Transpl Int (2002) 15: 188–195
DOI 10.1007/s00147-002-0415-z

ORIGINAL ARTICLE

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Persistence of mild parkinsonism 4 months after liver transplantation in patients with preoperative minimal hepatic encephalopathy: a study on neuroradiological and blood manganese changes

Received: 12 July 2001
Revised: 4 February 2002
Accepted: 26 February 2002
Published online: 4 April 2002

L.S. and F.L. contributed equally to this study. This work was partially supported by the Swiss National Science Foundation Grant no. 32–51090.97

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Abstract Pallidal hyperintensity at magnetic resonance imaging (MRI) correlates to blood manganese (Mn) levels and parkinsonian signs in patients with cirrhosis. Similarly, metabolite changes in the basal ganglia (BG) at proton spectroscopy are related to these neurological signs. The evolution of these abnormalities after liver transplantation (OLT) is incompletely described. We evaluated 14 unselected consecutive patients with cirrhosis (minimal hepatic encephalopathy [HE] $n=8$, no HE $n=6$) before and 4 months after successful OLT for the evolution of parkinsonism using a validated scale (the United Parkinson's Disease Rating Scale, or UPDRS). Pallidal intensity at MRI, spectroscopic changes in the BG at magnetic resonance spectroscopy (MRS), and whole blood manganese concentrations were measured. After OLT in patients with preoperative minimal HE, the UPDRS scores improved, but mild parkinsonism persisted (16.1 ± 3.6 to 6.2 ± 4.8, $P < 0.05$). Pallidal hyperintensity remained abnormal in 5/8 of cases, but spectroscopic changes normalized in all patients. Blood Mn remained elevated in 4/6 patients. In patients without HE, UPDRS values remained negligible (2.42 ± 1.5 to 2.5 ± 1.4). Pallidal hyperintensity normalized in 7/8 patients and spectroscopic changes normalized in all patients. Blood Mn remained elevated in 5/6 patients. Four months after successful OLT, patients with preoperative minimal HE and severe pallidal hyperintensity showed persistent mild parkinsonism. The role of blood manganese determination appears limited in the monitoring of MRI and parkinsonian signs changes after OLT.

Keywords Liver transplantation · Hepatic encephalopathy · Basal ganglia · Magnetic resonance imaging · Proton spectroscopy · Manganese

Introduction

Hepatic encephalopathy (HE) is a major complication of cirrhosis, present in an important proportion of liver transplant candidates [1]. Clinically, HE is a neuropsychiatric disorder typically characterized by a fluctuating level of consciousness, deterioration of intellectual function, and alteration in sleep pattern. In addition, clinical manifestations of HE include movement abnormalities such as bradykinesia, rigidity, tremor, and speech disturbances [2, 3], pointing towards specific alterations of basal ganglia (BG) in these patients.

A majority of patients with cirrhosis show bilateral pallidal hyperintensities at magnetic resonance imaging (MRI) in T1-weighted images [3, 4, 5, 6, 7]. This neuroradiological finding is associated with abnormal

manganese (Mn) deposition in the pallidum [6, 8]. In addition, brain magnetic resonance spectroscopy (MRS) studies in these patients show a characteristic pattern of increased glutamine and decreased choline and myoinositol resonances [9, 10, 11]. These changes parallel the degree of cognitive impairment and are believed to be the consequence of increased ammonia metabolism and cellular osmotic dysequilibrium [12].

Liver transplantation (OLT) is considered the optimal therapy for endstage liver disease [13]. It represents the treatment of choice for the HE syndrome, as removal of the diseased liver corrects the metabolic disturbances responsible for the clinical manifestations of HE. In addition, the lack of histological neuronal damage supports the reversible character of HE [14]. Although overt clinical signs of HE disappear after OLT, careful postoperative examination may point to persistent subtle neurological [15] and neuropsychological problems [16, 17, 18]. These signs may be attributed to prolonged exposition to gut-derived neurotoxins [19], alcohol [20], or postoperative complications due to infectious, vascular, or drug-induced causes [21]. Thus, a comprehensive preoperative neurological examination is mandatory to interpret accurately post-transplantation neurological troubles.

Blood Mn levels are elevated in a majority of patients with cirrhosis [3, 6, 22] and correlate with pallidal hyperintensities at MRI [3]. A role for BG dysfunction in these patients is suggested by the correlations between MRI and MRS alterations and parkinsonian signs [23].

