Liver transplantation for neuropsychiatric Wilson disease

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Wilson disease is an autosomal recessive condition of impaired hepatic copper excretion, resulting in excessive amounts of body copper. Up to 40% of patients with Wilson disease present with primarily neurological manifestations, which, although varied, predominantly involve the motor system. Psychiatric symptoms may manifest as behavioural, affective, psychotic or neurotic disorders (1).

Left untreated, Wilson disease is uniformly progressive and fatal within a period of weeks to years. Treatment for all manifestations of Wilson disease is the use of a copper chelator, most commonly D-penicillamine or alternatively trientine (2). The majority of patients are effectively treated medically, but a small number may require orthotopic liver transplantation (OLT).

Recommended indications for OLT in Wilson disease are fulminant hepatic failure; decompensated cirrhosis despite an adequate trial of chelation; or progressive hepatic insufficiency after discontinuation of chelation (3).

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BRIEF COMMUNICATION

Transplantation hépatique pour maladie neuropsychiatrique de Wilson

RÉSUMÉ : Bien que les manifestations neuropsychiatriques soient importantes chez certains patients atteints de la maladie de Wilson, peu de publications ont mentionné l’efficacité de la transplantation hépatique chez ces patients. On présente ici le cas d’un homme de 22 ans souffrant d’une atteinte neurologique avancée et de manifestations neuropsychiatriques importantes liées à la maladie de Wilson et qui a subi une transplantation hépatique. Après la transplantation, la teneur en cuivre et en ceruloplasmine a été normalisée et les anneaux de Kayser-Fleischer ont éventuellement disparu. La récupération neurologique a été très lente et partielle et les troubles du comportement et de la personnalité sont restés inchangés. Il s’est suicidé 43 mois après la transplantation. Un survol des cas peu nombreux publiés en langue anglaise révèle des taux variables de récupération neurologique après la transplantation, mais on ne mentionne pour ainsi dire nulle part l’évolution des manifestations psychiatriques. Ce cas souligne la prudence qui s’impose en matière de transplantation hépatique chez des patients atteints de la maladie de Wilson et dont les manifestations psychiatriques sont déjà en place. Un traitement médical énergique risque d’être préférable dans la plupart des cas.

Key Words: Liver transplantation, Wilson disease
OLT to treat hepatic failure in Wilson disease has been very successful, with demonstrable decoppering within weeks. A recent survey by Schilsky et al (4) reported 55 patients with Wilson disease who had undergone OLT in the United States and Europe, of whom eight had neurological or psychiatric manifestations. At a mean of 2.7 years (range three months to 20 years) follow-up, 43 (78%) were still alive; of the 12 who died, four had had central nervous system (CNS) manifestations pretransplantation. The authors concluded that Wilson disease patients with overt CNS pathology had a poor outcome following OLT. However, as illustrated by the absolute numbers, experience with OLT in neurological Wilson disease is limited and therefore its role still remains unclear. Even less clear is the effect of OLT on the psychiatric manifestations of Wilson disease.

CASE PRESENTATION
A 22-year-old male was admitted to hospital on October 11, 1989 with marked neurological deterioration secondary to Wilson disease for consideration of OLT. He had first noticed symptoms – difficulty driving, ataxia and falling grades at university – in autumn 1988. The diagnosis of Wilson disease was made in early 1989, by which time the patient displayed dysarthria, dystonia, bradykinesia and prominent Kayser-Fleischer rings. His ceruloplasmin was 73 U (normal range 210 to 570) and urine copper was 50 μmol/L (0.1 to 0.8). He was promptly started on D-penicillamine at a dose of 250 mg qid. Although his mobility improved mildly, his speech continued to deteriorate and he was moderately dystonic. Seven months later he was switched to trientene 250 mg tid but nevertheless his gait became progressively more broad based and eventually he became immobile. He displayed significant behaviour and personality abnormalities including sexual disinhibition.

At the time of liver transplant assessment, liver function tests were aspartate aminotransferase (AST) 355 U/L (normal range 0 to 35), alkaline phosphatase (ALP) 350 U/L (30 to 120), bilirubin 12 μmol/L (2 to 18) and albumin 36 g/L. Ceruloplasmin level was 43 U, urine copper was 5.2 μmol/L and serum copper was 5.8 μmol/L (normal range 11 to 28). A liver biopsy was fragmented, and a diagnosis of cirrhosis could not be made. There was evidence of chronic hepatitis, with interface necrosis and lobular changes including focal necrosis, hepatocyte ballooning, multinucleation and nuclear glycogen inclusions. Insufficient tissue was obtained for copper quantification but was subsequently performed on the explanted liver (see below). Computed tomographic (CT) scan of the head showed extensive low density changes in the basal ganglia bilaterally and frontal atrophy, consistent with Wilson disease. These CT findings are common in most patients with Wilson disease and often are reversed with treatment (5).

