Liver Transplantation for Wilson's Disease: The Burden of Neurological and Psychiatric Disorders

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A retrospective data analysis on liver transplantation for Wilson's disease (WD) was performed among Italian Liver Transplant Centers. Thirty-seven cases were identified. The main indication for liver transplantation was chronic advanced liver disease in 78% of patients. Mixed hepatic and neuropsychiatric symptoms were recorded in 32.3%. Eight patients presented with fulminant liver failure; 44.8% were on medical treatment. Patient and graft survival at 3 months, 12 months, 3 years, 5 years, and 10 years after transplantation were, respectively, 91.8%, 89.1%, 82.9%, 75.6%, and 58.8%, and 85.3%, 83.0%, 77.1%, 70.3%, and 47.2%. Neurological symptoms significantly improved after orthotopic liver transplantation (OLT), but the survival of patients with mixed hepatic and neuropsychiatric involvement was significantly lower than in patients with liver disease alone (*P* = 0.04). WD characterized by hepatic involvement alone is a rare but good indication for liver transplantation when specific medical therapy fails. Patients with neuropsychiatric signs have a significantly shorter survival even though liver transplantation has a positive impact on neurological symptoms. In conclusion, a combination of hepatic and neuropsychiatric conditions deserves careful neurological evaluation, which should contraindicate OLT in case of severe neurological impairment. (*Liver Transpl 2005;11: 1056-1063.*)

Wilson's disease (WD) is an inherited autosomal recessive copper accumulation and toxicity disorder that is estimated to affect about 1 in 30,000 people, with a carrier rate of 1 in 90.[1] The disease results from a copper-transport adenosine triphosphatase dysfunction in the liver that is responsible for excreting copper into the bile.[2,3] A number of mutations can impair protein function with subsequent copper accumulation occurring mainly in the liver, though toxic concentrations may also be found in brain, cornea, or kidney tissue. The disease is considered fully penetrant, so its diagnosis makes medical treatment mandatory,[4,5] based on copper chelating agents and zinc salts that take effect mainly by blocking intestinal copper absorption.[6] Compliance is essential because a rapid deterioration of the hepatic symptom has been reported after discontinuing anti-copper therapy.[7] Orthotopic liver transplantation (OLT) represents the ultimate treatment for this disease when medical therapy fails,[8] but the indication for, and timing of, this procedure have yet to be fully established: although the metabolic hepatic defect can certainly be treated, with survival rates reportedly ranging from 100% at 33 months[9] to 62% at 1 year,[10] the outcome of patients with neuropsychiatric symptoms after liver transplantation is still uncertain. Most studies have reported neurological improvement after OLT,[11,12] simply describing every single case or by the use of very unspecific instruments like the performance status. Considering that the data available in literature on WD outcome after OLT are not yet conclusive and based on short-term follow-up, and that the issue of the neurological symptoms evolution has not been solved yet, in this paper we report a relatively large experience on liver transplantation for WD with a view to investigating which factors might affect post-OLT survival and the outcome of patients with associated neurological symptoms.

Materials and Methods

A retrospective data analysis was carried out on 37 patients who underwent OLT for WD between 1985 and 2000 at Italian liver transplant centers, out of a total of 3,026 adult

transplantations (1.2%). Data were collected retrospectively by the reference centers using printed forms: the forms were sent to a single filing center, where a team of physicians supported by experts on statistical analysis recorded all the forms simultaneously. This procedure ensured an acceptable homogeneity in the interpretation of the data collected. Whenever a considerable amount of data was missing from the form, the patient concerned was excluded from the specific analysis. OLT for WD had been performed at 7 out of 15 transplant centers. The diagnosis was suspected on the basis of clinical hepatic and/or neurological symptoms, the finding of Kayser-Fleischer ring, or family history. Copper metabolism was then evaluated and considered diagnostic of WD if serum ceruloplasmin was less than 20 mg/dL (the mean concentration was 10.1 mg/dL), 24-hour urine copper excretion was more than 100 μg/24 hours, and copper concentration in the liver exceeded 250 μg/gm dry weight. The patients were followed up by the Transplant Centers, monitoring the evolution of clinical hepatic and neurological symptoms, biochemical tests, and liver histology. The items considered included:

1. Pretransplantation data:

- Patients' demographic features (gender, age), clinical features of liver disease, indications for transplantation, time on the waiting list, anti-copper medical treatment, association with other liver conditions, and biochemical and serological data;
- Donors' features (age, time in intensive care).

