ARTICLE CLASS OF EVIDENCE

Liver transplantation as a rescue therapy for severe neurologic forms of Wilson disease

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Abstract

Objective

To evaluate the effect of liver transplantation (LT) in patients with Wilson disease (WD) with severe neurologic worsening resistant to active chelation.

Methods

French patients with WD who underwent LT for pure neurologic indication were retrospectively studied. Before LT and at the last follow-up, neurologic impairment was evaluated with the Unified Wilson's Disease Rating Scale (UWDRS) score, disability with the modified Rankin Scale (mRS) score, and hepatic function with the Model for End-stage Liver Disease score, together with the presence of a Kayser-Fleischer ring (KFR), brain MRI scores, and copper balance. The survival rate and disability at the last follow-up were the coprimary outcomes; evolution of KFR and brain MRI were the secondary outcomes. Prognosis factors were further assessed.

Results

Eighteen patients had LT. All were highly dependent before LT (median mRS score 5). Neurologic symptoms were severe (median UWDRS score 105), dominated by dystonia and parkinsonism. The cumulated survival rate was 88.8% at 1 year and 72.2% at 3 and 5 years. At the last follow-up, 14 patients were alive. Their mRS and UWDRS scores improved ($p < 0.0001$ and $p = 0.0003$). Eight patients had a major improvement (78% decrease of the UWDRS score), 4 a moderate one (41% decrease), and 2 a stable status. KFR and brain MRI scores improved ($p = 0.0007$). Severe sepsis ($p = 0.011$) and intensive care unit admission ($p = 0.001$) before LT were significantly associated with death.

Conclusions

LT is a rescue therapeutic option that should be carefully discussed in selected patients with neurologic WD resistant to anticopper therapies (chelators or zinc salts) as it might allow patients to gain physical independency with a reasonable risk.

Classification of evidence

This study provides Class IV evidence that for patients with WD with severe neurologic worsening resistant to active pharmacologic therapy, LT might decrease neurologic impairment.

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Glossary

ARDS = acute respiratory distress syndrome; **Cp** = ceruloplasmin; **ICU** = intensive care unit; **IQR** = interquartile range; **KFR** = Kayser-Fleischer ring; **LT** = liver transplantation; **MELD** = Model for End-stage Liver Disease; **mRS** = modified Rankin Scale; **NRCWD** = National Reference Centre for Wilson's Disease; **UWDRS** = Unified Wilson's Disease Rating Scale; **WD** = Wilson disease.

Wilson disease (WD) is an autosomal recessive inherited disorder leading to a toxic copper overload mainly in the liver and the brain.[1] Copper chelators and zinc therapy are effective conservative treatments in most patients. However, treatment initiation is followed by neurologic deterioration in up to 20% of patients with initial neuropsychiatric form.[2] Inefficacy of intracerebral chelation or excessive copper mobilization by the chelating agents leading to oxidative stress and an accentuation of brain tissue damage are the classical hypotheses proposed to explain this paradoxical worsening.[3,4] The neurologic worsening is irreversible in 44% of patients, resulting in severe disability or even death despite optimal therapy.[5–7]

Liver transplantation (LT) is the recommended therapeutic option in WD with acute liver failure or end-stage liver cirrhosis, with a survival rate of 87% at 15 years.[8] In contrast, the place of LT in managing WD with severe neurologic worsening without liver failure remains controversial. Since 1993, only 32 patients transplanted for pure neurologic or neuropsychiatric indication were reported: the majority were case reports with heterogeneous and incomplete evaluation and follow-up (table 1).[9–22]

The aims of this collaborative study were to report the French experience of LT in patients with WD with pure neurologic worsening despite accurate medical therapy and to determine prognostic factors.

Methods

Standard protocol approvals, registrations, and patient consents

This study was conducted by the French National Reference Centre for Wilson's Disease (NRCWD) in Paris in collaboration with the French WD network (Lyon, Bordeaux, Besançon, Toulouse, Tours). All patients gave their informed consent for the genetic analysis and for anonymous study of their data (consent for research) before their inclusion in the French WD Registry. This study was approved by the Institutional Review Board of Hôpitaux Universitaires Paris Nord Val de Seine, Paris 7 University, AP-HP (no 1343579).

Study design and patient characteristics

Patients with WD who underwent an LT for neurologic indication between June 1994 and June 2016 were selected from the WD National Registry for a retrospective study. All patients fulfilled the 3 conditions below and had a:

1. Leipzig score for the diagnosis of WD >4 and 2 *ATP7B* mutations. This score is based on a combination of clinical symptoms (neuropsychiatric symptoms and Kayser-Fleischer ring [KFR] at slit-lamp examination), laboratory tests (Coombs negative hemolytic anemia, urinary copper, serum ceruloplasmin (Cp), liver copper concentration, and rhodanine-positive hepatocytes), and the result of genetic testing; diagnosis of WD is highly likely if the score is >4.[23]
2. Constant neurologic worsening over a maximum of 18 months and despite a minimum of 2 months of appropriate copper chelation. Copper chelation was initiated in all patients immediately after the diagnosis of WD. Worsening was defined as a minimum of 20% increase of the Unified Wilson's Disease Rating Scale (UWDRS) score and a 2-point increase in the modified Rankin Scale (mRS) score. The UWDRS is a 35-item validated tool to assess the severity of neurologic symptoms, a high score being even higher than the neurologic damage is severe.[24] The mRS is a global measure of physical disability on a 7-level scale, with scores ranging from 0 (no symptoms) to 6 (death).[25]
3. Severe neurologic impairment with an mRS score ≥4 at the time of LT.

Neurologic worsening could be primary in newly diagnosed and treated patients or secondary to the interruption of chelators.

Criteria of noninclusion were neurologic patients with hepatic indication of LT, severe neurologic patients with stable condition or without recent worsening, and patients who did not have a regular follow-up in the NRCWD network.

