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Case Report

Liver Transplantation in a Patient with 1p36 Deletion Syndrome

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ABSTRACT

1p36 deletion syndrome is a rare, genetic disorder often affecting neurological, cardiac, renal, and physical development, without a known associated liver manifestation. We present the case of a young woman with 1p36 deletion syndrome and chronic liver failure requiring liver transplant evaluation who subsequently went on to successfully undergo orthotopic liver transplantation. With multidisciplinary post-operative care, including developmentally appropriate rehabilitation and strong family support, >3-year post-transplant survival has been achieved. This case, the first reported liver transplant among patients with 1p36 deletion syndrome, suggests that liver transplantation can be safely performed in patients with this condition.

Introduction

1p36 deletion syndrome is a rare genetic disorder. It is associated with a variable presentation and many of its manifestations are evident at birth and irreversible [1]. It is more properly identified as a telomeric deletion syndrome and is the most common of its type with an incidence of 1/5,000 to 1/10,000 live births [2]. Patients with 1p36 deletion syndrome present with prototypical appearance and non-specific developmental delay. Additionally, these patients are often affected by seizures, congenital heart defects (most commonly ventricular septal defect and patent ductus arteriosus), non-specific brain abnormalities that result in spasticity and hypotonia, abnormalities of the genitalia, and renal abnormalities. Findings tend to vary tremendously between individuals. 1p36 deletion syndrome does not generally have an associated pattern of liver pathology [3]. Liver transplantation has not previously been described in patients with this genetic syndrome who also have cirrhosis or liver failure. Herein, we describe the first reported case of successful liver transplantation in a patient with 1p36 deletion syndrome.

Case Presentation

A 20-year-old female presented to the hepatology office with a history of cirrhosis complicated by hepatic encephalopathy and esophageal varices that was presumed to be caused by non-alcoholic steatohepatitis (NASH) in the setting of 1p36 deletion syndrome, obesity and insulin-dependent diabetes. She had previously been followed by pediatric genetics and hepatology programs at a pediatric transplant center and had been listed for liver transplant with Model for End-Stage Liver Disease (MELD) scores ranging from 15-17 since age 19 and was looking to transition to adult transplant care.

The patient's diagnosis of 1p36 deletion syndrome was made after she displayed features of the syndrome during childhood. The first sign of her condition was idiopathic nystagmus. Ophthalmologic, neurologic, and genetic workup resulted an eventual positive genetic diagnosis at age 6. However, the clinical diagnosis of 1p36 deletion syndrome was not made until the patient displayed worsening features at age 14. The deletion was detected with a Fluorescent in-situ hybridization (FISH) subtelomere probe study showing a 1.2 megabase pair deletion. She had significant vision loss, a history of seizures and developmental delay. She did not have any significant cardiac or renal abnormalities. She also was diagnosed with autoimmune uveitis and had been maintained on biologic therapy with adalimumab. The etiology of her liver disease was uncertain. Liver biopsy performed during childhood showed evidence of steatohepatitis As such, the etiology of her cirrhosis was presumed to be NASH. At presentation to our center, she had decompensated cirrhosis

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manifested by the presence of encephalopathy, jaundice, varices, and fluid overload and a MELD score of 39.

The patient's functional status as assessed by Karnofsky performance status was approximately 45, due to her 1p36 deletion syndrome. She was able to speak, maintain herself on oral nutrition, and ambulate independently. She did have significant developmental delay and her parents maintained legal guardianship. Her physical exam was notable for obesity and characteristic facial features including deep set eyes, mid-face hypoplasia, and microbrachycephaly. She had scleral icterus and conjunctival pallor. Peripheral edema was present bilaterally. Her abdomen was obese (BMI 40.24) with hepatomegaly and splenomegaly. She did not have asterixis and was on chronic lactulose and rifaximin for the prevention of hepatic encephalopathy. She was able to converse in short phrases and follow one-step commands.

