**Abstract**

Although liver transplant for decompensated cirrhosis secondary to Wilson disease is well accepted, the use of transplant for patients with severe neurologic manifestations of this condition remains controversial, and these can be perceived as a contraindication. Here, we describe a 45-year-old woman who presented with an incidental hepatocellular carcinoma at the time of transplant. The patient had severe neurologic manifestations of Wilson disease pretransplant, including dysarthria, hyperreflexia, asymmetrical ataxia, tremor, bradyphrenia, and shuffling gait. She underwent successful transplant from a hepatic and surgical standpoint, but her postoperative course was marked by protracted mutism, hypophonia, and fluctuating akinesia and immobility that did not respond promptly to withdrawal of calcineurin inhibitors or pramipexole but did respond robustly to amantadine. At 9 months posttransplant, there was marked neurologic improvement, and, at 18 months, she exhibited subtle memory and organizational difficulties but was fully ambulatory and otherwise completely functional. Our experience suggests that even patients with severe neurologic Wilson disease may recover after transplant, albeit slowly, demonstrating the need for a multidisciplinary approach, including pre- and posttransplant neurologic and neuropsychiatric consultations.

**Keywords:** Amantadine, Catatonia, Mutism, Neurologic, Neuropsychiatric

**Introduction**

Wilson disease (WD) is a rare but well-known metabolic copper storage disease that has neurologic, neuropsychiatric, and hepatic manifestations. Although WD is a well-recognized indication for liver transplant, this is typically for patients with either end-stage cirrhosis or acute WD-associated liver failure. The use of liver transplant in patients with WD and neurologic and neuropsychiatric manifestations is rare and not well reported. In particular, severe neurologic and neuropsychiatric WD has been previously regarded as a possible contraindication, given the potential for irreversibility. Even today, the role of liver transplant in this setting remains controversial. Here, we report a patient with severe neurologic and neuropsychiatric manifestations of WD extending into the early posttransplant period who experienced a dramatic response to liver transplant in the long term.

**Case Report**

We describe a previously high-functioning 45-year-old Asian woman who had longstanding WD since the age of 14 years. Until her early forties, her clinical manifestations had been primarily hepatic, namely, biochemical abnormalities. She had been treated over the years with penicillamine and oral zinc but complied somewhat erratically with her treatment regimen. She remained able to work full time in a high-pressure job in the financial industry until neurologic WD supervened. This exacerbation occurred 2 years before her liver transplant and was initially characterized by slowly progressive executive dysfunction and impaired short-term memory. Eight weeks before hospitalization, she decompensated further neurologically with dysarthria, hyperreflexia, a new asymmetric ataxic upper limb tremor, and parkinsonism, manifested by...
profound bradyphrenia, facial hypomimia, bradykinesia, a short-stepped, shuffling gait with en bloc turning, and a retropulsive tendency. She became very “quiet,” more disorganized, and socially withdrawn. She was noted to manifest significant rapid eye movement sleep behavior disorder symptoms, including sleep talking and limb movements in relation to dream imagery. At the time of hospitalization, she was icteric, with ascites and pleural effusions. While she was not clinically encephalopathic (serum ammonia and electroencephalogram were also normal), she became immobilized with severe parkinsonism, which was minimally responsive to pramipexole.

Magnetic resonance imaging showed a diffuse linear increase in T2-FLAIR signal in both basal ganglia and throughout the pons. The latter finding raised the possibility of osmotic demyelination. Serum copper level was 8 μmol/L (normal, 11-26 μmol/L), and 24-hour copper excretion was elevated at 1.4 μmol/d (normal < 0.6 μmol/d). Penicillamine was restarted, but she developed a rash and her neurologic symptoms worsened. Penicillamine was therefore discontinued.

