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Liver transplantation in the treatment of ornithine transcarbamylase deficiency

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Summary

Ornithine transcarbamylase deficiency (OTCD) is a genetic disorder causing disturbed urea metabolic cycle with a high mortality rates. It's a genetic metabolic disease manifesting as hyperammonemia. Drugs and hemodialysis may reduce blood ammonia levels in the patients. Liver transplantation may improve the long-term survival rate of patients, but it cannot reverse the nervous system damage that has occurred before, and cannot improve cognition. If the liver transplant is performed early in childhood, neurodevelopment may be normal at later terms. Late-onset patients should also be transplanted when required. Heterozygosity for OTCD in the donor is still risky and should only be used when there are no other options. Hepatocyte transplantation can be tried if necessary. Prevention of infection, long-term monitoring of liver function and blood ammonia are required post-transplant. Liver transplantation should be considered for all patients with genetic OTCD. The final decision of whether and how to use this treatment mode depends on individual clinical circumstances.

Keywords

Ornithine transcarbamylase deficiency, urea cycle disorder, liver transplantation, hepatocyte transplantation.

Introduction

Ornithine transcarbamylase deficiency (OTCD) is an X-linked genetic urea cycle disorder (UCD) caused by the mutation of the ornithine transcarbamylase (*OTC*, Xp2.1) gene. OTC is a mitochondrial enzyme synthesized in the cytoplasm. Following OTC transfer to the mitochondria, carbamoyl phosphate and ornithine are catalytically converted to citrulline. Then citrulline is transported to the cytoplasm to participate in the urea cycle reactions. The OTC gene mutations block normal urea metabolism. Therefore, increased blood ammonia, decreased blood citrulline and increased urine orotic acid are typical biochemical phenotypes of OTCD. High blood ammonia could cause the nervous system damage, epilepsy-like symptoms, disturbed consciousness, and cognitive impairment appear.

Early-onset OTCD mainly occurs in male heterozygous infants, usually with a rapid onset and a high mortality in the neonatal period [1]. The patient can be normal at birth. Then irritability, deteriorating feeding, drowsiness and tachypnea appear soon. It often develops into metabolic encephalopathy rapidly and leads to death if treatment is not applied. Severe intellectual impairment will be left in survivors due to the extensive damage to the brain caused by elevated blood ammonia [2]. Late-onset OTCD can occur in hemizygous males and heterozygous females. The clinical symptoms are variable and mild compared with early-onset OTCD.

The main principle of treatment is to control diet, reduce protein intake, avoid hyperammonemia, and use drugs to promote blood ammonia metabolism. However, excessive restriction of protein intake can lead to hypertrophy of endogenous protein catabolism, increase blood ammonia, and affect the patient's intelligence and physical development [3]. If the drug treatment is not effective, dialysis treatment should be considered as soon as possible.

Liver transplantation (LTx) is the most effective treatment of this disease, since OTC activity is mainly expressed in liver tissue. In these cases, the patients can stop anti-hyperammonemia drugs and return to normal diet after LTx. Hyperammonemia will not occur again, and the quality of life

is significantly improved [4, 5]. Though LTx can correct the patient's urea cycle disorder and reduce blood ammonia substantially, it cannot reverse the nervous system damage that has occurred before LTx [5].

Indications for surgery

For the neonatal-onset patients, LTx should be performed as soon as possible if the patient's condition is stable, independently on the blood ammonia levels. Considering the patient's tolerance for surgery and the risk of post-transplant hyperammonemia, the age of 3 months to 1 year, or body mass of >5 kg are appropriate pre-requisites for surgery [3]. It is usually done at six months of age. Early transplantation in the neonatal-onset patients may be associated with normal neurodevelopment compared with those without LTx.

For late-onset patients, it is now generally believed that, even with mild current manifestations, there is a risk of sudden, potentially life-threatening hyperammonemia at any age. Therefore, surgery should be considered for any OTCD patient. Final decision of LTx depends on the individual circumstances.