After successful OLT, neurospectroscopic alterations at MRS normalize within weeks [24] or months [25], but more rapidly than cerebral MRI hyperintensities [25, 26]. Except for a pediatric case report [27], the evolution of blood Mn and parkinsonism after OLT has not been described in detail.

The aim of this study was to assess the evolution of parkinsonian signs, pallidal hyperintensity, MRS alterations in the BG, and whole blood Mn concentrations in an unselected population of patients with cirrhosis before and 4 months after successful OLT.

Patients and methods

Patients

From December 1997 to October 1998, 30 consecutive patients with biopsy-proven cirrhosis were evaluated for OLT in our hospital. The indications for OLT were: endstage liver disease in 17, hepatocellular carcinoma in nine, and primary biliary cirrhosis in two. For technical reasons ($n=3$), claustrophobia ($n=2$), refusal to participate ($n=2$), or right-sided hemiparesis ($n=1$), eight patients did not complete the study. The clinical and neuroradiological data of 19 patients before OLT are detailed in a recent publication [23]. Of the remaining 22 patients, 14 underwent OLT and constituted our study group. Their characteristics are summarized in Table 1. The severity of liver disease was determined according to the Child-Pugh score [28], and the Child class was based on the albumin and bilirubin levels, prothrombin time, presence of HE, and ascites. Patients with alcoholic cirrhosis were abstinent for more than 6 months, and all patients were free of neuroactive drugs. Nine patients were on chronic oral lactulose therapy. The hepatic encephalopathy status was determined using a neurological examination and neuropsychological tests, as detailed in the section "Neurological assessment." Both OLT surgical technique and postoperative care were in accordance with the present standard of hepatic surgery [29]. Immunosuppression consisted of monitored doses of cyclosporine A or tacrolimus, azathioprine or mycophenolate mofetil, and methylprednisolone in tapered doses. Episodes of rejection were treated by boluses of methylprednisolone. Follow-up liver biopsy was performed after OLT when clinically indicated.

The study protocol was approved by the Ethics Committee of the Hôpitaux Universitaires de Genève in 1997 and performed in accordance with the ethics standard of the Declaration of Helsinki. Written informed consent was obtained from each patient or from the patient's relatives in case of overt HE.

Neurological assessment

The assessment included a detailed neurological examination, neuropsychological tests, and the Unified Parkinson's Disease Rating Scale (UPDRS), a currently accepted and validated clinical scale for the evaluation of patients with Parkinson's disease [30]. The neurological examination was performed while the patients were in stable condition by senior neurologists (R.D.P, P.B, F.V.) trained in the evaluation of liver transplantation candidates, in order to exclude neurological disorders other than HE. The mental state was assessed semiquantitatively using the Parson-Smith classification as modified by Conn et al. [31]. The neuropsychological examination was performed using the Trail tests A and B, a recommended method to assess the presence of subtle neurological deficits in patients with cirrhosis [32]. These tests measure cognitive

Table 1. Patient characteristics ($n=14$). *HCC* hepatocellular carcinoma, *HE* hepatic encephalopathy, *OLT* orthotopic liver transplantation

	Minimal HE[a]	NO HE
Mean age (range)	55 (44–69)	53 (45–65)
Gender (M/F)	4/4	4/2
Hepatitis C-related cirrhosis	4	5
Other cause	4	1
Pugh score	8.9 ± 0.4	7 ± 0.5
Child class (A/B/C)	0/6/2	3/3/0
Serum bilirubin (μmol/L) (normal 6.8–25)	52 ± 9 < ?1 >	65 ± 35 < ?1 >
Alkaline phosphatase (IU/L) (normal 30–125)	148 ± 28	140 ± 18
Albumin (g/L)	30.6 ± 1	34.3 ± 2.1
Prothrombin (% of normal)	61 ± 3.8	73 ± 4
Presence of ascites	6/8	0/6
Indication for OLT		
Liver failure	8	3
HCC	–	3
Time interval between evaluation and OLT (days)	180 ± 40*	55 ± 9

[a]According to [29] and to age-normative data of Trailmaking tests [30]

*$P < 0.05$ vs patients without HE

motor abilities. In part A, the patient must connect numbers on a sheet of paper consecutively from 1 to 25. The test score is the time the patient needs to perform the test, including the time used to correct the errors. A low score indicates a good performance. In the Trail B test, the patient must connect in order a randomly presented series of numbers and letters in a minimum of time. As these tests are influenced by age and education, the results are interpreted using normative data [33]. Thus, according to the mental state evaluation and the Trail test results, six patients were neuropsychologically unimpaired, and eight were classified as having minimal HE, a term that is presently used for subclinical or grade 1 HE [34, 35].