2. Posttransplantation data:

- Graft and patient survival with causes of graft loss and patients' death, immunosuppressive regimen, occurrence of acute and/or chronic rejection, and biochemical data over a 24-month follow-up;
- Complications (renal failure, hypertension, cancer, osteoporosis);
- Outcome of neurological symptoms during follow-up.

A score was developed to describe the evolution of neurological symptoms after OLT, selecting the neurological signs and symptoms that seemed to be the most representative of WD and the easiest to apply retrospectively, using the experience of a group of physicians, both gastroenterologists and neurologists, with expertise in dealing with WD patients. The parameters included in the scoring system are shown in Table 1. Each function could score a maximum of 3: the higher the score, the better the neurological sign or function considered. The maximum score was 30. The same score was applied to the patient's neurological condition no more than 14 days before OLT and then after 1 year.

The degree of disability was ascertained by interviewing the patient's physicians, from the clinical records or, in a few cases, by means of a telephone questionnaire.

Table 1. Evaluation of the Neurological Impairment in Wilson's Disease Cases

| Neurological signs |
| A |
| Rigidity |
| Bradykinesia |
| Ataxia |
| Tremors |
| Dyskinesia (coreoatetosis) |
| Dystonia |
| Neurological functions |
| B |
| Walking |
| Eating |
| Talking |
| Dayliving activities |

NOTE. Maximum score for each function is 3 (3, no impairment; 2, mild impairment; 1, moderate impairment; 0, severe impairment); Maximum total score is 30.

Statistical Methods

All data are presented as mean values $\pm$ standard deviation. Student's *t* test for unpaired data (2-tailed) was used for statistical analysis.

The analysis of survivals was performed using the Kaplan-Meier method and differences between curves were compared using the Breslow test. A *P* value ≤ 0.05 was considered significant.

Results

The report concerns 37 adult patients (20 men, 54.1%) who underwent transplantation for WD and 41 transplantations (4 retransplantations) performed in Italy.

The location and the number of OLTs are outlined in Table 2.

Medical History

Detailed data on the clinical symptoms at onset of the disease were available on 33 patients: 27 (82%) had hepatic symptoms at onset and the other 6 (18%) had both hepatic and neuropsychiatric symptoms at onset. The initial hepatic symptoms were those of a fulminant hepatic failure (FHF) in 8 patients; 5 were diagnosed with WD on the basis of abnormal aminotransferase serum level, and the remaining 14 presented with de novo chronic hepatic failure (ascites, edema, porto-systemic encephalopathy, and jaundice). Patient features at time of disease onset are summarized in Figure 1.

Table 2. Liver Transplantation Centers and Procedures Performed

Center	Number of Patients	Number of OLT
1	6	8
2	1	1
3	2	2
4	9	11
5	4	4
6	1	1
7	3	3
8	11	11

Seven of 8 patients presenting with FHF had porto-systemic encephalopathy graded as I-II grade (5 patients), III grade (1 patient), and IV grade (1 patient). Only 1 of the patients presenting with FHF had a history of neurological symptoms that may have been clouded by porto-systemic encephalopathy.

The patients' age at the time of the first symptoms was 21.2 ± 10.6 years (range 7-52), with no significant difference between hepatic (30.3 ± 12.3) and mixed disease (hepatic + neuropsychiatric) (29.6 ± 10.7) patients ($P = 0.91$).

The mean interval between onset of symptoms and diagnosis was 32 ± 48 months (range 1-168); the mean time elapsing between WD diagnosis and OLT was 50 ± 53.2 months (range 1-159), excluding the 8 cases presenting with FHF.

Of the patients presenting with advanced liver disease, 13 (44.8%) received continuous anti-copper therapy for their disease: 9 had only D-penicillamine, 4 had DPCA followed by zinc, 1 had D-Penicillamine followed by trientine, and 4 were treated with zinc supplements alone. The mean duration of the pre-OLT medical therapy was 36.2 ± 65.3 months for the D-Penicillamine-treated patients and 43 ± 57.3 months for the patients administered zinc salts. Compliance with medical therapy had been highly variable over this period, especially in patients with psychiatric symptoms: All the patients who were still on medical therapy at the time of OLT showed a worsening of their disease due to the failure of the specific therapy. Most of the patients were being treated with D-Penicillamine (including the neurological patients): it is well known that D-Penicillamine treatment often worsens the neurological symptoms and this might help to explain the failure the medical treatment.

