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Case Report

Orthotropic Liver Transplantation for Intractable Neurological Manifestations of Wilson's Disease

Vaibhav K. Sutariya[1], Anad H. Tank[1], Pranjal R. Modi[2]

Department of Surgical Gastroenterology and Liver Transplantation, Smt. G. R. Doshi and Smt. K. M. Mehta Institute of Kidney Diseases and Research Centre and Dr. H. L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad, Gujarat, India

ABSTRACT. Wilson's disease (WD) is an inherited autosomal recessive disorder characterized by copper accumulation and toxicity, affecting mainly the liver and brain. Orthotopic liver transplantation (OLT) is the definitive therapy for patients with WD. Acute fulminant hepatic failure and decompensated cirrhosis are well-established indications for OLT. Patients with severe neurologic impairment can also be benefited by OLT. Here, we present a patient who underwent OLT for isolated neurological WD.

Introduction

Wilson's disease (WD) is an inherited autosomal recessive genetic disorder characterized by progressive copper accumulation and toxicity, mainly in the liver, brain and kidneys. The affected patients usually develop hepatic or neuropsychiatric symptoms. The disease frequency is estimated to be between one in 35,000 to one in 100,000, with a carrier frequency of one in 90.[1] Depending on the most severely affected organ, patients present with various clinical syndromes like fulminant hepatic failure, decompensated cirrhosis and neurologic syndromes.[2,3] Management of most patients is accomplished through life-long medical treatment, including copper chelating agents, mainly d-penicillamine. However, use of this drug is limited by its side-effects. The use of other drugs such as triemetine and ammonium tetrathiomolybdate has also been advocated, although long-term trials are not available yet.[4] Orthotopic liver transplantation (OLT) can reverse the basic underlying metabolic abnormality of WD and can improve both hepatic and neurologic symptoms.[4,5] Acute fulminant hepatic failure and decompensated chronic liver disease are well-established indications for liver transplantation. Additionally, patients with severe intractable neurologic manifestations of WD with normal

Correspondence to:

Dr. Pranjal R. Modi
Department of Surgical Gastroenterology and Liver Transplantation, Smt. G. R. Doshi and Smt. K. M. Mehta Institute of Kidney Diseases and Research Centre and Dr. H. L. Trivedi Institute of Transplantation Sciences, Civil Hospital Campus, Asarwa, Ahmedabad, Gujarat 380016, India
E-mail: dr_pranjal@yahoo.com

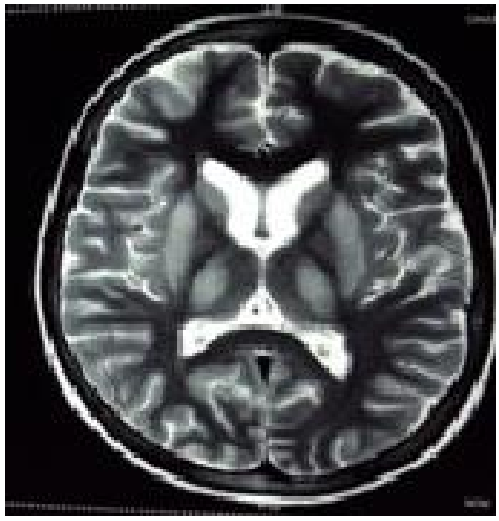

Figure 1. Magnetic resonance imaging of the brain, before orthotopic liver transplantation, showing copper deposition in the basal ganglia.

liver function can also be benefited by liver transplantation. We herewith present a patient with WD who underwent OLT for severe neurological impairment with stable liver function.

Case Report

A 14-year-old female patient presented with inability to speak, eat, write and walk as well as involuntary movements of all four limbs. She did not have any previous history of hemetemesis, malena or pedal edema. She had taken D-penicilamine and oral zinc for two years and discontinued the medications on her own. The patient developed irritability, mood swings and behavioral changes. She gave a history of one sibling who died of suspected neurologic disease. She was completely bedridden with severe rigidity, spasticity, bradykinesia, dystonia and tremor. She did not have ascites, jaundice, dilated abdominal veins or pedal edema. Slit-lamp examination revealed Kayser–Fleischer's (KF) ring in the corneas. Her liver function and renal function tests were within normal limits, with normal random blood sugar. Twenty-four-hour urinary copper was 247 µg/dL. The serum ceruloplasmin level was 14 mg/L. Ultrasonography of the abdomen and computed tomography scan showed altered echotexture of the liver with normal portal and splenic veins. Magnetic resonance imaging (MRI) of the brain showed hyper-intense basal ganglia (Figure 1). Electromyogram and nerve conduction studies were normal.