Baseline data before LT

Demographic data with age at diagnosis, time between worsening and LT, age at LT, and clinical, biological, genetic, and imaging data pre-LT were reviewed. The clinical evaluation included the mRS score, the UWDRS score with details of the main neurologic symptoms (dystonia, parkinsonism, tremor, and behavioral disturbances), and an ophthalmologic KFR score (0: no KFR; 1: incomplete KFR; and 2: complete KFR).[26] For patients included before the UWDRS publication in 2007, the UWDRS score was retrospectively calculated from clinical data available in the medical and nurses' files. The severity of liver disease was evaluated by the Model for End-stage Liver Disease (MELD) and Child scores. Copper metabolism was assessed by serum and urinary copper and Cp levels. For patients transplanted after 2010, exchangeable copper (corresponding to the direct dosage of free copper)

Table 1 LT for pure neurologic indication: characteristics and outcome of 32 patients (review from 1993 to 2018)

Authors, journal, y	Country	No. of patients and age at LT	Evaluation	Duration of follow-up	Neurologic outcome	Death
Laurencin et al.,[9] *Eur Neurol*, 2017	France	2 (17 y, 19 y)	Rankin score, UWDRS score, and MRI	3 and 4 y	Clinico-radiologic improvement in both patients (could walk unaided, no more gastrostomy feeding, and dysarthria and dystonia improved). Patient 1: the Rankin score improved from 4 to 3, and UWDRS score from 79 to 45 Patient 2: the Rankin score improved from 4 to 2, and UWDRS score from 74 to 28	0
Modi et al.,[10] *Saudi J Kidney Dis Transpl*, 2015	India	1 (14 y)	Medici score, KFR, and MRI	1 y	Major improvement (pre-LT score: 14/30; post-LT: 27/30). Walked and went back to school 6 months after LT. No need for tracheostomy after LT. MRI improvement. KFR disappeared 9 months after LT	1 (12 months after LT after stopping medications for 2 months)
Mocchegiani et al.,[11] *Transplant Proc*, 2014	Italy	1 (19 y)[a]	Medici score, KFR, and MRI	4 y	Major improvement (pre-LT score: 8/30; post-LT score: 28/30) with full recovery of neuropsychiatric symptoms. MRI: significant improvement KFR disappearance	0
Guillaud et al.,[8] *J Hepatol*, 2014	France	6 (range 14.5–42 y)	Clinical examination and MRI	Up to 79 mo	3 had major clinical and MRI improvement	3 (sepsis 2, 4, and 36 mo after LT)
Cheng et al.,[12] *Transplantation*, 2009	China	2	Medici score	6 mo	1 complete improvement 1 partial improvement	0
Duarte-Rojo et al.,[13] *Rev Gastroenterol Mex*, 2009	Mexico	2[a]	Clinical evaluation and MRI	80 mo	Complete clinical remission and MRI improvement	0
Marin et al.,[14] *Transplant Proc*, 2007	Spain	4	Clinical examination, MMSE, and MRI	1–17 y	1 had an incomplete neurologic improvement and is alive 17 y after LT 3 became normal at 6 mo MRI improvement in all	0
Suess et al.,[15] *Mov Disord*, 2007	Germany	1 (31 y)	Clinical examination and MRI	2 y	Major improvement. Slight dysarthria and mild tremor MRI improvement	0
Suzuki et al.,[16] *Transplant Proc*, 2003	Japan	1 (17 y)	Clinical examination and MRI	12 mo	Major neurologic improvement—residual symptoms (dysarthria and tremor). MRI improvement	0
Schumacher et al.,[17] *Transplant Proc*, 2001	Germany	4 (range 15–34 y)	Clinical examination	Range 5–10 y	4 major improvement (more rapid in young patients and mild residual symptoms in 2)	0
Robles et al.,[18] *Transplant Proc*, 1999	Spain	4	Clinical and neuropsychiatric examination and MRI	Range 1–9 y	2 fully recovered and went back to work 1 improved incompletely	1 (sepsis 4 months after LT)
Bax et al.,[19] *Neurology*, 1998	Germany	1 (14 y)	Neurologic score and MRI	1 y	Major improvement with almost normal neurologic status Stable MRI	0
Kassam et al.,[20] *Can J Gastroenterol*, 1998	United States	1 (22 y)[a]	Clinical and neuropsychiatric examination and CT	43 mo	Progressive neurologic improvement Psychiatric disturbances persisted with behavioral disinhibition	1 (suicide)
Schilsky et al.,[21] *Hepatology*, 1994	United States	1 (25 y)	Neurologic examination	ND		1 (ruptured splenic artery aneurysm)
Mason et al.,[22] *Dig Dis Sci*, 1993	United States	1 (27 y)	Neurologic examination	6 wk	Early onset of improvement	1 (ruptured splenic artery aneurysm)

[a] Patient with neuropsychiatric symptoms.
Abbreviations: KFR = Kayser-Fleischer ring; LT = liver transplantation; Medici score = neurologic scoring system; ND = no data; UWDRS = Unified Wilson's Disease Rating Scale.

was also recorded.[26,27] Imaging data from a 1.5T brain MRI with fluid attenuated inversion recovery (FLAIR) sequences were collected, and hypersignal lesions were examined to evaluate their dissemination. All MRI scans were reviewed by 2 experts of the NRCWD (A.P. and F.W.) who calculated the brain MRI score.[26] A point was attributed to each bilateral location to define a score from 0 to 6. The different regions of interest were the lenticular nucleus, the caudate nucleus, the thalamus, the mesencephalon, the pons, and the dentate nucleus. The presence of a bilateral FLAIR hyposignal in the lenticular nucleus indicative of necrosis was also recorded as well as cortical lesions in FLAIR sequences. Type and number of drugs (D-penicillamine, trientine, and zinc acetate), occurrence of severe sepsis, admission to an intensive care unit (ICU), need for tracheostomy, and nutritional support through gastrostomy or jejunostomy before LT were reviewed.

Liver transplantation

All patients received grafts from cadaveric donors and were treated with standard immunosuppression including steroids during the early post-LT period, calcineurin inhibitors, and mycophenolate mofetil. If they were resumed after LT, type and duration of treatment with chelators or zinc acetate were noted. A systematic histopathologic analysis of the native liver was performed, and measurements of intrahepatic copper levels were documented.

Outcomes following LT

Duration of follow-up, mRS score, UWDRS score, results of liver function tests (prothrombin time and total bilirubin), KFR score, copper metabolism, and brain MRI score were reviewed for each patient. Late complications after LT were analyzed. Number and cause of death and the interval between transplantation and death were retrieved.