The patient was accepted for OLT on the basis of progressive medically unresponsive neurological deterioration from Wilson disease despite seemingly mild hepatic disease. Transplantation was carried out on October 21, 1989 without complication. The explanted liver revealed established cirrhosis and patchy inflammatory changes. The liver’s copper content was 3.3 μmol/g (normal 0.25 to 1.0). Postoperatively the patient had evidence of good early graft function and showed progressive decline in his urinary copper levels (Figure 1). Induction immunosuppression comprised Minnesota anti-lymphocyte globulin for three days, then conversion to OKT3 due to profound thrombocytopenia for an additional seven days. The patient received azathioprine and corticosteroids starting perioperatively, and cyclosporine was added on day 5. His postoperative course was complicated by cytomegalovirus (CMV) infection, which responded well to treatment with CMV hyperimmunoglobulin.

Two weeks post-transplantation the patient remained dystonic with no spontaneous limb movement. Two months after transplantation he had mild reduction in tone and rigidity with increasing limb movement. By three months, he was able to transfer from bed to chair, and put on a shirt without assistance. By four months, he remained dystonic but was able to move all four limbs spontaneously and was able to bear weight. Throughout the postoperative course he displayed significant behavioural disturbance and was unco-
operative with his caregivers, at times displaying aggressive and defiant behaviour, as well as emotional lability and disinhibition. These behaviours were similar to his pretransplantation state. Psychological testing revealed no intellectual impairment.

At six months post-transplantation, the patient demonstrated increasing displays of sexual disinhibition and aggression. Neurologically, he had dystonia, especially of his neck, and generalized hypertonia and bradykinesia, for which he was started on carbidopa-levadopa and bromocriptine. His mobility improved; one year after transplantation he was able to roll, sit up, transfer and stand up for brief periods. The Kayser-Fleischer rings gradually faded and completely disappeared. He was discharged from hospital to a group home, but he repeatedly alienated himself due to inappropriate behaviour and demands.

His liver function remained completely normal until 19 months post-transplantation when he developed progressively raised liver enzymes: AST 436 U/L, ALP 148 U/L and bilirubin 21 µmol/L. Liver biopsy showed parenchymal changes consistent with hepatitis, as well as mild acute rejection. Hepatitis C was diagnosed serologically (positive by enzyme immunoassay and recombinant immunoblot assay testing). At 26 months post-transplantation, although his neurological function was improving and he was increasingly mobile, he started to display suicidal gestures and required antipsychotic medication to control his behaviour. Three years after transplantation, he refused to take cyclosporine because of perceived association with chronic foot pain. Liver biopsy showed moderate cellular rejection and cholestasis. He was treated with pulse corticosteroids and OKT3. Upon discharge, however, he continued to take cyclosporine only sporadically, resulting in significant ongoing rejection with evolution to ductopenia on repeat biopsy and further deterioration of liver function. OLT was performed 16 months after initial presentation. Over the ensuing two months, the patient showed considerable improvement and by four months he was mobile and conversing two months, the patient showed considerable improvement and by four months he was mobile and conversing, feeding and caring for himself. He displayed mild extrapyramidal signs, as well as emotional lability and immature behaviour. The neurological symptoms completely disappeared by eight months but no further comment was made about the psychiatric symptoms.

Two cases were reported by Polson et al (9). A 30-year-old male presented with jaundice and fatigue with progressive neurological deterioration over one year. Despite treatment with D-penicillamine, he developed dysarthria, dysphagia, akinesia and rigidity, eventually becoming bedridden and unable to walk, speak or feed himself. OLT was performed 16 months after initial presentation. Over the ensuing two months, the patient showed considerable improvement and by four months he was mobile and conversing, feeding and caring for himself. He displayed mild extrapyramidal signs, as well as emotional lability and immature behaviour. The neurological symptoms completely disappeared by eight months but no further comment was made about the psychiatric symptoms.