Patient Features at Time of OLT

The mean age at OLT was 27.5 ± 9.8 years (range 15-56); there was a statistically significant age difference at transplantation between men and women (men 31.89 ± 9.89 years; women 22.1 ± 6.82 years; $P = 0.002$). In our general liver transplant population, mean age at transplantation was 47.3 ± 10.6 years, median 50 years (range 15-72 years),[13] significantly higher than WD patients ($P < 0.0001$).

The patients' age at transplantation was 29.6 ± 10.7 years (range 21-56) for the mixed hepatic and neuropsychiatric cases, while it was 28.2 ± 9.4 years (range 16-56) for the chronic hepatic patients ($P = 0.5$). The median age at transplantation was 25.2 ± 11.8 years (range 15-43) among the FHF cases ($P = 0.4$).

In accordance with the pre-1997 classification of the United Network for Organ Sharing, 6.7% of the patients were Status 1 and 2A (intensive care unit), 46.7% were Status 2 (in hospital), and 46.7% were in Status 3-4 (at home) at the time of transplantation.

The Child-Turcotte-Pugh score was class B for 35.1% of cases (13 patients), and 48.6% (18 patients) were class C (the score was unavailable for the remaining 6 patients). The patients scored as Child-Turcotte-Pugh B (5 B8, 8 B9) included patients with chronic liver failure, unresponsive to anti-copper medical therapy, or never treated specifically for WD, and 1 chronic liver failure with severe neurological impairment.

Five of the 9 patients with neurological symptoms were properly studied with pre-OLT brain magnetic resonance imaging: 4 of them showed involvement of basal nuclei; in 1, the magnetic resonance imaging quality was reduced by the patient's uncontrollable movements. (The main features of WD patients at time of OLT are summarized in Table 3, compared with the general liver transplantation population in Italy.)
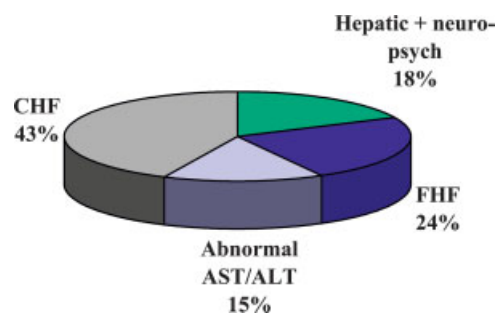

Figure 1. Patient features at time of WD onset. CHF, chronic hepatic failure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hepatic + neuro-psych, hepatic plus neuropsychiatric.

Table 3. Patient Features at Time of OLT Compared to the Italian General Liver Transplant Population

	Wilson's Disease	All OLT
Mean age at OLT	27.5 ± 9.8*	47.3 ± 10.6*
Male/female	1:1	2:3
Mean waiting time (months)	6.9 ± 9.3	7.2 ± 8.4
FHF (%)	8 (21.7)	148 (4.9)
CHF (%)	29 (78.3)	—
Mixed (hepatic + neurologic) (%)	10 (32.3)	—

NOTE. Alcohol abuse 1; HCV positive 1; HBsAg positive 1.
Abbreviations: HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; FHF, fulminant hepatic failure; CHF, chronic hepatic failure.
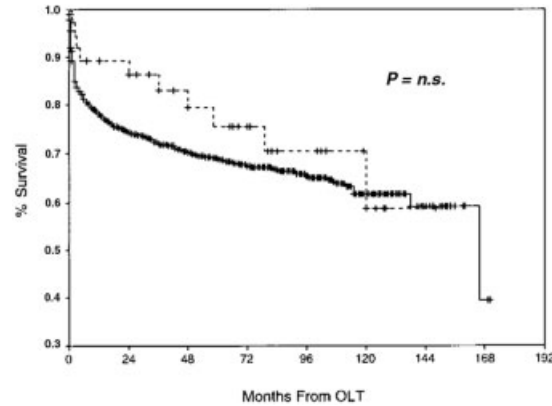*$P < 0.0001$.

Figure 2. Kaplan-Meier estimates of patients' survival after OLT, stratified by diagnosis. WD patients (dotted line) and general OLT population (solid line).