The coprimary outcomes were (1) the overall survival rate and (2) the disability at the last follow-up after LT as assessed by the mRS and the UWDRS. A decrease of UWDRS scores above 66% was arbitrarily considered as major improvement, a 33%–65% decrease as moderate improvement, and a decrease below 33% as mild improvement or stable condition. The secondary outcomes were the KFR and the brain MRI at the last follow-up.

Prognosis factors

Prognosis factors were assessed by comparing baseline data of patients who survived (group 1) and those who died (group 2). Within group 1, baseline data of patients with a major improvement were further compared with those with only moderate or poor outcome.

Statistical analysis

Quantitative variables were expressed as median (interquartile range [IQR]) and categorical variables as frequencies and percentages. The overall survival rate was estimated using the Kaplan-Meier method starting from the date of LT to the date of death or the last follow-up visit. Comparisons between 2 groups were made using the Mann-Whitney *U* test for continuous variables and the Fisher exact test for qualitative variables. Paired comparisons to test the evolution of continuous variables used the paired Wilcoxon test. The Kruskal-Wallis test by ranks was used for comparing the time period between worsening and LT in the 3 groups of patients with different improvement at the last follow-up. Statistical testing was performed at the 2-tailed level of 0.05. Data were analyzed using the SAS software package, release 9.3 (SAS Institute, Cary, NC).

Data availability

Anonymized data not published within this article will be made available on request from any qualified investigator.

Results

Study population

Between June 1994 and June 2016, 435 patients with WD were included in the French WD Registry, and 131 presented a neurologic phenotype. Among them, 18 patients (10 men; median age 18.5 years [range 16–20.8 years]) underwent LT for strict neurologic indication. One was transplanted in 1994, 6 between 2002 and 2007, and 11 in the 2010–2016 period. Data from the 2 patients from Lyon have already been published.[9] Thirteen patients were de novo patients and presented a primary worsening with a median time between diagnosis and LT of 6.7 months (5.3–14.5 months). The median delay between their first neurologic symptoms and the diagnosis was 5 months (IQR 5–8 months); 5 patients had a secondary worsening with a median time between the beginning of aggravation and LT of 7 (5–7) months and a median time between the diagnosis of WD and LT of 84 (24–181) months. For the entire group of 18 patients, the median time between neurologic worsening and LT was 6.7 (5.3–14.5) months. Individualized data for every single patient are detailed in table 2.

Patient characteristics at inclusion before LT

The mRS score was 5 in 16 (89%) patients and 4 in 2 (11%) (figure 1). The median UWDRS score was 105 (79–117). The median MELD score was 8.5 (7–10.8). Seventeen (94.5%) patients were Child-Pugh A. One patient was Child B7 because of severe hypoalbuminemia (24 g/L). None of the patients presented an episode of liver decompensation before LT. Fourteen patients (78%) had a jejunostomy or a gastrostomy and 10 (55.6%) a tracheostomy. Seven patients had severe sepsis before LT; 5 required an ICU admission in the month before LT with acute respiratory distress syndrome (ARDS). All patients had a circumferential KFR (median score 2). Brain MRI was abnormal in all patients with a median brain MRI score at 4.5 (IQR 3–5) and constant lenticular nucleus involvement. The mesencephalon, pons, caudate nucleus, and thalamus were abnormal in respectively 94.5%, 77.7%, 72.2%, and 50% of patients. All patients had abnormal copper balance and received specific decoppering therapy

Table 2 Detailed data of patients with WD at diagnosis and at inclusion before LT

Patient	At diagnosis					Treatment before LT (max dose + duration)			Time between worsening and LT, mo	Neurologic status before LT		
	Phenotype	Delay to diagnosis, mo	Age, y	UWDRS score	Rankin score	Treatment 1	Treatment 2	Treatment 3		Rankin score	UWDRS score	Major neurologic symptoms
Primary worsening												
1-M	Neuro	4	17	23	3	Trientine (1,200 mg/d, 9 mo)	DP (900 mg/d) + zinc acetate (100 mg/d), 4 mo		13	5	79	Dystonia, parkinsonism, and myoclonus
2-F	Neuro	9	16	29	3	Trientine (900 mg/d) + zinc acetate (100 mg/d), 5 mo	DP (1,800 mg/d, 17 mo)		22	5	75	Dystonia
3-M	Neuro	11	17	33	3	Trientine (1,200 mg/d, 12 mo)	Zinc acetate (200 mg/d, 8 mo)	DP (900 mg/d, 11 mo)	31	5	74	Dystonia and parkinsonism
4-M	Neuro	5	15	27	3	Trientine (900 mg/d, 5.5 mo)	Zinc acetate (200 mg/d, 0.5 mo)		6	5	117	Parkinsonism and dystonia
5-M	Neuro	6	39	43	3	DP (900 mg/d, 11 mo)	Trientine (900 mg/d) + zinc acetate (150 mg/d), 6 mo		17	5	118	Parkinsonism
6-M	Neuro	10	18	41	3	DP (900 mg/d, 6 mo)			6	5	104	Dystonia and parkinsonism
7-M	Neuro	2	19	37	2	DP (300 mg/d; 1 mo, stopped due to side effects: ageusia and insomnia)	Trientine (900 mg/d, 5 mo)		6	5	110	Parkinsonism and dystonia
8-F	Neuro	8	23	19	2	DP (900 mg/d, 10 mo)	Trientine (900 mg/d, 5 mo)		15	4	61	Chorea, tremor, and dystonia
9-F	Neuro	22	16	62	4	DP (900 mg/d, 2 mo)			2	5	93	Dystonia, parkinsonism, and behavioral troubles
10-F	Neuro	12	11	15	1	DP (900 mg/d, 5 mo)			5	4	75	Parkinsonism and dystonia
11-F	Neuro	4	14	15	1	Trientine, 1,200 mg/d, 8 mo			8	5	136	Behavioral troubles, parkinsonism, and dystonia
12-M	Neuro	10	16	78	4	DP (900 mg/d, 6.3 mo)			6,3	5	96	Parkinsonism and dystonia

