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 fulminating 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. 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. Exceptionally, LT has been considered in patients with WD to resolve the neurological deterioration, 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 bradyarthria and dysarthria, bilateral hand postural tremor that was more severe on the left side, head and left arm dystonic movements, and mild ataxia. Mild asterixis was superimposed on the tremor. An electroencephalogram showed a bilateral posterior activity of 7 Hz, without focal abnormalities. After therapy with lactulose, ammonia levels decreased, and his general condition improved, asterixis disappeared, and no other remarkable changes were seen in neurological status. Neuropsychological examination showed a full-scale IQ of 62 (verbal, 70; performance, 55) and a moderate impairment of information processing control (attention, vigilance, psychomotor speed, intelligence) and verbal and visuospatial abilities (Table 1). Memory was grossly preserved. T2-weighted magnetic resonance imaging (MRI) revealed bilateral lucencies on lentiform nuclei (Figure 1). Kay-
ser-Fleischer (K-F) rings and an initial sunflower cata-
рак 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 di-
agnosed and treatment with penicillamine, 600 mg/d, was
given, with initial improvement of motor impairment. Af-
ter 6 months, his neurological status and liver function
deteriorated rapidly. At this time, the patient exhibited
a severe enhancement of the motor impairment, espe-
cially tremor and dysarthria, and a reduced psychomo-
tor speed. Liver transplantation was performed, with a
successful course and a rapid copper balance normaliza-
tion. One month after LT, only a mild postural hand
tremor persisted. Findings on cerebral MRI at this time
were unchanged. The electroencephalogram was nor-
mal. Nine months later, results of the neurological ex-
amination 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). Neuropsycho-
logical testing 22 months after LT showed a full-scale IQ
of 71 (verbal, 76; performance, 69), with a slight ame-
lioration of the performances on information processing
task 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 neu-
rological examination, expressed by means of a severity
index of 4 domains (tremor, dystonia, ataxia, and dys-
arthria), showing a dramatic improvement of the neu-
rological symptoms after LT.

**Comment**

In this patient, LT had a favorable effect on the neuro-
logical 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 sev-
eral months. The good outcome also included improve-
ment 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 symp-
toms that progressively worsened despite adequate med-
ical therapy. Considering the whole group of 40 patients,
neurological manifestations resolved completely after LT in 11 patients, a remarkable improvement was achieved in 20, and no changes or worsening of neurological status were observed in 6. Three patients died soon after LT, and no information was available on the outcome of their neurological symptoms. In some patients, neuropsychological abnormalities disappeared after LT, as seen in our patient. Very few data are available on the outcome of cognitive performance. In 2 patients no recovery was noted, 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. 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. 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.

**Table 2. Longitudinal Neurological Examination Data***

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

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

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**Figure 2.** Axial cerebral magnetic resonance imaging scan 18 months after liver transplantation showing the regression of the basal ganglia abnormalities on 2 different slices (inferior [top] and superior [bottom]).