The UPDRS has an excellent inter-rater reliability [36]. It evaluates the following signs related to movement abnormalities: speech, facial expression, action tremor and tremor at rest (face and four limbs), rigidity (four limbs), finger taps, hand grips, hand pronate/supinate, leg agility, rise from a chair, posture, gait, postural stability, and body bradykinesia. Each item was scored from 0 (normal) to 4 (worst) by one of the three neurologist (R.D.P, P.B, F.V.) experts in movement disorders and blinded to patients' biological and neuroradiological data. A similar neurological examination was repeated 4 months after OLT.

Neuroradiological studies

Magnetic resonance imaging was performed using a 1.5 Tesla Eclipse imaging system (Picker International, Cleveland, Ohio, USA). T1- (TR/TE 400/18 ms) and T2- (TR/TE 16/80 ms) weighted images were obtained in axial and sagittal planes (slice thickness 4 mm, interslice gap 0.5 mm, field of view 22 cm, matrix size 256×256 pixels). The pallidal intensity was normalized to the noise and expressed as signal-to-noise ratio. The images were interpreted by a neuroradiologist (J.D.) blinded to the patients' conditions and MRS results.

Magnetic resonance spectroscopy was performed during the same session. A short TE STEAM acquisition (TR/TE 1500/20 ms, 256 averages) was centered on the BG (12.3 ml) including the pallidum, putamen, and part of the thalamus. The spectral data analysis is described in detail elsewhere [23]. The following neurometabolites were measured: myoinositol (Ino), choline-containing compounds (Cho), N-acetylaspartate (NAA), glutamine-glutamate (Glx), and creatine (Cr). The results are given as ratios, with Cr used as an internal reference, as this metabolite has been reported not to vary significantly in patients with HE [11]. The interpretation of the data were performed by a blinded observer (F.L.). Neuroradiological studies, clinical examination and blood sampling were performed within 3 days while the patients were in stable condition.

Five healthy subjects (mean age 35 years, range 29 to 47) were used as controls for MRI and MRS results.

Biological analysis

The determination of Mn concentration was performed on whole blood obtained in a fasting state using flameless atomic absorption spectrophotometry [37] (Perkin Elmer AAS 4100 with a graphite heater HGA 700 and a wavelength of 279.5 nm, Norwalk, Conn., USA). All blood samples were collected in an identical fashion and blindly assayed. Normal values were obtained from a group of 15 age-matched controls. We measured Mn concentration in whole blood because only a small fraction is in the serum [38]. In addition, whole blood Mn concentrations correlate with pallidal hyperintensity in patients with cirrhosis [3]. Because Devenyi et al. [27] reported a normalization of blood Mn concentration 4 months after OLT in a pediatric case of Alagille syndrome, we decided to use the same time interval for the follow-up examination.

Statistical analysis

Neuroradiological results and blood Mn levels are expressed as median ± interquartile range and considered abnormal if above 2 SD of control values. The pre- and postoperative results were calculated using the non-parametric Wilcoxon's signed rank and Mann-Whitney U tests. Correlation between neuroradiological and clinical changes after OLT was performed using the Spearman's r-test. The level of statistical significance was set at $P < 0.05$.

Results

Although the differences were not significant, there was a trend towards a more advanced liver disease in patients with minimal HE. In this group, ascites was present in six patients, and liver function parameters including albumin, bilirubin, and prothrombin were severely altered. The mean time between the initial evaluation and OLT was 180 ± 40 days in the group of patients with pretransplantation minimal HE and 55 ± 9 days in the group of patients without preoperative HE. During this period, the degree of liver failure remained stable in all patients (data not shown). Liver transplantation was successful in all patients. The postoperative evaluation was performed after 4 months. All patients who received OLT for viral cirrhosis presented abnormal transaminases (three times normal value) and alkaline phosphatase (1.5 times normal value), as well as a histological recurrence of hepatitis C at follow-up.

