Effect of Liver Transplantation on Neurological Manifestations in Wilson Disease

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Background: Liver transplantation (LT) is the sole resolutive therapy for Wilson disease (WD) and is the treatment of choice for patients with WD who have fulminant hepatic failure or end-stage cirrhosis. Although its role in managing the neurological manifestations of WD is not yet conclusive, LT has recently been advocated as a therapy for neurologically affected patients with WD with stable liver function.

Objective: To evaluate the effect of LT on the neurological manifestations of WD.

Observation: A 44-year-old man with WD with cirrhosis and neurological symptoms (motor dysfunction and cognitive impairment) experienced a dramatic improvement in motor function early after LT, as well as normalization of copper balance and the disappearance of Kayser-Fleischer rings. Abnormalities seen on magnetic resonance imaging scans were reversed 18 months after LT. Cognitive testing 2 years after LT showed a moderate global improvement.

Conclusions: In this case, LT healed the neurological manifestations of WD. To date, this favorable result has been seen in almost 80% of cases. However, the decision to perform LT in patients with WD solely on the basis of neurological impairment must be considered experimental.

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IN PATIENTS with Wilson disease (WD), liver transplantation (LT) is the only resolutive therapeutic approach, since removal of the liver should reverse the metabolic disorder. Liver transplantation has been considered for resolving the hepatic failure associated with WD, as it corrects the metabolic defect, though not completely.1 Liver transplantation reverses several pathological, clinical, and biochemical features of the disease and no recurrence of WD after LT has been observed, but the effect on neurological symptoms is not established. Thus, the indications for LT in patients with WD depend on the severity of the hepatic disease according to the criteria of Sternlieb.2 Exceptionally, LT has been considered in patients with WD to resolve the neurological deterioration,3-5 but this approach is debated.

We describe a patient with WD-related cognitive impairment and disabling motor dysfunction who recovered after LT. The literature on this topic is also reviewed.

REPORT OF A CASE

The patient came to our observation in April 1992 when he was 44 years old. He had a history of chronic hepatic disease, which had begun some years before. At 42 years, he had noticed a subtle onset of slowness, mental impairment, and bilateral hand tremor, with a gradual progressive course and episodic worsening related to temporary liver insufficiency. He had no family members with neurological problems; his mother had had an undiagnosed liver disease. When seen, he was recovering from a hepatic decompensation, with still-elevated ammonia serum levels (199 µmol/L). He was alert, oriented, and cooperative, but with a slight slowness of psychomotor speed. The neurological examination showed bradyar-
ser-Fleischer (K-F) rings and an initial sunflower cataract were found by slitlamp examination. Laboratory tests showed a low plasma copper level (8.3 µmol/L) and high urinary copper level (61 µg/d). Wilson disease was diagnosed and treatment with penicillamine, 600 mg/d, was given, with initial improvement of motor impairment. After 6 months, his neurological status and liver function deteriorated rapidly. At this time, the patient exhibited a severe enhancement of the motor impairment, especially tremor and dysarthria, and a reduced psychomotor speed. Liver transplantation was performed, with a successful course and a rapid copper balance normalization. One month after LT, only a mild postural hand tremor persisted. Findings on cerebral MRI at this time were unchanged. The electroencephalogram was normal. Nine months later, results of the neurological examination were normal, K-F rings disappeared, and MRI showed attenuation of the basal ganglia lucencies, which were no longer present on a fourth MRI examination 18 months after orthotopic LT (Figure 2). Neuropsychological testing 22 months after LT showed a full-scale IQ of 71 (verbal, 76; performance, 69), with a slight amelioration of the performances on information processing control tasks and of some instrumental abilities (especially visuospatial) (Table 1). No other neurological problems have emerged during 5 years of follow-up. Table 2 summarizes the data of the longitudinal neurological examination, expressed by means of a severity index of 4 domains (tremor, dystonia, ataxia, and dysarthria), showing a dramatic improvement of the neurological symptoms after LT.

**COMMENT**

In this patient, LT had a favorable effect on the neurological manifestations of WD. Early after LT, neurological status improved, reaching normality within a few months. The K-F rings also disappeared early, whereas the neuroradiological abnormalities disappeared after several months. The good outcome also included improvement of cognitive impairment, even though this was not as dramatic as the motor recovery.

Reviewing the literature on LT for patients with WD who have neurological manifestations, we found data for 40 patients.1,3-17 Most of them received LT because of liver function deterioration. In 5 patients,3-5 2 of whom were described in detail,3,5 the decision to perform LT was based on deteriorating neurological status, despite stable liver function. They had severe disabling neurological symptoms that progressively worsened despite adequate medical therapy. Considering the whole group of 40 patients,
neurological status after LT, especially in motor control, suggesting that LT may be an important therapy for the neurological manifestations of WD in most cases. Examining the reports, we were not able to find predictors of outcome. The reasonable hypothesis that better results could be obtained in patients who undergo LT early after the onset of neurological symptoms has not been confirmed.

Caution is necessary when considering LT for patients with WD showing intractable neurological manifestations, but with stable liver function. We know that LT is not a safe procedure, with a risk of neurological complications.\(^7\)\(^,\)\(^8\) Even in experienced centers, the incidence of complications is still high and the risk of mortality after LT in patients with WD is estimated at about 20% at 1 year.\(^1\)\(^,\)\(^1\)\(^5\) To accept this kind of risk, we need more information on the role of the neurological deterioration in the prognosis of patients with WD.

The decision to perform LT in patients with WD should be strictly dependent on liver function status. In patients with stable liver function, LT must be considered experimental, and should be considered only in the presence of intractable life-threatening neurological deterioration.

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Table 2. Longitudinal Neurological Examination Data*  

<table>
<thead>
<tr>
<th>Symptom</th>
<th>First Visit</th>
<th>Before LT</th>
<th>After LT</th>
<th>1 mo</th>
<th>9 mo</th>
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</thead>
<tbody>
<tr>
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<td>4</td>
<td>1</td>
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<td>0</td>
</tr>
<tr>
<td>Dystonia</td>
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<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ataxia</td>
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<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>5/16</td>
<td>11/16</td>
<td>1/16</td>
<td>0/16</td>
<td></td>
</tr>
</tbody>
</table>

* Severity index: 0 = absent; 1 = mild; 2 = moderate; 3 = severe; and 4 = extremely severe. Maximum global impairment = 16. LT indicates liver transplantation.

REFERENCES