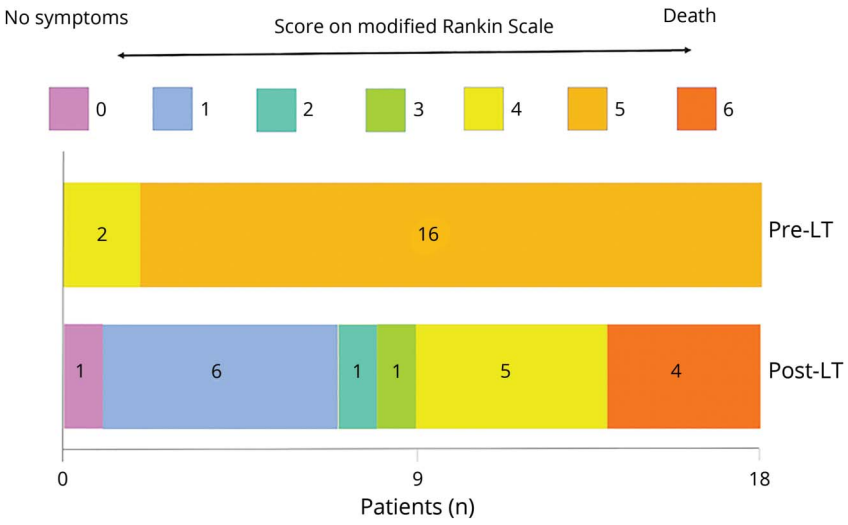
Continued

Table 2 Detailed data of patients with WD at diagnosis and at inclusion before LT *(continued)*

Patient	At diagnosis					Treatment before LT (max dose + duration)			Time between worsening and LT, mo	Neurologic status before LT		
	Phenotype	Delay to diagnosis, mo	Age, y	UWDRS score	Rankin score	Treatment 1	Treatment 2	Treatment 3		Rankin score	UWDRS score	Major neurologic symptoms
13-F	Neuro	21	17	57	3	Trientine (900 mg/d, 2 mo)			2	5	112	Dystonia and parkinsonism
Secondary worsening after interruption of treatment[a]												
14-M	Hepato	7	13	0	0	DP (600 mg/d, 2 mo, stopped due to side effect: thrombopenia)	Trientine (900 mg/d; 7 mo; then, the patient stopped the treatment for 4 mo	Trientine (900 mg/d) + zinc acetate (100 mg/d), 7 mo[b]	7	5	129	Dystonia
15-F	Hepato	2	10	0	0	DP (900 mg/d, 11 y, low compliance)	Zinc acetate (150 mg/d, 4 y, low compliance)	DP 900 mg/d, 12 mo[b]	12	5	111	Chorea and tremor
16-F	Hepato	4	6	0	0	DP (1,200 mg/d, 15 y, low compliance)	Zinc acetate (150 mg/, 3 mo[b]		3	5	127	Dystonia
17-M	Hepato	1	19	0	0	DP (900 mg/d, 1 y, stopped due to side effect: myasthenia)	Trientine (900 mg/d) + zinc acetate (150 mg/d), 5 y, low compliance	Trientine (900 mg/d) + zinc acetate (150 mg/d), 24 mo[b]	24	5	115	Dystonia, tremor, and behavioral troubles
18-M	Hepato	14	18,5	0	0	DP (900 mg/d, 10 mo, stopped due to side effect: proteinuria)	Trientine (900 mg/d, low compliance, 5 mo and stopped for 2 mo	Trientine (900 mg/d, 7 mo[b]	7	5	105	Parkinsonism, dystonia, and frontal syndrome

Abbreviations: DP = D-penicillamine; LT = liver transplantation; UWDRS = Unified Wilson's Disease Rating Scale; WD = Wilson disease.
[a] Patients with a liver phenotype at the time of diagnosis who have progressed to a neurologic phenotype after discontinuation of treatment.
[b] Treatment reintroduced after apparition of neurologic symptoms.

Figure 1 mRS scores before and after LT in the 18 patients with WD

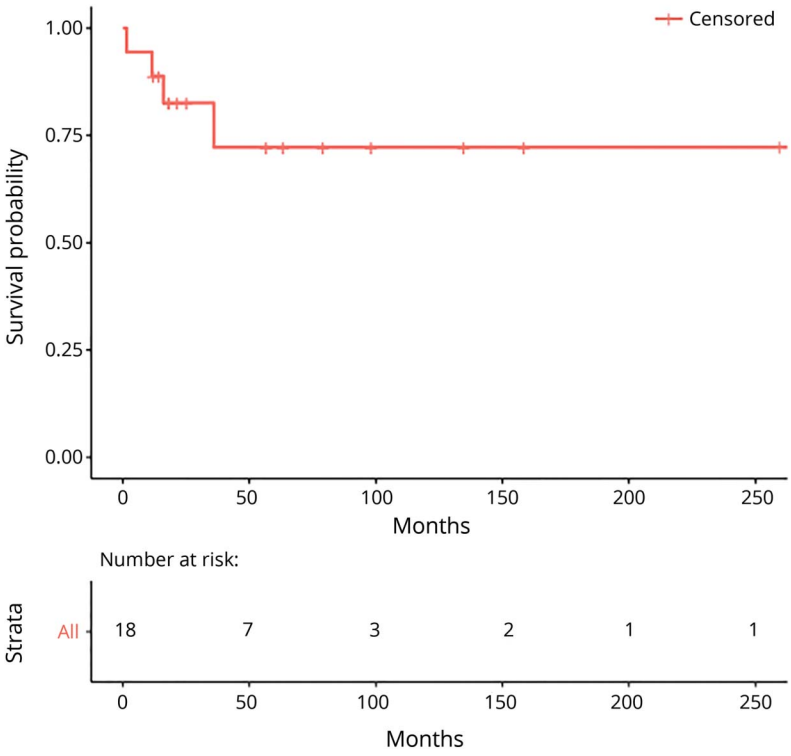


LT = liver transplantation; mRS = modified Rankin Scale; WD = Wilson disease.

before LT. The median number of decoppering drugs used before LT was 2 (1–3). The median (IQR) daily doses of the different treatments were D-penicillamine 900 mg (900–1,050), trientine 900 mg (900–1,200), and zinc acetate 150 mg (150–200). Histopathologic data of the explanted liver (available in 9 patients) demonstrated cirrhosis in all patients with mild activity including widespread fibrosis with nodular parenchyma median intrahepatocyte copper value was elevated (2.9 μmol/g of dry tissue [IQR 1.8–6.7 μmol/g]; N: 0.2–0.9).

Following LT, all patients received standard immunosuppression combining corticosteroid therapy for a limited time, a calcineurin inhibitor, and mycophenolic acid. Decoppering

Figure 2 Survival rate of patients with WD after LT for neurologic indication



LT = liver transplantation; WD = Wilson disease.