Donor Features

The donors' mean age was 30.6 ± 17.3 (range 8-82). Survival was correlated with donor age; i.e., donor age >40 years correlated with a shorter survival than with donors <4 years (overall survival rates were 55.5% and 90%, respectively, $P = 0.01$). Seven donors (26.9%) had been in intensive care for more than 7 days and 19 (73.1%) for less than 7 days. The mean post-OLT survival in patients receiving a liver from the former 7 donors was 56 ± 10 months (range 36-75); in the second group it was 125 ± 12 months (102-149; $P = 0.65$). The parameters considered are general and their influence on post-OLT outcome in WD patients should be no different from cases with other transplantation indications.

Post-OLT Data

Graft and Patient Survival

The cumulative overall patient survival curve is shown in Figure 2. The mean follow-up period was 64.6 ± 43 months (range 2-152) and overall patient survival rates at 3, 6, and 12 months and at 3, 5, and 10 years after transplantation were, respectively, 91.8%, 89.1%, 89.1%, 82.9%, 75.6%, and 58.8%, while graft survival rates were 85.3%, 83%, 83%, 77.1%, 70.3%, and 47.2%, respectively.

There was no significant difference in patient ($P = 0.11$) and graft ($P = 0.30$) survival between our general OLT population[17] and the WD patients (Fig. 2). Nor was there any difference in patient survival rates, according to gender ($P = 0.75$), age at transplantation ($P = 0.31$), blood group ($P = 0.52$), Child-Turcotte-Pugh status

before transplantation ($P = 0.80$), United Network for Organ Sharing status ($P = 0.71$), medical therapy ($P = 0.36$), morbidity cofactors ($P = 0.47$), and transplantation period (before and after 1993) ($P = 0.54$). The clinical liver-related indication, FHF, or chronic liver disease, did not affect survival ($P = 1$). The combination of neuropsychiatric and hepatic symptoms was the only factor influencing survival after OLT, with neuropsychiatric patients showing a significantly lower survival rate than the other WD patients ($P = 0.04$) (Fig. 3): patients with liver disease alone and those with both hepatic and neuropsychiatric conditions had a mean survival of 135 (range 118-152) and 79 months (range 46-113), respectively.

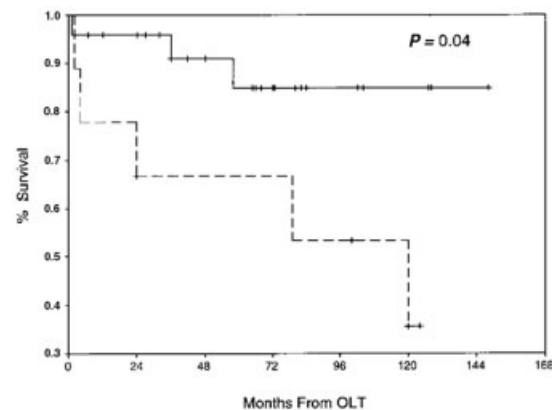There were 10 deaths after OLT, occurring at a mean 38 ± 13 months (range 13-62) after OLT; 5 of

Figure 3. Kaplan-Meier estimates of patients' survival after OLT, stratified by clinical features. Hepatic patients (solid line) and mixed hepatic plus neuropsychiatric patients (dotted line).

the deaths involved patients with neuropsychiatric symptoms.

The most common cause of death was sepsis, which occurred in 5 (50%) of 10 cases. One patient died as a result of a severe, rapidly-progressive deterioration in neurological status within the first month after OLT combined with sepsis (included in the 5 cases of sepsis); 1 died of de novo cancer (pancreatic cancer with hepatic metastasis), occurring 22 months after liver transplantation; and 1 died because of primary liver nonfunction. The cause of death was not known in 3 cases.

Four patients (3 of them presenting with mixed symptoms) had 2 liver transplantations; the reasons for retransplantation were: acute rejection (1), vascular complications (1), de novo hepatitis C virus infection (1), and primary nonfunction (1). The last 1 of these had de novo hepatitis C virus infection diagnosed within 1 year of the second transplantation: he developed renal failure that eventually required kidney transplantation. He had mixed hepatic and neuropsychiatric symptoms at presentation.

