Argininosuccinic aciduria is a urea cycle disorder caused by an argininosuccinate lyase enzyme deficiency that ends with nitrogen accumulation as ammonia. Argininosuccinic aciduria patients are at risk for long-term complications including poor neurocognitive outcome, hepatic disease, and systemic hypertension despite strict pharmacologic and dietary therapy. As the liver is the principle site of activity of the urea cycle, it is logical that a liver transplant should be an option, with careful patient selection, even in the absence of cirrhosis.

We present 2 pediatric argininosuccinic aciduria patients who underwent a living-donor liver transplant from their mothers. After the liver transplant, the general well-being of the patients and their quality of life improved significantly. Liver transplant should be an option for argininosuccinic aciduria patients to prevent further neurologic deterioration and improve the patient’s quality of life.

Key words: Argininosuccinic aciduria, Urea cycle disorder, Liver transplant

Introduction

Argininosuccinic aciduria (ASA) is an autosomal recessive disorder affecting the second to last step in the urea cycle that converts ammonia into urea, primarily in the liver. A deficiency in one of the urea cycle enzymes, argininosuccinate lyase (ASL), causes this disorder, which is the second most common enzyme deficiency in the urea cycle. Its estimated incidence is 1:70 000 live births. Hyperammonemia with accumulation of argininosuccinate and citrulline and depletion of arginine in body fluids are the main biochemical findings. Biochemical and clinical manifestations change according to the degree of enzyme deficiency. The disease may present in an early form with severe neonatal hyperammonemia, which causes serious brain damage and death; or in subacute and late forms, with varying degrees of intellectual disability, failure to thrive, vomiting episodes, and hepatomegaly.1-3

The long-term prognosis for patients with ASA under pharmacologic and dietary therapy remains poor. Liver transplant (LT) should be considered a treatment option in select cases. Liver transplant provides sufficient enzymatic activity to correct the deficiency, and removes the risk of metabolic decompensation with dietary protein restriction. Here, we present 2 pediatric ASA cases with significantly improved well-being and quality of life after LT.

Case presentations

Between August 2006 and August 2014, seven hundred thirty-one liver transplants (525 adult and 206 pediatric) were performed in 703 recipients from both deceased donors (n = 147) and living donors (n = 584) in a single center. Liver transplant was performed because ASA in only 2 pediatric patients (approximately 0.3%). Both patients underwent living-donor LT from their mothers, with no mortality or life-threatening morbidity in either donor.

Case 1

The first case was a 2.5-year-old boy whose findings were normal at birth. Two days after birth, symptoms developed including nausea, vomiting, loss of
appetite, and poor feeding. Laboratory tests revealed hyperammonemia, with a blood ammonia level of 943 μmol/L (normal range, 15.0-74.0 μmol/L). Argininosuccinic aciduria and congenital hypothyroidism were diagnosed by additional blood testing and newborn screening testing (tandem mass spectrometry). Argininosuccinic acid blood level was 7.0 μmol/L (normal range, 0.0-0.1 μmol/L) and citrulline blood level was 220 μmol/L (normal range, 0.00-0.00 μmol/L). The mutation in the argininosuccinate lyase gene was detected on molecular genetic testing. During the next 2.5 years, the patient was treated with pharmacologic and dietary therapy, during which time he had multiple hospital admissions for hyperammonemic coma and convulsive episodes. Complications of his disease included neurocognitive deficiencies and failure to thrive. The results of a cranial magnetic resonance imaging scan were normal. He could not sit, walk, or talk during his first 2.5 years of life. After evaluation, a left lateral segment living-donor liver transplant from his mother was performed. During the surgery, his liver appeared normal, and pathological investigation reported grade 2 fibrosis. He was in the intensive care unit for 2 days after surgery, and was discharged 17 days after LT. He is now 8.5 years-old, and his neurologic status and quality of his life have improved significantly after the LT. He is not receiving pharmacologic or dietary therapy for ASA and the results of his blood tests are normal. Now 4.5 years after the LT, he is walking and eating with minimal help and is beginning to speak. He continues to show improvement in his learning abilities and has no neurologic symptoms.