Considering the patient's neurological condition, she was subjected to OLT. In the immediate post-operative period, the patient developed adult respiratory distress syndrome and was kept on ventilatory support for 15 days. Tracheostomy was performed on the fifth post-operative day and kept till the 17th day. Once the patient became stable, she was subjected to various neuro-rehabilitative physiotherapy techniques like neuro-development therapy, motor relearning program, proceptive neuromuscular facilitation, fine motor training and postural and gait training. The patient was discharged 45 days after transplantation. At the time of discharge, she was able to walk with support and the tremors and spasticity improved. After six months of follow-up, the patient was able to walk without support with normal gait. Subsequently, she started her schooling with normal speech and improved handwriting (Figure 2).

Unfortunately, after one year of follow-up, the patient presented with severe liver allograft

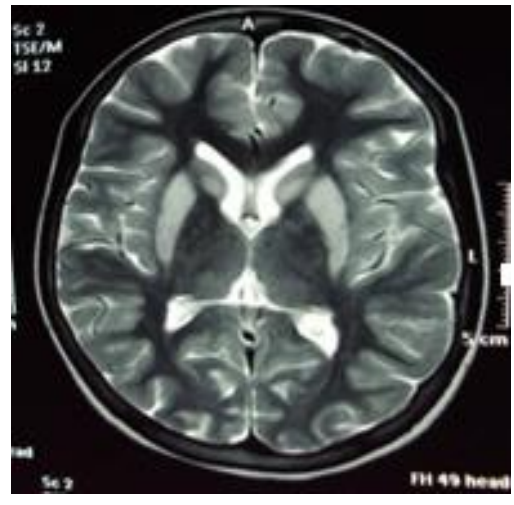

Figure 2. Magnetic resonance imaging of the brain, after orthotopic liver transplantation, showing receding copper deposition in the basal ganglia.

dysfunction caused by discontinuation of the immunosuppression drugs on her own. She was not taking medications for almost two months. She died 12 months after transplantation.

Discussion

WD, also known as hepato-lenticular degeneration, is a systemic disorder of copper metabolism. The disease results from dysfunction of the copper transport enzyme adenosine triphosphatase in the liver, which is responsible for excretion of copper in bile. The gene for WD has been indentified on the long arm of chromosome 13. Patients with severe hepatic involvement present with fulminant hepatic failure, chronic active hepatitis or decompensated cirrhosis of the liver. Patients with neurologic involvement present with dysarthria, tremor, incoordination and ataxia. Patients with neurologic WD are more likely to have KF's ring in their corneas. Hepatic copper concentration, as determined by atomic absorption spectrophotometry, is the gold standard for diagnosis.

In patients with WD, liver transplantation is the optimal therapeutic approach as replacing the liver reverses the underlying metabolic defect. The first case of successful liver transplantation for WD with complete reversal of metabolic manifestations was reported in 1971.[6] Liver transplantation reverses several clinical, pathological and biochemical features of WD, and no recurrence of the disease has been reported after transplantation. However, the effect on neurological symptoms is not well established.

The neurological status of this patient, both before and after transplantation, was evaluated by an experienced neurologist with the system proposed by Medici et al.[7] In this system, neurological functions (walking, talking, eating and daily living activities) and neurological signs (rigidity, bradykinesia, ataxia, tremor, dystonia, dyskinesia) were evaluated. Each function scored a maximum of 3 (3 - no impairment, 2 - mild impairment, 1 - moderate impairment, 0 - severe impairment). The maximum total score was 30. A higher score is suggestive of better neurological status while a lower score is indicative of poor neurological status. The neurological evaluation score of this patient before OLT was 14, suggestive of severe impairment. Her neurological evaluation score six months after transplantation was 27, suggestive of complete regression of neurological manifestations. KF's ring disappeared nine months after transplantation. Serum ceruloplasmin and 24-h urinary copper became normal nine months after transplantation. D-penicilamine was discontinued immediately after transplantation.

Reviewing the literature, one study has reported that 10 out of 37 patients with WD presented with neuropsychiatric symptoms and improved significantly after OLT. However, survival of patients with both hepatic and neuropsychiatric involvement was still significantly lower than that of patients with liver disease alone.[7] One recent study of living-related liver transplantation for WD showed no significant difference in the survival of patients with both hepatic and neurologic involvement and of patients with liver disease alone. This study also excluded neurologic involvement as a negative prognostic factor for survival after liver transplantation.[8] There is a case report of a 15-year-old patient with WD who was bedridden with severe neurological impairment, even with maximum medical therapy. This patient improved after OLT.[9] Mason et al suggested that even after their patient died, liver transplantation should be considered for severe neurologic impairment in patients with WD.[10]

In this patient, OLT had a favorable effect on neurological manifestations of WD. There was an almost complete regression of her neurological impairment before she died because of severe liver allograft dysfunction.

In conclusion, OLT for isolated neurological WD is beneficial, but it is still to be considered experimental.

Conflict of interest: None declared.

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