Immunosuppression and Rejection

There were 17 cases (46%) of acute rejection (16 patients had 1 episode and 1 patient had 2 episodes), which was comparable ($P = 0.7$) with the rejection rate in our general OLT population (43.55%), a mean 4.3 weeks (first episode) and 30.6 weeks (second episode) after OLT. The mean number of steroid boluses used to treat the acute rejection episodes was 2.4 (range 1-4). For baseline immunosuppression, cyclosporine A was used in 67.6% of patients and FK506 was administered in 29.7%.

None of the hepatitis C virus–positive recipients was treated with antiviral therapy.

Complications

Five patients (13.5%) developed renal failure after OLT, and hypertension was recorded in 9 patients (24.3%). Metabolic changes (dyslipidemia, hyperuricemia) were found in 3 patients.

Neurological Symptoms Outcome

Ten patients had associated neuropsychiatric dysfunction with chronic liver failure (3 had neurological symptoms alone, 1 had psychiatric symptoms alone, and the other 6 had both symptoms). Using the previously described score, the neurological signs and symptoms recorded before and after OLT are shown in Table 4. Neurological disability improved in 6 cases after OLT, regressing completely in 2 cases whose symptoms where mild at presentation (scoring 26-27 before

Table 4. Neurological Scores for Patients 1-9 Before and After OLT.

Patient Number	Pre-OLT Score	Post-OLT Score
1	10	24
2	14	23
3	13	21
4	20	26
5	27	30
6	26	30
7	25	13
8	19	14
9	18	0

NOTE. Patients from 1 to 6 presented improvement of the neurological score after OLT; patients from 7 to 9 presented worsening of the neurological score.

OLT). An improvement was evident in all cases within 6 months of OLT. The neurological condition deteriorated in 3 patients: 1 developed de novo severe neurological symptoms immediately after OLT and died with a diagnosis of pontine myelinolysis; 1 had neurological impairment within 2 months (though cerebral nuclear magnetic resonance imaging failed to show any variation compared with the situation prior to OLT), but subsequently remained clinically stable for 2 yr after OLT, when a pancreatic cancer was diagnosed; 1 had neurological impairment after OLT, but was subsequently lost to follow-up and died of sepsis about 10 years after OLT.

The psychiatric symptoms included paranoid psychosis, hysterical neurosis, depression, and insomnia. Drug dependence was involved in 3 cases: 2 of them died after OLT and none of them showed any improvement during the post-OLT follow-up.

Laboratory Parameters

The laboratory data before OLT and during the 24-month follow-up on the surviving patients are given in Table 5.

Discussion

Since the first successful liver transplantation for WD in 1971,[14] a number of reports in the literature have considered WD as an excellent indication for transplantation, because this treatment can reverse biochemical and clinical signs and offer long-term survival.[9,10] This study retrospectively analyzes WD patients who underwent transplantation, describing their clinical and bio-

Table 5. Laboratory Data Before and After OLT

| | Pre-OLT | | | | | |
	CHF	FHF	Post-OLT	1 Month	12 Months	24 Months
Hb (gm/L)	10.7 ± 2	9.1 ± 1.5	10.2 ± 1.6	10.6 ± 1.8	12.4 ± 2.3	12.7 ± 2
AST (U/L)	67.6 ± 39.7	433.6 ± 773.5	52 ± 46	31 ± 19.7	23.4 ± 10	22.5 ± 8.8
ALT (U/L)	57.2 ± 46	356.5 ± 637	200 ± 249.8	52.7 ± 44.5	24.6 ± 18	25 ± 17.3
ALP (U/L)	284.3 ± 236.4	400 ± 346.4	1177.7 ± 141.3	150.5 ± 74.3	164.7 ± 74.5	125 ± 68.7
Bilirubin (mg/dL)	6.1 ± 7.2	18 ± 14.1	4.3 ± 2.5	1.8 ± 0.75	1.1 ± 0.62	1.1 ± 0.72
Urea (mg/dL)	39 ± 12.8	57.6 ± 45	96 ± 90	57.5 ± 32	48.8 ± 18	51.4 ± 25
Creatinine (mg/dL)	0.9 ± 0.28	1.1 ± 0.8	1.2 ± 0.6	1.4 ± 0.85	1.1 ± 0.22	1.1 ± 0.26

NOTE. Laboratory data before (within 14 days for CHF and 2-3 days for FHF) and after liver transplantation (OLT) (at 2 weeks and at 1, 12, and 24 months). Data are expressed as mean ± standard deviation.
Abbreviations: CHF, chronic hepatic failure; FHF, fulminant hepatic failure; Hb, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

chemical features before and after OLT, during a 24-month follow-up.