She was listed for liver transplant with a MELD of 39. Secondary to infectious complications, her liver disease worsened, and she developed acute renal failure requiring hemodialysis. After clearing her infections, she was reactivated on the waitlist and underwent an orthotopic liver transplantation with a MELD at transplant of >40 (bilirubin 37.2, INR 2.63). Her donor was a 66-year-old heart-beating donor. Her explant pathology interestingly showed cirrhosis with hemosiderosis grade 4/4, concerning for hemochromatosis. Genetic testing for known hemochromatosis mutations was negative. Her post-operative course was notable for delayed renal recovery, though she did not require hemodialysis again. She had poor oral intake and poor participation in rehab at first, but with a temporary gastrojejunostomy tube placement and significant family and team support, including participation of physical medicine and rehab team, she was able to recover and be discharged home 3.5 weeks after transplant with plans for intensive outpatient physical therapy at a pediatric rehab specialty center.

Her rehab was somewhat prolonged based on her liver-related debility with high MELD at transplant and her baseline functional status. After 2 months of outpatient rehab, she was able to ambulate again. At three years follow-up, she has normal liver function tests and remained free of acute or chronic rejection of the liver. In addition, her renal function has recovered (most recent serum creatinine is 0.8 mg/dL, estimated glomerular filtration rate >60). She has returned to her pre-transplant functional status. She has experienced episodes of recurrent cellulitis of the gluteal region and lower extremities, which have been successfully managed with antibiotics. These are thought to be related to her immunosuppression and biologic therapy for uveitis.

Discussion

With an incidence of 1/5,000 to 1/10,000, 1p36 deletion syndrome is the most common telomeric deletion syndrome and is among the most commonly known genetic syndromes [2]. Presentation is often varied. The typical clinical features include: craniofacial features (straight eyebrows, deep-set eyes, mid-face hypoplasia, long philtrum, pointed chin, broad nasal bridge, and microbrachycephaly), late closing anterior fontanel, epicanthal folds, short feet, developmental delay/intellectual disability, hypotonia, seizures, congenital heart defects, eye and vision problems, hearing loss, skeletal abnormalities, abnormalities of external genitalia, renal abnormalities, dilated cardiomyopathy and cleft lip/palate [1]. Our patient presented initially as a child with signs that suggested this diagnosis and her diagnosis was confirmed with a FISH probe study identifying a deletion on chromosome 1 at the p36 location. The range of deletions in this disease is approximately 1.5-10 megabases [2].

Our patient presented with a mild phenotype of the 1p36 deletion syndrome in that she was more functional than most patients who carry the diagnosis. Studies have suggested that phenotype may be dependent on break point on the chromosome. However, there is no evidence suggesting that deletion size is related to phenotype or that smaller deletions result in milder phenotypes [2, 4]. There is limited evidence of a correlation between 1p36 deletion syndrome and liver pathology. An association between loss of heterozygosity at the 1p36 chromosome locus and the development of hepatocellular carcinoma has been suggested [5, 6]. One report describes a lysosomal storage disorder secondary to 1p36 deletion, and another report found biliary atresia present in a patient with 1p36 deletion, successfully treated with a portoenterostomy [3, 7]. In our patient, it is difficult for to conclude the specific etiology of her liver disease, but biliary atresia was excluded. She clearly had risk factors for NASH including insulin-dependent diabetes and obesity (BMI approximately 40 at transplant), but explant pathology only showed cirrhosis with evidence of hemosiderosis and no obvious steatohepatitis. It is possible that her genetic syndrome contributed to either of these possible etiologies, but this is not confirmed.

There are no reported cases of liver transplantation in patients with 1p36 deletion syndrome and liver failure. Liver transplantation has gained acceptance as an effective therapeutic intervention in patients with other genetic syndromes of similar magnitude of systemic effects who experience liver failure, with many successes [8, 9]. Notable examples of inherited toxic metabolic disorders similar to 1p36 deletion syndrome that have been studied and effectively treated include hereditary hemochromatosis, Wilson's disease, cystic fibrosis, and lysosomal storage diseases causing liver failure [8, 10]. Our patient's positive transplant outcome and good health more than three years removed from transplant suggest that this intervention is effective and could be applied to other patients with such pathology. Significant family support and developmentally appropriate rehabilitation post-transplant were needed, and we believe were crucial to her success.

In conclusion, 1p36 deletion syndrome should not necessarily be viewed as a contraindication to liver transplantation. Due to their widespread systemic effects, genetic disorders can often be considered as contraindication to transplantation. This case suggests that liver transplantation, accompanied by good perioperative support, can be safely performed in patients with 1p36 deletion syndrome.

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