Neurological examination

The evolution of the UPDRS in the first three transplanted patients was briefly described in a recent publication [23]. Here we provide the results of the UPDRS in 14 patients before and after successful OLT. Preoperatively, UPDRS alterations were mostly related to bradykinesia and rigidity, while tremor was negligible. Thus, the following items were typically abnormal: facial expression, rigidity of upper and lower limbs, finger taps, gait, and postural bradykinesia.

In the early postoperative period, except for mild transient tremor related to calcineurin inhibitors toxicity which responded to drug dosage reduction, no patient presented severe neurological complications (seizures, cerebral vascular disease, or coma). At follow-up examination, no patients had neuropsychological signs of HE (data not shown).

The evolution of the UPDRS before and 4 months after OLT in patients with minimal HE and in those without preoperative HE is depicted in Fig. 1. As mild

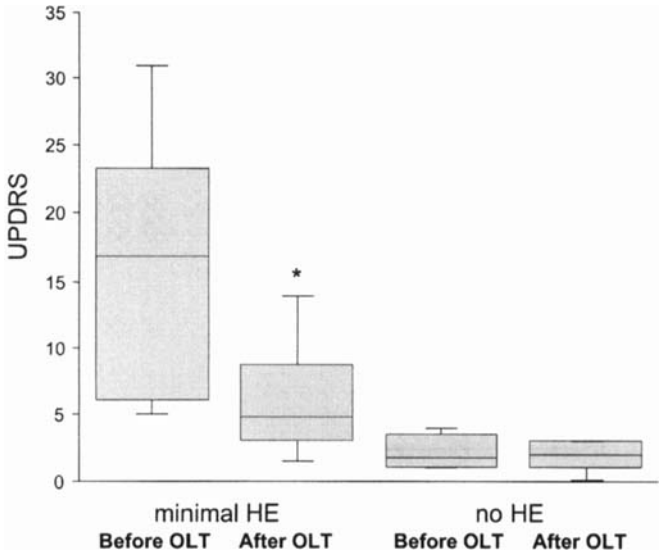

Fig. 1. Evolution of parkinsonian signs measured by the Unified Parkinson's Disease Rating Scale (UPDRS) before and 4 months after OLT in 14 patients. (*$P < 0.05$ vs preoperative values)

parkinsonism persisted in the former group, (16.1 ± 3.6 to 6.2 ± 4.8, $P < 0.05$), the UPDRS in the latter showed persistent negligible values (2.42 ± 1.5 to 2.5 ± 1.4).

Neuroradiological studies

MRI

Preoperatively, T1-weighted MR pallidal hyperintensity was observed in all patients with minimal HE and in 3/6 patients without HE. Four months after OLT, hyperintensities normalized in 3/8 patients with minimal HE and in 5/6 of those without HE. A typical complete regression of pallidal hyperintensity after OLT is illustrated in Fig. 2. Results in all patients are depicted in Fig. 3. No T2-weighted hyperintensities were observed in the study population.

MRS

All patients presented decreased Cho/Cr and Ino/Cr in the BG, but Glx/Cr and NAA/Cr were not altered. These metabolic alterations normalized 4 months after OLT in all patients, as shown in Fig. 4.

Manganese concentrations

Whole blood Mn was measured in 12 patients. Preoperative blood levels were elevated in 4/6 patients with minimal HE and in 2/6 of those without HE. After OLT, blood levels remained abnormal in 4/6 patients with preoperative minimal HE and in 5/6 of those without HE. The evolution of blood Mn concentrations is depicted in Fig. 5.

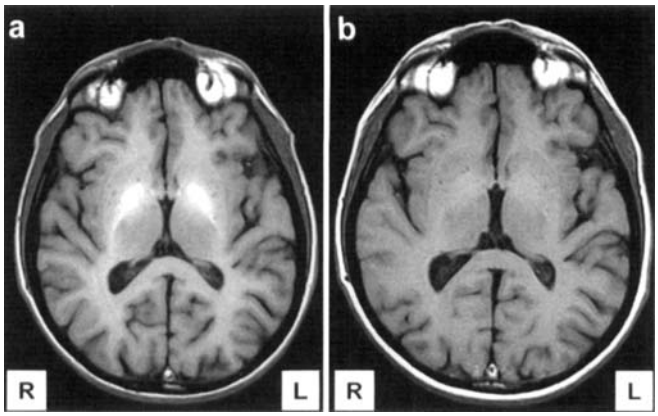

Fig. 2a, b. Typical MRI brain scan of a patient with cirrhosis and minimal HE showing pallidal hyperintensity (**a**), with complete resolution 4 months after successful OLT (**b**)

Correlations

The improvement in parkinsonian signs paralleled the changes in Cho/Cr ratio in the BG ($r = -0.8$, $P < 0.01$, see Fig. 6). No clinical correlations could be found with MRI or blood Mn changes.