The peak of death with OTCD is noted at the age of 12-15 years in female patients, thus considering LTx before that time [6]. LTx in adolescents may also promote normal neurodevelopment. The patients should undergo LTx at peak blood ammonia levels of >300 μmol/L [7]. In cases of severe progressive liver disease, repeated metabolic abnormalities after standard treatment or poor compliance with current treatment, LTx can be also performed [3].

Analysis of data on the patients under 18 year subjected to LTx between February 2002 and September 2020, the waiting list time and male sex were associated with long-term risk for a cognitive delay. Minimizing the waiting time is quite important, in order to maintain the patient's cognition capacities at later terms and improve the quality of life [8].

All the patients with OTCD should be considered for LTx to prevent progressive neurological injury. But the decision is usually taken in cases of unstable condition and frequent episodes of hyperammonemia.

Donor selection

Liver transplants from either living or deceased donors are acceptable for the children of 1.5 to 3.0 years old. Three patients received cadaveric LTx at this age period. They developed well after this operation, and no recurrences were observed within follow-up for 13 years [9].

LTx from living donors is the most effective method in these cases. Living donors for the LTx should be in healthy condition, but sometimes there is no time to wait for another donor, except for subjects heterozygous for the mutated gene. A symptom-free carrier may be a donor for LTx, if OTC enzyme activity is high enough, and if no other options exist. The mutation carrier must undergo careful and comprehensive examination. OTC activity in liver biopsy samples must be tested to determine the suitability of heterozygote to be a donor [10]. According to Wakiya, T, the OTC activity of late-onset patients requiring LTx, ranges from 4.4% to 18.7%. Meanwhile, in those cases where LTx is not necessary, the residual enzyme activity ranges from 33% to 38% [11]. Rahayatri et al. [12] reported two 5-year-old girls who received liver transplants from heterozygous mutation carriers. The OTC activity in the first case and in her donor was 15% and 62%, respectively. She developed hyperammonemia within 2 months after the surgery. OTC activity in the second case and the donor was 9.7% and 42.6%, respectively. She developed hyperammonemia within 12 days after the surgery. Following continuous intravenous/venous hemodialysis, they were performing well without intensive care [12].

However, this method has potential risks. The enzyme activity in selected biopsy samples cannot represent its activity in other parts of the liver. Hence, one cannot accurately predict, whether the transplanted liver lobe exhibits sufficient activity, nor to predict whether total enzyme activity retained in the left liver is sufficient for heterozygous carrier donors.

Transplantation of hepatocytes may be another treatment option. Enosawa et al. reported an 11-day-old baby who underwent hepatocyte transplantation. The patient needed urgent LTx, but there was no source of liver, thus requiring hepatocyte transplantation. The patient was later in good condition and without recurrence within 3 months after the operation [13]. For the patients with poor overall clinical conditions, hepatocyte transplantation is less risky than liver grafting. Following hepatocyte transplantation, biochemical parameters of a 12-year-old patient with repeated metabolic decompensation showed decreased levels of plasma ammonia and increased urea production. However, the patient died because of a nosocomial fungal sepsis [14].

Surgical methods

Orthotopic LTx is still the best choice in OTCD. It has fewer complications than auxiliary LTx [5]. Over recent years, a domino cross-auxiliary LTx has been tried in the clinical setting. This method is based on exchanging part of liver tissue with patients suffering from other metabolic diseases aiming to achieve metabolic complementation. It does not require additional organ donation. Of the three OTCD patients in China, subjected to domino cross-auxiliary LTx, two cases recovered well after the operation, without any complications during the follow-up period. One patient experienced occult graft rejection resulting into graft dysfunction and eventual disease recurrence [15]. The domino cross-auxiliary LTx is a feasible method, without any problems caused by the operation itself.

Post-transplant management

Due to long-term therapy with immunosuppressive drugs and postoperative weakness, one should notice prevention of postsurgical infections, which may cause failure of this intervention and death of the patient.