Further work-up demonstrated a 4.5-cm expansile hepatic lesion seen on computed tomography and ultrasonography. After orthoptic transplant with a liver from a deceased donor, pathology confirmed preoperative suspicion of hepatocellular carcinoma, apparently confined to the liver. Medical complications included *Bacteroides fragilis* bacteremia, *Bacteroides* urosepsis (without hemodynamic compromise) complicated by delirium with auditory and visual hallucinations, confusion, and asterixis. The patient also developed vancomycin-resistant enterococcal infection and evidence of coagulopathy restricted to laboratory test abnormalities, including serum markers of antiphospholipid antibody syndrome. The patient’s antinuclear antibody was initially 1:320 with a fine speckled pattern, but subsequently reverted to normal. Extranuclear antibody panel, anti-double-stranded DNA, antimitochondrial antibodies, and rheumatoid factor; viral serologies for hepatitis B and C, cytomegalovirus, human immunodeficiency virus 1 and 2, syphilis serology, and a paraneoplastic antibody panel, including N-methyl-D-aspartate receptor antibodies, were unremarkable. Cancer antigen 19-9(2) was elevated at 70 kU/L (normal < 35 kU/L). Thyrotrropin, morning cortisol level, carcinoembryonic antigen, and human chorionic gonadotropin beta levels were normal.

Although delirium cleared with antibiotics, recovery was marked by prolonged depression, frightening auditory hallucinations, mutism, and catatonia, with symptoms only briefly responsive to 6 to 12 mg of lorazepam per day. Repeat magnetic resonance imaging showed progression of signal hyperintensity throughout the pons and midbrain (pattern of the latter being suggestive of the “giant panda sign” of WD; see Figure 1), increased signal throughout the thalami, and new involvement of the pallidum (left greater than right).

The patient went on to have a celiac-hepatic artery bypass for severe hepatic artery stenosis. Following this surgery the patient experienced rapid improvement in hepatic function and neurologic function. The neurologic recovery was marked by spontaneous and purposeful speech and movement of all limbs. However, 1 week later, mutism and immobility again supervened. Lorazepam (up to 4 mg daily) became ineffective after a prolonged trial and was poorly tolerated due to drowsiness. Tacrolimus-associated hypomagnesemia was identified, but magnesium infusions had no effect.
Tacrolimus trough levels (n = 46) obtained during her course were well within the therapeutic range, with the exception of one markedly elevated level of 27.3 μg/L. Mycophenolic acid serum level was also within the normal therapeutic range. Substitution of cyclosporine for tacrolimus was briefly followed by improvement in cognition and speech; however, after 4 days, these worsened again and responded only minimally to upward titration of pramipexole to 1 mg daily, with discontinuation of cyclosporine. All 23 trough levels of this agent were well below the upper limit of the therapeutic range.

Recurrent catatonia was suspected, based on akinesia that fluctuated inexplicably from mild to severe over hours, and by marked hypophonia, which contrasted with temporally dissociated, variable cogwheel rigidity (sometimes absent and mild at most), and absence of resting tremor (a 6-Hz postural tremor was observed). Two more electroencephalograms obtained during periods of decreased responsiveness were normal. Although classical catatonic signs such as mitgehen, cataplexy, negativism, and grasp reflexes were typically absent, even when the patient was almost completely immobilized, she responded well to amantadine introduced at 25 mg daily and titrated up to 100 mg twice daily. Her neuropsychiatric symptoms improved slowly over approximately 1 month, until she was discharged into her mother’s care. She remained moderately ataxic, bradyphrenic, and dysarthric and was unable to ambulate without assistance.

She steadily recovered; by 9 months post-transplant, she had dramatically improved from her pre- and early posttransplant state, even approaching her baseline status before her neurologic decompensation.

When last evaluated neuropsychiatrically, at 18 months posttransplant, cognitive issues were restricted to mild short-term and prospective memory loss, as well as organizational and time management difficulties. Rapid eye movement sleep behavior disorder remained in remission, despite discontinuation of clonazepam several months earlier. While demonstrating intellectual insight into her deficits, her desire to return to work was unrealistic given that her prior occupation required excellent frontal/executive functioning and memory.