Discussion

Hepatic encephalopathy is increasingly recognized as a disorder of neurotransmission [1, 39]. The preferential location of glial cell alterations in the BG [14], the predominant MRI changes in the pallidum [2, 3, 4, 5], and the redistribution of cerebral blood flow in the subcortical brain region [40] stimulated our interest to explore the functional significance of BG alterations in patients with cirrhosis. Thus, we recently demonstrated that MRI and MRS alterations present in the BG were related to parkinsonian signs in an unselected population of patients with cirrhosis [23].

Because HE is a metabolic disturbance, complete reversibility is expected after removal of the diseased liver. However, while clinical signs may disappear, subtle [15, 18] neurological impairment may persist after OLT. In the absence of a detailed preoperative neurological evaluation, these signs may be attributed to neurological complications [21] occurring in the postoperative period.

The evolution of movement disorders after OLT has been described in three anecdotal reports. Devenyi et al.

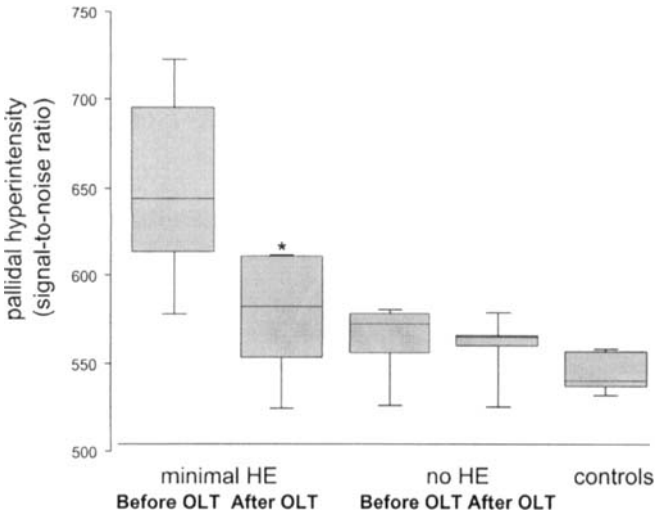

Fig. 3. Pallidal hyperintensities (expressed as signal-to-noise ratios) changes after OLT in patients with pretransplant minimal HE ($n=8$) and patients without HE ($n=6$)