The second patient reported by Polson et al (9) was a 27-year-old female who initially presented with abnormal liver function and pancytopenia. She developed unspecified psychological symptoms, ataxia, cogwheel rigidity and fine tremor. There was no improvement with D-penicillamine treatment, and within six months she displayed slurring dysarthria, increased muscle tone and dysdiadochokinesia. OLT was done eight years after the initial diagnosis for deteriorating neurological and liver function. Postoperatively, liver enzymes normalized but neurological function remained unchanged. By three months, she had improved, with only mild dysarthria, tremor and an unsteady gait remaining. By five months, her neurological signs had further improved, but she still displayed unspecified behavioural problems.

The fifth case, recently reported by Mason and co-workers (10), described a 20-year-old male with neuropsychiatric Wilson disease manifested by ataxia, dysarthria, dystonia and psychotic depression with mood swings. OLT was performed five years after diagnosis, when his symptoms were not improving on medical therapy. He showed inter-

DISCUSSION
This report describes a patient with severe neurological and psychiatric impairment secondary to Wilson disease who underwent OLT. Transplantation resulted in reversal of the metabolic defect and dramatic mobilization of copper, as demonstrated by normalization of the serum ceruloplasmin, decline of urine copper excretion (Figure 1) and disappearance of the Kayser-Fleischer rings. Clinically, he progressed from being bedridden to ambulating well enough to care for himself outside hospital. However, unlike most published cases (6-9), he did not show complete neurological recovery even up to 3.5 years after OLT. Moreover, he continued to display manipulative behaviour and emotional lability, resulting in noncompliance with medications, several acute rejection episodes and subsequently chronic ductopenic rejection.

Review of the English language literature reveals five published case reports in which OLT was performed in patients with severe neurological impairment secondary to Wilson disease. The first was a 14-year-old male who presented at age 11 years with liver disease (6). He developed moderate neurological impairment over one year with tremor and athetosis. Chelation treatment failed, and the patient developed progressive dysarthria, dystonia and choreoathetosis. OLT was performed primarily because of his crippling neurological status, although he also showed moderate hepatic impairment. In the first 12 months after OLT, he showed intermittent neurological improvement, and by 18 months he had definite improvement. A follow-up letter to the editor indicated that the patient displayed no neurological dysfunction at 50 months post-transplantation (7).

The second case involved a 13-year-old boy who presented with subacute hepatitis and developed ataxia and cogwheel rigidity (8). Despite medical treatment he went into liver failure. OLT resulted in gradual improvement of neurological function, except for a right-sided hemiparesis, which resolved by 15 months. Other psychiatric symptoms were not mentioned in either of these cases.

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mittent improvement three weeks after transplantation in all motor functions, and regained speech at six weeks. Unfortunately he died of a ruptured splenic artery aneurysm shortly thereafter.

These cases all showed favourable, if not dramatic, improvements in neurological symptoms after OLT. Publication bias may lead to under-reporting of those with an unfavourable outcome; indeed, we did not come across any of the latter in our search. In addition, the psychiatric symptoms so prominent in our patient were not clearly documented in the published cases, and therefore the outcome after OLT of patients with symptoms similar to those of our patient is uncertain.

Despite increasing experience with liver transplantation in Wilson disease and confidence that the biochemical defect will be reversed, it is still unclear whether OLT should be considered in all patients with neuropsychiatric manifestations of Wilson disease who do not respond to chelation. If a patient has already achieved complete or near complete copper clearance, any persisting neuropsychiatric abnormalities might be considered permanent. Our patient had a poor outcome despite high postchelation hepatic copper levels (3.3 μmol/g). Despite 43 months of follow-up until his death, our patient showed no discernable improvement of his psychiatric disorder. Unfortunately, the only previously published example of OLT in Wilson disease primarily for neuropsychiatric indications had only six weeks of follow-up due to early death from a ruptured splenic aneurysm (10). Patients with psychiatric manifestations may be especially poor candidates for OLT because reversal of these features has never been reported and because these patients also have severe neurological impairment (1).

Would earlier liver transplantation be beneficial in patients who display a predominance of neuropsychiatric symptoms of Wilson disease? Past experience has shown that a majority of such patients respond well to medical treatment. Furthermore, it is impossible to predict which patients will not respond to medical treatment and who therefore should receive a transplant. The distinction between reversible and irreversible CNS functional changes remains difficult. It is hoped that newer imaging modalities will be useful in this regard (11). Currently, early OLT cannot be advocated with the limited data available. Indeed, early diagnosis and institution of medical treatment remain the primary goals in preventing irreversible damage to all organ systems from copper overload.

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REFERENCES
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