Table 3 Detailed data of patients with WD at the last follow-up

Patient	Outcome at the last follow-up				
	Duration of follow-up since LT, mo	Chelator/zinc resumed after LT (name, dose, and duration)	Rankin score	UWDRS score	Global outcome
Primary worsening					
1-M	158.4	No	1	10	Major improvement
2-F	63.2	No	1	48	Moderate improvement
3-M	56.7	No	1	15	Major improvement
4-M	36	Yes, trientine 600 mg/d, until death	6	—	Death
5-M	16	No	6	—	Death
6-M	11.5	No	6	—	Death
7-M	25	No	4	56	Moderate improvement
8-F	21.4	Yes, trientine 600 mg/d, still ongoing	4	53	Slight/no improvement
9-F	18	Yes, trientine 600 mg/d, still ongoing	2	30	Major improvement
10-F	18	No	1	13	Major improvement
11-F	18.2	No	4	77	Moderate improvement
12-M	14	Yes, DP 600 mg/d, still ongoing	4	93	No improvement
13-F	12	No	3	38	Major improvement
Secondary worsening after interruption of treatment[a]					
14-M	158.4	No	1	28	Major improvement
15-F	134.6	Yes, zinc acetate, 150 mg/d, 1 mo	1	18	Major improvement
16-F	78.9	No	4	82	Moderate improvement
17-M	268.3	No	0	39	Major improvement
18-M	1.5	No	6	—	Death

Abbreviations: DP = D-penicillamine; LT = liver transplantation; UWDRS = Unified Wilson's Disease Rating Scale; WD = Wilson disease.
[a] Patients with a liver phenotype at the time of diagnosis who have progressed to a neurologic phenotype after discontinuation of treatment.

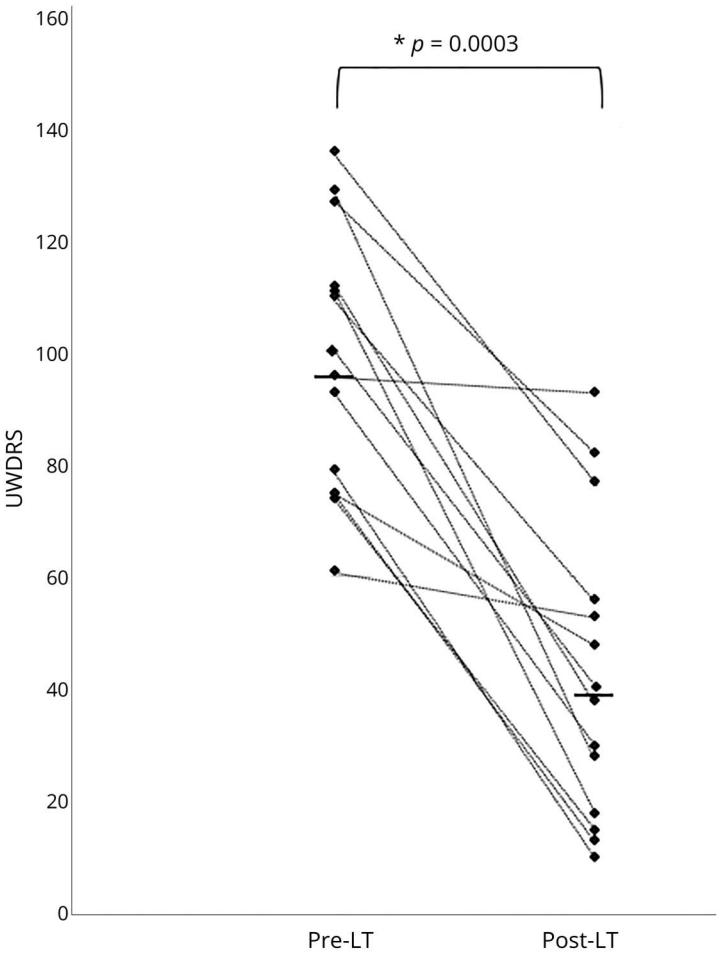
drugs were resumed in 5 patients due to the persistence of slightly elevated 24-hour urinary copper excretion. It was stopped 1 month after LT in 1 patient and continued in the others until the last visit.

Coprimary outcomes

Four patients (22%) deceased within a median interval of 13.8 (9–21) months after LT. The cumulated survival rate was 88.8% at 1 year, 82.5% at 1.5 years, and 72.2% at 3 and 5 years (figure 2). The cause of death was severe sepsis of pulmonary origin in all patients. All deceased patients had an ARDS in the month before the LT procedure.

At the last follow-up (median 40.9 [18.1–93.2] months), 14 patients (78%) were alive. Their median mRS score was statistically different from the pre-LT state (1.5 [1–4] vs 5 [5–5]) ($p < 0.0001$) (table 3); 9 patients (64%) had a score below 3 (figure 1). The median UWDRS score decreased

Figure 3 Evolution of the UWDRS score in the 14 patients with WD who survived



UWDRS = Unified Wilson's Disease Rating Scale; WD = Wilson disease.

from 96 (75–112) to 38 (18–56) ($p = 0.0003$). No patient had worsening of the UWDRS score at the last follow-up (figure 3). Eight patients had a major improvement (78% decrease of the UWDRS score), 4 had a moderate one (41% decrease), and 2 a mild improvement/stable status (8.1% decrease). Among the 3 patients with initial behavioral disturbances, 1 had persistent frontal disinhibition with attention deficit.

Secondary outcomes

The ophthalmologic KFR score statistically improved after LT, with a median score of 1 (0–2) at the last follow-up ($p = 0.0007$). Five patients had a complete regression and 2 a reduction of the KFR after a median time of 98 (60–146.5) months. The other patients had a stable score, but their follow-up was shorter (median 12 [9.1–16.3] months).

The brain MRI score significantly improved after LT ($p = 0.0007$), reflecting the disappearance of hyperintensities in some location. The first 7 patients transplanted (median follow-up of 98 [71–146.5] months) had a 75% decrease of the brain MRI score, whereas the last 7 patients with a shorter median follow-up of 18 (16–19.8) months had only a 33% reduction of their score. For the group of survivors, the brain MRI score statistically improved at the level of the nucleus caudate ($p = 0.008$), the pons ($p = 0.009$), the thalamus ($p = 0.03$), and the mesencephalon ($p = 0.01$). A lenticular nucleus hyposignal indicative of local necrosis persisted in 5/5 patients and appeared in 1; 1 patient presented a persistent cortical lesion (table 4).