Following transplantation, the liver function should be tested regularly, to discern graft injury. The graft-derived cell-free DNA in blood may be of similar discriminative value,

it was also able to differentiate between the trend for graft injury and normal liver function. However, this technique is not as convenient as routine liver function tests [16]. The peak blood ammonia level of >356 μmol/L predicted poor neurodevelopmental outcomes in the patients undergoing LTx [17].

Clinical effect

According to the data from United Network for Organ Sharing (UNOS) database including 403 patients with urea cycle disorders (46.2% were OTCD) who underwent transplantation, the 1-, 3-, and 5-year graft survival rates were 90.4%, 86.3%, and 85.2%, respectively. Increased mass of the liver graft and male sex are related to decreased risk of graft loss [8]. In Japan, the 1-, 5-, 10-, and 15-year graft survival rates comprised 91.2%, 87.9%, 87.0%, and 79.3% among pediatric patients with metabolic disorders (OTCD, 20.6% of total) as shown by Kasahara et al. [18].

The 1-, 5-, and 10-year overall survival rates among 278 UCD patients who underwent LTx between 1987 and 2010 were 93%, 89%, and 87%, respectively, according to the UNOS database [19]. However, the article only stated that most UCD patients are OTCD, without any specific data on OTCD patients.

13 of 69 Chinese OTCD patients received LTx, at a median age of 3 years and one-year survival rate of 100% [20]. In Japan, the 1-, 5-, 10- and 15-year survival rates in 194 pediatric patients with metabolic disorders (OTCD=40) who underwent living donor LTx, were 91.2%, 87.9%, 86.1%, and 74.4% [18].

Hence, LTx can improve long-term survival rates of the patients, prevent recurrent hyperammonemia, and reduce the blood ammonia level. However, it did not improve neurodevelopmental outcomes in the patients with severe symptomatics, because hyperammonemia exerts early brain damage. Urgent LTx in another UCD, i.e., arginine succinate synthase deficiency, may improve the longitudinal cognitive and behavioural outcomes [17].

Conclusions

LTx can improve the long-term survival rate of patients with OTCD, but it cannot reverse the nervous system damage that occurred previously, and cannot improve cognitive impairment. However, neurodevelopment may normally proceed after LTx if it is performed early in childhood. The patients with late-onset disease should also be transplanted when required. Donorship of heterozygote carriers is still risky and should only be used when there are no other options. Hepatocyte transplantation can be tried if necessary. Prevention of infection, long-term monitoring of liver function and blood ammonia are required post-transplant.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Трансплантация печени при лечении дефицита орнитин-транскарбамилазы

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Резюме

Дефицит орнитин-транскарбамилазы (ДОТК) представляет собой наследственное заболевание с нарушением цикла обмена мочевины, характеризующееся высокой летальностью. Это генетическое нарушение обмена веществ проявляется гипераммониемией. Лекарства и гемодиализ могут снизить уровень аммиака в крови у пациентов. Трансплантация печени может улучшить долгосрочную выживаемость пациентов, но не может излечить необратимые повреждения нервной системы, возникшие ранее, и не может улучшить когнитивные функции. Если трансплантацию печени проводят в раннем детстве, впоследствии нервное развитие может быть нормальным. При необходимости пациентам с поздним дебютом также следует проводить трансплантацию. Гетерозиготность по ДОТК у донора все же представляет существенный риск, и ее следует использовать только тогда, когда нет других вариантов. При необходимости можно попытаться сделать трансплантацию гепатоцитов. После трансплантации необходима профилактика инфекции, длительный контроль функции печени и содержания аммиака в крови. Трансплантация печени должна рассматриваться для всех пациентов с генетическим ДОТК. Окончательное решение о том, следует ли и как использовать этот режим лечения, зависит от индивидуальной клинической ситуации.

Ключевые слова

Дефицит орнитин-транскарбамилазы, нарушение цикла мочевины, трансплантация печени.