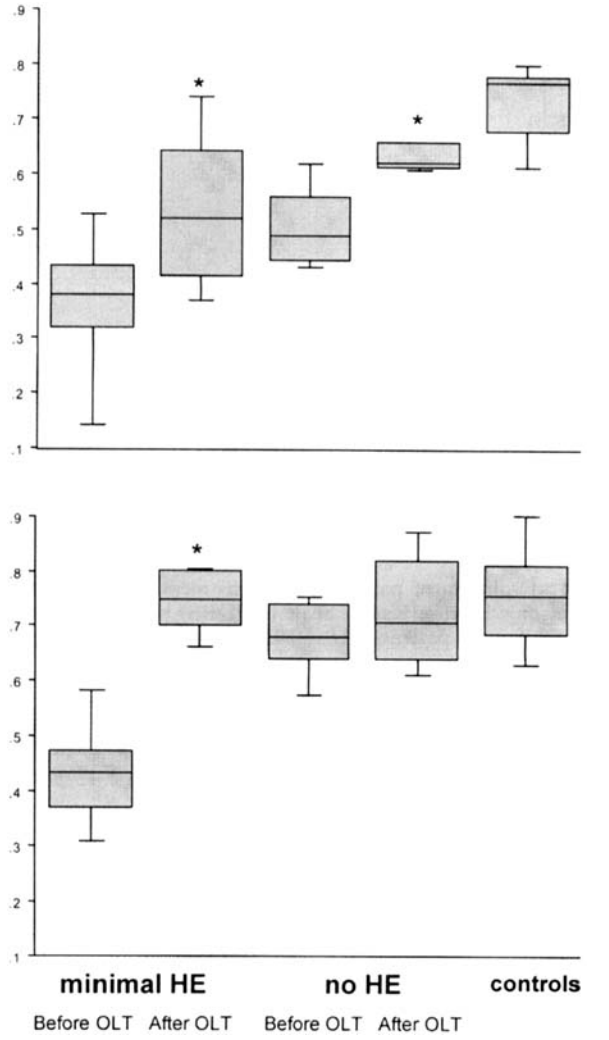

Fig. 4. Decreased Ino/Cr ratios (*upper figure*) and Cho/Cr ratios (*lower figure*) measured in the BG in patients with preoperative minimal HE ($n=8$) and in patients without pretransplant HE ($n=6$). *$P<0.05$ vs preoperative values

[27] reported a complete reversal of dystonia and tremor 4 months after OLT in a child with cholestatic liver disease, elevated blood Mn, and bilateral pallidal MRI hyperintensities. In another case report, liver transplantation in a patient with chronic hepatocerebral degeneration was followed by an improvement (but not a normalization) in both neurocognitive and motor functions [41]. More recently, buccolinguofacial dyskinesia, hyper-reflexia, and asterixis reported in a 60-year-old female with primary biliary cirrhosis were no longer detectable 2 months after OLT [42]. We report here the evolution of parkinsonian signs (tremor, rigidity, and bradykinesia) in 14 consecutive unselected patients following successful OLT. In addition, we describe changes in whole blood Mn levels – a recently recognized neurotoxic substance in chronic liver disease – as well as neuroradiological alterations measured in the BG, an important brain region for the control of movement. The persistence of mild parkinsonism 4 months after successful OLT in patients with preoperative minimal HE is unexpected. Thus, we raise the hypotheses that (1) these neurological signs could be related to transplantation-related events, (2) these neurological abnormalities have delayed improvement after transplantation, and (3) neuronal cell damage occurred.

The most frequent neurotoxic manifestations of calcineurin inhibitors in liver transplant recipients consist of mental status changes and seizures in the early postoperative period [43, 44]. However, these immunosuppressive drugs are not associated with extrapyramidal dysfunction. A marked improvement in bradykinesia – an extrapyramidal sign – as well as other neurological aspects, was reported by Powell et al. [41] in a patient with chronic hepatocerebral degeneration 12 months after OLT. Thus, significant neurological improvement can be expected in the presence of neuronal cell damage. In chronic Mn intoxication [45], the persistence of bradykinesia and rigidity following the cessation of Mn exposure [46] may be explained by severe neuronal damage at autopsy [47]. Because patients with cirrhosis and HE present with pallidal Mn overload [6, 8], mild persistent parkinsonism after OLT could be related to neuronal cell damage in the BG.

Postoperative resolution of pallidal hyperintensity 4 months after OLT was observed in some but not all patients, which is consistent with previous results [24, 25]. In fact, restitution of normal signal intensity may take as long as 10 to 20 months after successful OLT [5]. In our patients, the evolution of pallidal hyperintensities was independent of parkinsonian sign changes. How-