Discussion

The urea cycle is a metabolic pathway occurring mainly in the liver which is responsible for ammonia detoxification. The enzymes carbamoyl phosphate synthase, ornithine transcarbamylase, argininosuccinate synthase, argininosuccinate lyase, arginase, and N-acetyl glutamate synthase are enzymes in this important pathway. Carbamoyl phosphate synthase and ornithine transcarbamylase are found in the mitochondria and others are located outside of the mitochondria (Figure 1). Genetic defects involving these enzymes cause urea cycle disorders. Argininosuccinate lyase catalyzes conversion of argininosuccinic acid into arginine and fumarate and is the only mammalian enzyme that generates endogenous arginine. The clinical manifestations of ASA change according to the degree of enzyme deficiency.
abnormal hair, failure to thrive, hepatomegaly, and progressive hepatic fibrosis.\textsuperscript{1-3} Though ASA has a lower risk of recurrent hyperammonemic episodes compared with proximal disorders of the urea cycle’s enzyme deficiencies; it carries with it a high risk for long-term complications including poor neurologic outcomes, hepatic fibrosis, failure to thrive, and systemic hypertension. In addition, patients with ASA have a significantly higher risk of developing neurologic abnormalities, developmental disabilities, attention deficit hyperactivity disorder, and seizures compared with other urea cycle disorders.\textsuperscript{2}

The prognosis of urea cycle disorders has improved with the introduction of alternative medical pathway treatments. Pharmacologic and dietary treatments for ASA include oral arginine supplementation and a protein restrictive diet, partly substituted by essential amino acids to decrease substrate load on the urea cycle. In addition, sodium benzoate and sodium phenylbutyrate are used during treatment for ammonia detoxification. Over the past 40 years, argininosuccinate lyase deficiency has been included in some newborn screening programs in an attempt to prevent chronic complications by early diagnosis and treatment.\textsuperscript{1,6}

Mercimek-Mahmutoglou and associates\textsuperscript{1} published the long-term outcome of patients diagnosed by newborn screening over 27 years and suggested that testing newborns for ASA is beneficial for the prevention of chronic neurologic and intellectual sequelae in late onset variants. The prognosis has improved significantly in the last 20 years.\textsuperscript{4,6} In addition to pharmacologic and dietary treatment, LT, liver cell transplant, stem cell transplant, and gene therapy are other treatment options (eg, liver cell transplant, stem cell transplant, and gene therapy are the other treatment options, which we can find some data in the literature; these treatment options need more clinical trials). Other than LT, these treatment options remain regarded as experimental or are currently in clinical trial status.\textsuperscript{7}

During the past 30 years, LT has become the definitive treatment for many liver diseases. In the late 1980s, some centers began to perform LT for liver-based metabolic disorders with normal parenchyma, including urea cycle disorders, with the exception of ASA. Argininosuccinic aciduria is the only urea cycle disorder in which liver fibrosis can develop as a late complication.\textsuperscript{5,6,8,9} The number of cases in which LT has been performed for urea cycle disorders is limited. Perito and associates\textsuperscript{9} published data from the United Network for Organ Sharing-USA between 2002 and 2012, and reported 186 pediatric LT performed for urea cycle disorders from a total of 5672 pediatric LT recipients, indicating ASA as one of the rare disorders in this LT group. Japanese registry data was published by Kasahara and associates.\textsuperscript{10} In this group, LT was performed in only 2 pediatric patients with ASA from a total of 2224 pediatric living-donor liver transplant patients between 1989 and 2010. The indications for LT in urea cycle disorders have been summarized previously and include: (A) severe disease with a poor prognosis; (B) progressive liver disease that will result in liver failure; and (C) major life threatening complications that cannot be controlled with other treatment options.\textsuperscript{11} Liver transplant is now an important alternative to pharmacologic and dietary therapy for successful long term outcomes. Because every episode of hyperammonemia, even under aggressive pharmacologic and dietary treatment, results in further neurologic damage, it is crucial to perform LT as early as possible. Major neurologic damage can only be prevented by performing LT during the first month of life in infants diagnosed with ASA. However, LT in neonates and small infants is technically challenging and has a high morbidity and mortality rate. Additionally, with improved survival in patients under 1 year of age who undergo living LT, early LT in patients with urea cycle disorders is being reported in the literature.\textsuperscript{3,6}

Campeau and associates\textsuperscript{6} reported their experience with early LT in urea cycle disorders and concluded that a combination of early liver transplant, aggressive metabolic management, and early childhood intervention lead to improvements in neurologic outcomes in children with ornithine transcarbamylase and carbamoyl phosphate synthase deficiencies. Argininosuccinate lyase and argininosuccinate synthase deficiencies are more complicated, because hyperammonemic crises can be more effectively prevented and managed. Nagamani and associates\textsuperscript{2} discussed improvements in treating ASA using nitric oxide as therapy for late hypertension; however, questions remain about this strategy.

Similar to other reports in the literature, our center’s experience is limited to 2 cases of this rare indication for LT. In the 2 cases, both patients have had an improved quality of life with improvement in neurologic development without pharmacologic or
dietary treatments during the follow-up of 4 to 5 years after the LT. As seen in other reports, an early LT appears to have been important in these cases as well. In the first case, transplant was performed at an earlier age, and this patient saw greater improvement in neurologic development than did the second patient.

As therapeutic improvements are made and studies are undertaken that optimize treatment of patients with ASA, LT appears to be a treatment option for select patients with ASA and other urea cycle disorders.

References