Laboratory testing

Prothrombin time and bilirubin levels were normal at the last follow-up. Cupremia and Cp values normalized in all patients, whereas 24-hour urinary copper excretion was slightly elevated in 7 patients at the last follow-up (table 4).

Late complications

One patient had arterial complications of the graft and needed to be retransplanted 7 and 11 months after the first LT. One patient developed a Burkitt lymphoma 3 years after LT. He is currently considered into complete remission 7 years after LT. One patient with millimetric frontal cortical hyperintensities at baseline developed 8 months after LT complex partial seizures due to the extension of the cortical lesions. Two years after LT, epilepsy was controlled, the UWDRS

Table 4 Baseline data and long-term follow-up of the 14 patients (group 1) who survived after LT

	Pre-LT status	Post-LT status	*p* value
Duration of the follow-up, mo	—	40.9 (18.1–93.2)	—
mRS score	5 (5–5)	1.5 (1–4)	<0.0001
UWDRS score	96 (75–112)	38 (18–56)	0.0003
KFR score	2 (2–2)	1 (0–2)	0.0007
Brain MRI score	4 (3–5)	1.5 (1–2)	0.0007
Brain localization (%)			
Lenticular nucleus (putamen and pallidum)	14 (100)	11 (78.6)	0.07
Caudate nucleus	9 (64.3)	2 (14.3)	0.008
Thalamus	6 (42.8)	1 (7.1)	0.03
Mesencephalon	13 (92.8)	7 (50)	0·01
Pons	11 (78.5)	4 (28.5)	0.009
Dentate nucleus	4 (28.5)	2 (14.2)	0.38
Cortex	1 (7.1)	1 (7.1)	ns
Brain MRI lenticular hyposignal (%)	5 (35.7)	6 (42.8)	ns
Copper metabolism			
Cu, μmol/L	1.7 (1.3–3.3)	15.2 (13.5–16.9)	<0.0001
CuU, μmol/L	6.1 (3.8–7.8)	0.4 (0.3–0.6)	<0.0001
ExCu, μmol/L	0.9 (0.5–1.1)[a]	0.9 (0.8–0.9)[a]	ns
Cp, g/L	0.10 (0–0.10)	0.20 (0.20–0.20)	<0.0001

Abbreviations: Cu = total serum copper (N: 12.7–22.2 μmol/L); CuU = urinary copper excretion (N: 0.02–0.40 μmol/L); Cp = ceruloplasmin (N > 0.20 g/L); ExCu = exchangeable copper (N: 0.62–1.15 μmol/L); KFR = Kayser-Fleischer ring; ns = statistically nonsignificant; LT = liver transplantation; mRS = modified Rankin Scale; UWDRS = Unified Wilson's Disease Rating Scale.
Values are median (interquartile range) unless otherwise indicated.
[a] Data available for 7 patients.

score improved, and the basal ganglia and mesencephalon hyperintensities were less pronounced.

Prognosis factors

Baseline data of the groups of patients who survived (group 1) or died (group 2) are summarized in table 5. Severe sepsis ($p = 0.011$) and ICU admission ($p = 0.001$) in the month before LT were significantly associated with death.

Within group 1, baseline demographic and clinical data, time between neurologic worsening and LT, laboratory features, KFR, and brain MRI scores did not significantly differ between patients with major, moderate, or mild improvement. Patients with moderate and mild improvement had a shorter follow-up compared with patients with major improvement ($p = 0.02$).

Discussion

The objective of this longitudinal retrospective study was to evaluate the efficacy of LT proposed as a rescue treatment in patients with WD without liver failure but extremely severe neurologic symptoms resistant to decoppering agents (chelators or zinc salts). It is currently the largest cohort published with a prolonged follow-up in this specific indication of pure neurologic presentation where patients were all bedridden and required constant nursing care and attention before LT. The decision for LT was motivated by the high risk of irreversible cerebral lesions or death in these patients as reported by Litwin et al.[5] In a cohort of 15 patients with early neurologic worsening despite medical treatment, the authors showed that outcomes depended on the severity of the neurologic involvement: patients with a UWDRS score >75 did not recover, and those with a score >97 died in less than 2 years.

The main result highlights that LT had a favorable effect in the majority of patients. For the 78% of patients still alive after a mean follow-up of almost 6 years, LT allowed patients to gain physical independence. Fifty-seven percent of patients with a severe initial mRS score close to 5 had a score below 2 at the last follow-up, indicating that they became independent

Table 5 Comparison of baseline data of patients with WD who survived (group 1) with those who died (group 2)

	Group 1	Group 2	*p* Value
Number	14	4	
Male	6 (43)	4 (100)	0.09
Age at diagnosis, y, median (IQR)	16 (13.2–17)	18.5 (17.2–24)	ns
Age at LT, y, median (IQR)	18 (16–20.5)	19.5 (18.3–25.2)	ns
Primary worsening	10/14 (71.4)	3/4 (75)	ns
Time between worsening and LT, mo, median (IQR)	6.7 (5–14.5)	6.5 (6–9.5)	ns
mRS score, median (IQR)	5 (5–5)	5 (5–5)	ns
UWDRS score, median (IQR)	96 (75–112)	111 (105–117.3)	ns
Major neurologic symptoms			
Dystonia	13/14 (93)	3/4 (75)	ns
Parkinsonism	8/14 (57)	4/4 (100)	ns
Tremor	3/14 (21.5)	0/4 (0)	ns
Behavioral troubles	3/14 (21.5)	0/4 (0)	ns
KFR score, median (IQR)	2 (2–2)	2 (2–2)	ns
MELD score, median (IQR)	8 (7–11.3)	10 (9.3–10.3)	ns
Brain MRI hypersignal score, median (IQR)	4 (3–5)	5 (4.5–5.2)	ns
Localization of brain MRI hypersignal			
Lenticular nucleus (putamen and pallidum)	14/14 (100)	4/4 (100)	ns
Caudate nucleus	9/14 (64.2)	4/4 (100)	ns
Thalamus	6/14 (42.8)	3/4 (75)	ns
Mesencephalon	13/14 (93)	4/4 (100)	ns
Pons	11/14 (78.6)	3/4 (75)	ns
Dentate nucleus	4/14 (28.5)	1/4 (25)	ns
Cortex	1/14 (7)	0	ns
Brain MRI lenticular hyposignal	5/14 (36)	2/4 (50)	ns
Medications used before LT, median (IQR)	2 (1–3)	2 (1.8–2.3)	ns
D-penicillamine	12/14 (86)	3/4 (75)	ns
Trientine	8/14 (57)	3/4 (75)	ns
Zinc acetate	7/14 (50)	2/4 (50)	ns
Procedures before LT			
Jejunostomy or gastrostomy	11/14 (78.6)	3/4 (75)	ns
Tracheostomy	6/14 (43)	4/4 (100)	0.09
Sepsis before LT	3/14 (21.4)	4/4 (100)	0.011
ICU admission within the month before LT	1/14 (7)	4/4 (100)	0.001
Liver pathology			
Mean intrahepatocyte copper value, μmol/g of dry tissue, median (IQR)	2.6[a] (1.9–5.8)	5.3[b] (3–6.2)	ns