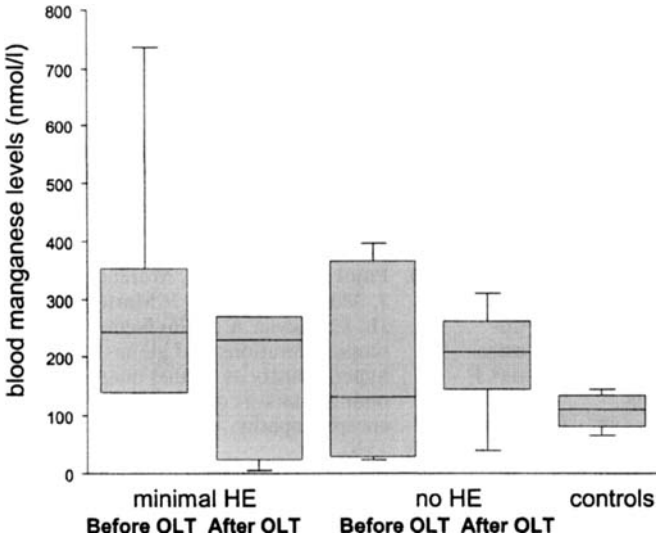

Fig. 5. Evolution of whole blood Mn levels before and 4 months after OLT

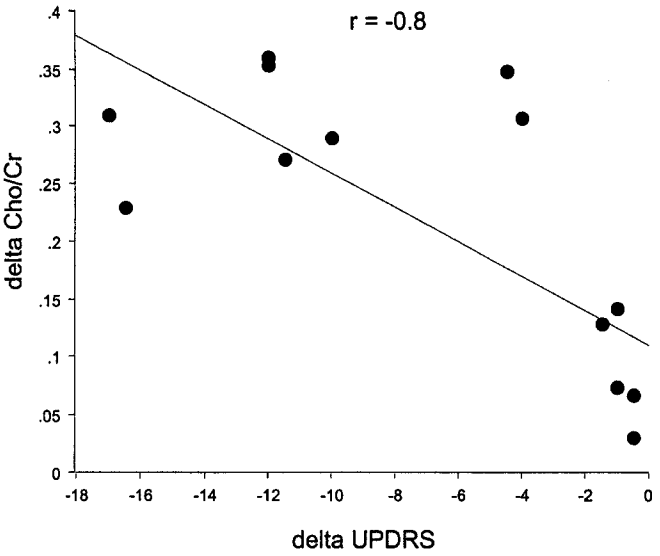

Fig. 6. Clinicoradiological correlation between changes in parkinsonian signs and changes in Cho/Cr in the BG (expressed as delta changes) 4 months after OLT

ever, it has to be kept in mind that MRI changes provide only a semiquantitative measurement of brain Mn overload.

Because our patients presented with minimal HE, spectroscopic abnormalities were confined to a reduction in Cho/Cr and Ino/Cr ratios without an increase in the glutamine-glutamate resonance. The correction of these neurospectroscopic abnormalities after OLT follows a different time course compared to MRI changes [5], as a return to normal values may be seen within weeks after OLT [25]. The exact significance of low Cho/Cr and Ino/Cr ratios observed in cirrhosis remains hypothetical. It has been suggested that the reduced Cho/Cr ratio could be related to disrupted cell membrane metabolism in response to astrocytes' protoplasmic organelle proliferation [10]. The decreased Ino/Cr may be the consequence of glial cell swelling and osmotic dysequilibrium [12]. Thus, the positive correlation between changes in Cho/Cr ratio and parkinsonian signs after OLT strongly suggests that altered choline metabolism in the BG plays a clinically significant role in the movement abnormalities observed in our patients.

Elevated blood Mn was observed in a substantial number of patients with cirrhosis [3, 6, 22]. In addition, elevated concentration of Mn has been reported in the cerebrospinal fluid in patients with cirrhosis and pallidal hyperintensities [48]. Both impaired hepatobiliary excretion [49] and portal-systemic shunting [50], which are typical features of chronic liver disease, have been demonstrated to influence Mn accumulation. The use of long-term parenteral nutrition with Mn supplementation has been associated with abnormal brain Mn accumulation [51, 52], possibly because regulatory mechanisms of Mn metabolism are bypassed. However, none of our patients received prolonged intravenous complete nutritional support.

Pathophysiological mechanisms of Mn neurotoxicity are still speculative. As removal of the diseased liver may correct the altered Mn metabolism, the persistence of high blood Mn concentrations 4 months after surgery was unexpected and raises the following hypotheses: (1) blood Mn determination after OLT had been done too early to detect significant changes, and (2) an associated condition might have contributed to high blood Mn. Indeed, the persistence of portal-systemic collaterals, known to facilitate Mn deposition several months after OLT [53], may have participated in the abnormal blood Mn levels. In addition, the presence of recurrent hepatitis in most of our patients after OLT could be associated with abnormal blood Mn concentrations consecutive to hepatocellular necrosis [38].

In fact, the present study does not support a major role for blood Mn dosage in the monitoring of parkinsonian signs in cirrhosis. Nevertheless, it must be stressed that blood Mn may not adequately reflect the accumulation of the metal in brain tissue and that other factors may participate in pathophysiological mechanisms involved in movement disorders in cirrhosis [42].

Acknowledgements We thank Frank Henri for excellent radiological technical assistance.

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