Taking pre-OLT data into account, it was surprising that only half the patients in our population received anti-copper therapy: this is partly due to poor compliance in some cases (about 60% of cases), but may also point to an underestimation of the utility of medical therapy for WD. In fact, a rapid worsening of the disease after withdrawing medical therapy is described in many previous reports;[15,16] the specific medical therapy currently used for WD is very effective, improving the outcome of the disease in most cases. We confirmed a potential role of hormonal factors in the evolution of WD-related hepatitis, previously described both in patients[17] and animal models,[18] by observing a significantly higher age at OLT for women, while the cases of FHF included slightly more women than men; however, no statistical difference in survival was observed according to gender. On the other hand, we did not find the same alkaline phosphatase /bilirubin level <2 and aspartate aminotransferase/ alanine aminotransferase >4 correlations in FHF patients previously described by Berman et al.,[19] as being highly specific for WD FHF. This could be due to the poor pre-OLT data collection for fulminant hepatitis (in particular alkaline phosphatase and bilirubin level), but the same correlations were not confirmed by previous studies.[20,21] Therefore, their diagnostic value needs to be further investigated. Liver functions tests became normal within 1 year after OLT, showing that the transplant ameliorates metabolic defect.

After OLT, the overall 1-year survival rate in our patients was 89%, which is similar to the figure reported elsewhere;[10,17,22] the presence of chronic liver disease or FHF did not affect survival rate, but this observation is limited by the small sample size and by the poor statistical power.

We observed a reduction in overall survival starting from 6 years after OLT, with sepsis as the major cause of death. No significant difference in survival was shown between WD patients and the general OLT population, however.[13] Taking into account the different clinical features at the time of OLT, we observed a significantly shorter survival in patients with neuropsychiatric as well as hepatic symptoms, though their clinical hepatic condition did not differ significantly from the cases with hepatic symptoms alone. The concomitant presence of neuropsychiatric symptoms, in our experience, is a negative prognostic factor, though we observed an improvement and even a complete regression (in the milder conditions) of the neurological symptoms, as reported elsewhere.[9,10,23,24] Sepsis was the main cause of death in our WD population, but it is a common cause of morbidity and death in the general transplant population, too. One might speculate on whether a severe psychiatric and/or neurological dysfunction could, even indirectly, increase the risk of infection due to such patients often being bedridden for lengthy periods of time and frequently hospitalized.

In 1 case, the difficulties encountered in communicating with the patient certainly interfered with the identification of the symptoms of advanced pancreatic cancer.

Our observation on this point is partially limited by the fact that it is retrospective, so the scoring and interpretation of the clinical signs and symptoms may be biased or inaccurately reproducible. Previous studies described neurological symptoms after OLT, using performance status[22] or simply recording individual patient neurological functions.[12,23,25,26] In the present

study, using prior experience on WD, we adopted a simple, new scoring system (that can be applied not only by neurologists, but also by surgeons and gastroenterologists), which may represent an objective way to describe and assess neurological symptoms, not only retrospectively, but also prospectively. In our series of patients, those whose score worsened died during the follow-up period, but no correlation was observed between pre-OLT score and survival. The proposed score may be of value in describing neurological function before and after OLT, but its association with survival has yet to be demonstrated.

No psychiatric improvement was observed in our population, although it is clearly difficult to evaluate psychiatric outcome due to the complexity of the presenting signs and the variety of factors potentially influencing clinical outcome (immunosuppressive therapy, WD itself, individual features). However, in our experience the presence of psychiatric symptoms could be considered as a partial contraindication for OLT.

In conclusion, our data show that WD-related liver disease, be it chronic hepatic failure or FHF, is a good indication for OLT, but the WD patients to recommend for OLT have to be carefully selected, given the efficacy of medication specific for WD. In our experience, the indications for liver transplantation for WD might be better defined:

1. Chronic liver failure: WD patients should be considered for OLT only after suitable medical therapy has failed;
2. Isolated neuropsychiatric symptoms are a contraindication for OLT;
3. Combination of hepatic and neuropsychiatric conditions deserves careful neurological evaluation, which has to contraindicate OLT only in case of severe neurological impairment. However, although the mild neurological symptoms may improve after OLT, concomitant severe or moderate neurological and particularly neuropsychiatric symptoms are negative prognostic factors for post-OLT survival.

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