Abbreviations: KFR = Kayser-Fleischer ring; ICU = intensive care unit; IQR = interquartile range; LT = liver transplantation; mRS = modified Rankin Scale; MELD = Model for End-stage Liver Disease; UWDRS = Unified Wilson's Disease Rating Scale; WD = Wilson disease.
Group 1: patients who survived; group 2: patients who died. Values are numbers (%) unless otherwise indicated.
[a] Data available for 6 patients.
[b] Data available for 3 patients.

for daily living activities with a mild handicap. In parallel, the UWDRS score improved by 80% in 8/14 patients. This result is in agreement with the results of the 32 case reports published since 1993, which focused on the neurologic outcome of patients with WD transplanted for neurologic reasons.[9–22] Based on clinical evaluation but rarely on objective scores using the UWDRS or mRS, the final outcome was reported as major improvement in 71% of survivors.

The patient survival rate at 1 year (88.8%) was similar to those published for LT in WD because of liver failure.[8,28–31] By comparison, the global 1-year survival rate of all patients (of all ages and for all indications) transplanted in France between 1993 and 2014 is 84.7% (95% confidence interval: 84.2%–85.2%) (data from the French Agence de Biomédecine agence-biomedecine.fr). In our study, the survival rate at 5 years was lower than those published for LT in WD because of liver failure by Arnon et al.[30] (90%), and Guillaud et al.[8] (87%) but similar to the one from Medici et al.[29] (76%) and Cheng et al.[12] (75%), and superior to Weiss et al.[28] study (65%). Long-term prognosis stays reasonable because the neurologic presentation was extremely severe with important brain and cornea copper overload. This severe neurologic pre-LT status contrasts with the liver disease. Indeed, cirrhosis was present in all patients on the explanted liver but with only a mild activity.

In our study, pulmonary infection with sepsis was the unique cause of death that occurred between 1.5 and 36 months after LT. The fragile general condition of the patients, dysphagia, and immunosuppression were the main risk factors for infection. In previous case reports, infection also appeared as the main reason because 4/32 patients died of sepsis.[9–22] Our results are further in line with Medici et al.,[29] who showed that sepsis is the main cause of death in the general transplant population and more specifically in WD patients with neurologic symptoms. Therefore, the prevention of pulmonary infection and sepsis before and after LT is extremely important. A systematic use of appropriate procedures (jejuno/gastrostomy for patients with swallowing difficulties, adequate nursing, etc.) allowed us to avoid a fatal outcome in the last 10 transplanted patients. Other causes of death reported after LT for a neurologic indication were in the literature suicide, withdrawal of all medications and rupture of a splenic artery aneurysm.[9–22]

In our cohort, as in reports of LT for neurologic indication, no clinical worsening of pre-LT symptoms was observed.[9–22] One of our patients had an extension of a cortical lesion and developed epilepsy. The cortical lesion increased transitorily within the first year of LT while basal ganglia lesions vanished.

Predictive factors should be defined to select patients with the best chance to be improved by LT. In our study, the presence of a sepsis before LT and an ICU admission within the month before LT were associated with a higher risk of death, whereas male sex and tracheostomy showed a statistical trend. Therefore, the decision of LT should consider the general medical condition of each patient, as prolonged immobilization due to severe neurologic disability and the presence of dysphagia are the main causative factors of severe sepsis and ICU admission. For comparison, baseline dystonia, brain MRI diffusion, and male sex have been reported as poor prognostic markers in patients with WD with severe neurologic impairment who were treated by chelating drugs or zinc salts.[6,32,33] No prognostic factor of good recovery was identified, but this may be due to the small size of our cohort. The main challenge remains to identify patients who will not respond to chelating agents to consider early LT before they are bedridden with severe dysphagia and sepsis.

The mechanisms underlying the effect of LT on brain dysfunction in patients with WD with severe neurologic symptoms remain elusive. In the brain, both ATPases (ATP7A and ATP7B) transporters are coexpressed, with a predominance of ATP7A.[4] After LT, the brain seems to regulate its copper metabolism. The fading of pathologic images on brain MRI after LT points to a reversal of copper overload in the brain. A possible explanation is that ATP7A might compensate for the lack of ATP7B in a brain not submitted to copper overload because of liver dysfunction. This hypothesis is endorsed by observations in ATP7B−/− KO mice where ATP7A partially compensates the lack of ATP7B in Purkinje cells of the cerebellum.[34]

Although our study is the largest series ever published with the use of objective scores, it has some limitations: small number of patients, retrospective evaluation of the patients, and lack of a control group. The rarity of the disease explains the limits as in France only 906 prevalent cases were identified.[35]

In conclusion, this report shows that LT is a rescue therapeutic option that should be carefully discussed in selected patients with continuous neurologic worsening over months despite adequate decoppering therapies. The management of transplanted patients with severe neurologic WD is complex and should be handled by experienced multidisciplinary teams to improve long-term survival. LT may not be the solution for every patient but has a place as a rescue therapy while waiting for future therapies.

