Allewell, Mendel Tuchman. "'Late Onset' Ornithine Transcarbamylase Deficiency: Function of Three Purified Recombinant Mutant Enzymes", Human Molecular Genetics, 1997 8 words — < 1%

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11 Julia Pereira Muniz Pontes, Pedro Henrique Costa Ferreira-Pinto, Elington Lannes Simoes, Thaina Zanon Cruz et al. "Removal of the Retained Ventricular Catheter Using the Endoscopic Monopolar Instrument", Case Reports in Surgery 8 words — < 1%

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12 K. L. McBride. "Developmental Outcomes With Early Orthotopic Liver Transplantation for Infants With Neonatal-Onset Urea Cycle Defects and a Female Patient With Late-Onset Ornithine Transcarbamylase Deficiency", 8 words — < 1%

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