Cognitive screening revealed a Montreal Cognitive Assessment Scale score of 29/30, with 1 point lost for a minor error on delayed recall (immediately corrected after a category cue). She was able to complete serial subtractions from 90 down to 6 without errors in 33 seconds. She made no errors on the simple vigilance task but responded impulsively when the same stimuli were repeated in a sequential vigilance (go-no-go) paradigm, making 3 errors of commission. Verbal fluency and category fluency were at high average levels. Clock drawing was normal.

Neurologic examination demonstrated normal extraocular movements. Kayser-Fleischer rings were still evident in the corneas. Facial hypomimia and Myerson signs had resolved. There was no dysarthria or hypophonia. A mild action and postural tremor were evident on the finger-nose-finger maneuver. Tone was normal at baseline, with very slight rigidity (without cogwheeling) on the right during contralateral reinforcement maneuvers. Gait was unremarkable.

Although subtle frontal subcortical dysfunction still precluded a return to the patient’s previous occupation, transplant resulted in dramatic improvement in functional, neuropsychiatric, and cognitive impairment.

Discussion

Wilson disease is a copper-overload disease affecting mainly the brain and the liver, consequently manifesting predominantly with hepatic and neurologic symptoms and signs. In 1912, Dr. Kinnier Wilson published his classic report of 12 patients who presented with extrapyramidal motor symptoms, dysphagia, and dysarthria; on autopsy, he found basal ganglia atrophy and cirrhosis of the liver. He reported that, of these 12 patients, most had psychiatric involvement, including several with “emotionalism” and 2 with psychosis. Kinnier Wilson’s meticulous clinical and pathologic observations of the disease that now bears his name
have been borne out in numerous subsequent studies.

The neurologic form presents with severe motor abnormalities such as ataxia, tremor, dysarthria, dysphagia, and parkinsonism, as well as other symptoms corresponding to copper deposition in the thalamus, brain stem, and basal ganglia. Since Kinnier Wilson’s original series of WD patients, other series with detailed descriptions of neuropsychiatric symptoms have been limited. Wilson disease may present primarily with psychiatric symptoms and behavioral changes in 10% to 25% of patients, including depression, mania, antisocial behavior, and more rarely psychosis.3

Currently, there are no consensus guidelines to direct decisions on liver transplant for patients with significant and progressively deteriorating neurologic or neurobehavioral status, regardless of their hepatic condition. The body of existing literature consists largely of case reports or case series of patients with neurologic symptoms receiving transplant due to hepatic failure. Liver transplant for WD has been proposed to improve survival and quality of life in patients who have hepatic and neurologic manifestations; however, the response in neurologic WD is less certain, and there exists a significant paucity of literature on this topic, especially in those patients with severe neurologic and neuropsychiatric WD. Schumacher and associates4 reported a case series of 9 patients with neurologic complications of WD who received liver transplant. The neurologic manifestations among this patient group ranged from intention tremor to encephalopathy and cerebellar syndromes. Patients ranged in age from 15 to 47 years old, with a mean onset of neurologic symptoms of 6 years before transplant. All patients were reported to have some neurologic improvement within 1.5 years of transplant, with 1 patient returning almost to baseline. A single center (University of Pittsburgh) series by Eghtesad and associates5 found that 10 of 13 surviving patients had improvements in neurologic symptoms after transplant, and notably, a trend toward better neurologic outcomes when this procedure was performed earlier.

Smaller case series and single case reports have demonstrated a return to baseline in patients with very mild neurologic symptoms. Geissler and associates6 described 2 cases of hepatic failure with concomitant and progressive neurologic symptoms that resolved after transplant, one of whom presented with primarily psychiatric disturbance and tremor. Geissler and associates advocated for early transplant in such cases in an effort to prevent what may ultimately be irreversible neurologic deficits if treatment is delayed.