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References

1. Poujois A, Woimant F. Wilson's disease: a 2017 update. Clin Res Hepatol Gastroenterol 2018;42:512–520.
2. Weiss KH, Stremmel W. Clinical considerations for an effective medical therapy in Wilson's disease. Ann N Y Acad Sci 2014;1315:81–85.
3. Chen DB, Feng L, Lin XP, et al. Penicillamine increases free copper and enhances oxidative stress in the brain of toxic milk mice. PLoS One 2012;7:e37709.
4. Poujois A, Mikol J, Woimant F. Wilson disease: brain pathology. Handb Clin Neurol 2017;142:77–89.
5. Litwin T, Dzieżyc K, Karliński M, Chabik G, Czepiel W, Członkowska A. Early neurological worsening in patients with Wilson's disease. J Neurol Sci 2015;355:162–167.
6. Prashanth LK, Taly AB, Sinha S, et al. Prognostic factors in patients presenting with severe neurological forms of Wilson's disease. QJM 2005;98:557–563.
7. Svetel M, Pekmezović T, Petrović I, et al. Long-term outcome in Serbian patients with Wilson disease. Eur J Neurol 2009;16:852–857.
8. Guillaud O, Dumortier J, Sobesky R, et al. Long term results of liver transplantation for Wilson's disease: experience in France. J Hepatol 2014;60:579–589.
9. Laurencin C, Brunet AS, Dumortier J, et al. Liver transplantation in Wilson's disease with neurological impairment: evaluation in 4 patients. Eur Neurol 2017;77:5–15.
10. Modi P, Sutariya V, Tank A. Orthotropic liver transplantation for intractable neurological manifestations of Wilson's disease. Saudi J Kidney Dis Transpl 2015;26:556–559.
11. Mocchegiani F, Gemini S, Vincenzi P, et al. Liver transplantation in neurological Wilson's disease: is there indication? A case report. Transpl Proc 2014;46:2360–2364.
12. Cheng F, Li GQ, Zhang F, et al. Outcomes of living-related liver transplantation for Wilson's disease: a single-center experience in China. Transplantation 2009;87:751–757.
13. Duarte-Rojo A, Zepeda-Gómez S, García-Leiva J, et al. Liver transplantation for neurologic Wilson's disease: reflections on two cases within a Mexican cohort. Rev Gastroenterol Mex 2009;74:218–223.

14. Marin C, Robles R, Parrilla G, Ramírez P, Bueno FS, Parrilla P. Liver transplantation in Wilson's disease: are its indications established? Transplant Proc 2007;39: 2300–2301.
15. Suess T, Bokemeyer M, Schomerus G, et al. Video documented follow-up of liver transplantation in Wilson's disease with predominant neurological manifestation. Mov Disord 2007;22:1036–1038.
16. Suzuki S, Sato Y, Ichida T, Hatakeyama K. Recovery of severe neurologic manifestations of Wilson's disease after living-related liver transplantation: a case report. Transpl Proc 2003;35:385–386.
17. Schumacher G, Platz KP, Mueller AR, et al. Liver transplantation in neurologic Wilson's disease. Transpl Proc 2001;33:1518–1519.
18. Robles R, Parrilla P, Sicilia J, et al. Indications and results of liver transplants in Wilson's disease. Transpl Proc 1999;31:2453–2454.
19. Bax RT, Hässler A, Luck W, et al. Cerebral manifestation of Wilson's disease successfully treated with liver transplantation. Neurology 1998;51:863–865.
20. Kassam N, Witt N, Kneteman N, Bain VG. Liver transplantation for neuropsychiatric Wilson disease. Can J Gastroenterol 1998;12:65–68.
21. Schilsky ML, Scheinberg IH, Sternlieb I. Liver transplantation for Wilson's disease: indications and outcome. Hepatology 1994;19:583–587.
22. Mason AL, Marsh W, Alpers DH. Intractable neurological Wilson's disease treated with orthotopic liver transplantation. Dig Dis Sci 1993;38:1746–1750.
23. Ferenci P, Caca K, Loudianos G, et al. Diagnosis and phenotypic classification of Wilson disease. Liver Int 2003;23:139–142.
24. Członkowska A, Tarnacka B, Möller JC, et al. Unified Wilson's Disease Rating Scale—a proposal for the neurological scoring of Wilson's disease patients. Neurol Neurochir Pol 2007;41:1–12.
25. Uyttenboogaart M, Stewart RE, Vroomen PC, De Keyser J, Luijckx GJ. Optimizing cutoff scores for the Barthel index and the modified Rankin scale for defining outcome in acute stroke trials. Stroke 2005;36:1984–1987.
26. Poujois A, Trocello JM, Djebrani-Oussedik N, et al. Exchangeable copper: a reflection of the neurological severity in Wilson's disease. Eur J Neurol 2017;24:154–160.
27. El Balkhi S, Trocello JM, Poupon J, et al. Relative exchangeable copper: a new highly sensitive and highly specific biomarker for Wilson's disease diagnosis. Clin Chim Acta 2011;412:2254–2260.
28. Weiss KH, Schäfer M, Gotthardt DN, et al. Outcome and development of symptoms after orthotopic liver transplantation for Wilson disease. Clin Transpl 2013;27:914–922.
29. Medici V, Mirante VG, Fassati LR, et al. Liver transplantation for Wilson's disease: the burden of neurological and psychiatric disorders. Liver Transpl 2005;11:1056–1063.
30. Arnon R, Annunziato R, Schilsky M, et al. Liver transplantation for children with Wilson disease: comparison of outcomes between children and adults. Clin Transpl 2011;25:E52–E60.
31. Emre S, Atillasoy EO, Ozdemir S, et al. Orthotopic liver transplantation for Wilson's disease: a single-center experience. Transplantation 2001;72:1232–1236.
32. Burke JF, Dayalu P, Nan B, Askari F, Brewer GJ, Lorincz MT. Prognostic significance of neurologic examination findings in Wilson disease. Parkinsonism Relat Disord 2011;17:551–556.
33. Litwin T, Gromadzka G, Członkowska A. Gender differences in Wilson's disease. J Neurol Sci 2012;312:31–35.
34. Lutsenko S. Atp7b-/- mice as a model for studies of Wilson's disease. Biochem Soc Trans 2008;36:1233–1238.
35. Poujois A, Woimant F, Samson S, Chaine P, Girardot-Tinant N, Tuppin P. Characteristics and prevalence of Wilson's disease: a 2013 observational population-based study in France. Clin Res Hepatol Gastroenterol 2018;42:57–63.