Although some cases have shown degrees of benefit, the use of transplants in neurologic WD remains controversial. Notably absent from this body of literature are data on cognitive outcomes in neuropsychiatric WD. Medici and associates7 did compare long-term mortality between hepatic and mixed hepatic and neurologic populations after transplant. This retrospective Italian multicenter analysis of 37 patients demonstrated a mean decrease in life expectancy of 135 versus 76 months (P = .04) in patients with hepatic WD versus neurologic/neuropsychiatric symptoms in WD, highlighting the neurologic symptoms as a negative prognosticator. In the 10 patients with neurologic WD, there was neurologic improvement in 6 patients, resolving completely in 2 patients with milder involvement but deterioration in 3. It was reported that psychiatric symptoms did not improve. Although the excess mortality in those with neuropsychiatric manifestations of WD was not specifically attributable to WD, the authors speculated that neuropsychiatric WD may predispose some to events (such as sepsis) that may lead to excess mortality. Medici and associates concluded that liver transplant is a viable option in mild neuropsychiatric WD but is associated with excess mortality in moderate to severe neuropsychiatric WD, with contraindication in isolated severe neuropsychiatric WD. Similarly, it appears that transplant solely to treat neurologic or neuropsychiatric symptoms seldom occurs8,9 and is felt to be experimental10 even when successful.

In terms of outcomes in severe neurologic and neuropsychiatric WD, Mason and associates8 reported a young college student who deteriorated rapidly over a few months despite medical therapy. In the absence of significant liver disease, the patient developed catatonia, depression, dysarthria, dystonia, and ataxia, followed by hallucinations, emotional lability, and suicidality. For 5 years, he had no meaningful improvement and was frequently institutionalized. After transplant, he spoke in full sentences for the first time in 7 years, and his ataxia began to resolve. (Tragically, he had an acute
hypotensive episode in the context of ongoing rejection and died during an urgent surgical procedure for a ruptured splenic artery aneurysm.) Bax and associates described a 15-year-old boy with dysarthria and hypokinesia and intact hepatic and cognitive function, who recovered almost completely after transplant (performed after 1 year of failed medical therapy).

Reported posttransplant experiences with neurologic/neuropsychiatric WD after liver transplant have primarily involved deceased donors (ie, whole allografts), although good neurologic outcomes in 9 patients who had transplants from living donors (ie, partial allograft) have also been reported.

Although the limited published experiences with transplant in neurologic/neuropsychiatric patients as shown in the case reports and single-center series reviewed here seem to be favorable, we also note the possibility that this may represent reporting bias (ie, poor outcomes are not reported) or publication bias (negative reports are not published). Indeed, not all reports of transplant outcomes in neurologic and neuropsychiatric WD have been favorable. Kassam and associates reported a young man whose hepatic manifestations of WD resolved after liver transplant and who showed improved neurologic WD; however, he failed to improve from a psychiatric perspective and committed suicide 43 months after transplant. Similarly, Guarino and associates reported no neurologic improvements in a young man who appeared to have progression of neurologic involvement, with development of extrapyramidal symptoms and pontine and extrapontine myelinolysis 19 months after transplant.

Here, we describe a unique case of severe neurobehavioral complications of WD and its resolution with liver transplant. Both the degree of neuropsychiatric impairment before transplant and the degree of recovery are unprecedented in the literature thus far.

Mutism, catatonia, and akinesia may well have been partly or wholly related to treatment with calcineurin inhibitors, as these have been reported with cyclosporin and tacrolimus, even when levels have been within the therapeutic range. Magnesium infusions and pramipexole conferred no significant benefit, whereas amantadine was robustly effective. The use of amantadine to treat these complications of calcineurin inhibitor therapy has never been previously reported.

In summary, we describe an unusual case of late-onset, severe neurobehavioral complications of WD reversed dramatically and almost completely by orthoptic liver transplant, demonstrating the point that therapeutic nihilism in WD patients with severe neuropsychiatric manifestations and even magnetic resonance imaging evidence of widespread subcortical and white matter involvement may be unwarranted. Such patients require careful, multidisciplinary, preoperative assessment (including documentation of neuropsychiatric and neurocognitive baseline) and treatment planning and significant consideration of anticipated prognosis and quality of life if timely transplant is not performed.

References