ELSEVIER

Magnetic Resonance Materials in Physics, Biology and Medicine 12 (2001) 10–15

MAGMA

Magnetic Resonance Materials in Physics, Biology and Medicine

www.elsevier.com/locate/magma

Chronic liver disease: relaxometry in the brain after liver transplantation

Vít Herynek [a,*], Milan Babiš [a], Pavel Trunečka [b], Karel Filip [b], Josef Vymazal [c], Monika Dezortová [a], Milan Hájek [a]

[a] *MR-Unit, Department of Diagnostic and Interventional Radiology, Institute for Clinical and Experimental Medicine, Vídeňská 1958/9, 140 21 Prague 4, Czech Republic*

[b] *Hepatogastroenterology Clinic, Institute for Clinical and Experimental Medicine, Vídeňská 1958/9, 140 21 Prague 4, Czech Republic*

[c] *Department of Stereotactic Neurosurgery, Hospital Na Homolce, Prague, Czech Republic*

Received 29 August 2000; received in revised form 20 November 2000; accepted 22 November 2000

Abstract

Relaxometry revealed changes in the basal ganglia in T_1 and T_2 relaxation times due to liver disease. Manganese is probably responsible for T_1 and T_2 shortening (as the concentration is known to be higher in both the liver and blood due to hepatic cirrhosis). The aim of this study was to follow possible recovery after liver transplantation by MR relaxometry. Together with a group of 20 healthy volunteers we scanned 53 patients before and after liver transplantation (some of them repeatedly). Both T_1 and T_2 values were evaluated in the basal ganglia, thalamus, and frontal white matter. T_1 relaxation timewas shortened by approx. 20–25% compared to the control group, probably the result of manganese deposition in the brain caused by hepatic cirrhosis. After liver transplantation the relaxation time recovered gradually with almost normal values reached approx. 2 years after surgery. T_1 recovery was observed in all evaluated structures. Similar results were observed with T_2 relaxation in the basal ganglia and thalamus. In the white matter T_2 remained low even 2 years after surgery.

Keywords: Hepatic cirrhosis; Liver transplantation; Brain; MR relaxometry

1. Introduction

Signal alterations in the brains of patients suffering from hepatic cirrhosis have been reported with computed tomography (CT) [1] and later with magnetic resonance images (MR) [2]. Changes in the signal intensity were observed in both T_1- and T_2-weighted images, particularly in the globus pallidus [3] which appears hyperintense on T_1-weighted scans due to strong T_1 shortening. Similar changes have also been reported for patients suffering from other chronic liver diseases (with or without encephalopathy), in long-term parenteral nutrition, and in occupational manganese (Mn) toxicity [4].

The origin of such changes in the basal ganglia were evaluated by T_1 and T_2 relaxometry, which confirmed that signal intensity changes arise from alterations in T_1 and T_2 relaxation times [3]. Substantial changes were found, especially in the basal ganglia, cortex, and white matter. Thus, the T_1-, T_2-shortening of relaxation times is believed to be caused by some paramagnetic substance, which could be shunted away from the liver. We, like many other authors [3,5–8] speculated that (based on the T_1/T_2 alteration ratio, [3]) the agent responsible for the alteration is probably Mn.

Increased levels of Mn have been reported postmortem in specific brain areas [5–7]. Similarities between Mn neurotoxicity and chronic hepatic encephalopathy suggest that this metal may have a role in pathogenesis. This hypothesis was confirmed by Rose et al. [8] who proved, both in an animal model and also in humans, that liver dysfunction results in Mn deposition in the basal ganglia. Higher Mn concentrations were also found in the brain and blood of cirrhotic and portocaval-shunted rats. The Mn concentration was elevated by 186% in the globus pallidus, by

* Corresponding author. Tel.: +420-2-61362701-2; fax: +420-2-4728224.

E-mail address: vit.herynek@medicon.cz (V. Herynek).

1352-8661/01/$ - see front matter
PII: S1352-8661(00)00134-4

66% in the putamen, and by 54% in the caudate nucleus in patients suffering from liver cirrhosis compared to controls.

Besides metabolic problems, liver cirrhosis also affects the mental ability of the patient. Fortunately, chronic encephalopathy as a complication of cirrhosis is reversible by liver transplantation [9]. The goal of our study was to follow the recovery of the relaxation times after transplantation for longer than 24 months using in vivo MR relaxometry.

2. Methods

2.1. Subjects

The study group consisted of 53 patients with hepatic cirrhosis of various (mostly alcoholic and/or hepatitis) etiology (for group overview see Table 1). Patients' age varied from 9 to 63 years, mean 45 ± 13 years. Only subclinical or very mild encephalopathy was observed in these patients.

Although all patients were diagnosed for liver transplantation (Child–Pugh score varied from 8 to 12), only 40 subjects underwent transplantation. Biopsy examination performed 1 year after surgery proved that the liver in all transplanted patients had normal histology and organ function.

After transplantation, a standardized immunosuppression protocol was utilized [10]. This consisted of an induction and maintenance phase. Immunosuppression induction began the same day as surgery and consisted of ciclosporine A (CsA) orally, methylprednisolone intravenously, azathioprine orally, and anti-T-lymphocyte globulin (ATG, Fresenius, Munich, Germany) intravenously for the first 7 days. During the maintenance phase, adjusted doses of CsA and prednisone were used. Azathioprine was continued depending on patient's tolerance. After a rejection episode or decreased renal function patients received mycophenolate mofetil orally, which in turn enabled a CsA dose reduction.

Table 1
Diagnosis of the studied subjects

Diagnosis	No. of patients
Alcoholic and/or toxic cirrhosis	10
Primary or secondary biliary cirrhosis	9
Hepatitis type B and/or C cirrhosis (HBV and/or HCV)	7
Alcoholic and HBV and/or HCV cirrhosis	6
Primary sclerosing cholangitis	6
Autoimmune cirrhosis	3
Epithelial haemangioendothelioma	2
Budd-Chiari syndrome	1
Haemochromatosis	1
Congenital liver fibrosis	1
Secondary fibrosis	1
Alpha-1-antitrypsin deficiency	1
Cryptogenic cirrhosis	5
Total	53

Twenty-nine patients were scanned before, 12 patients 0–3 months after surgery, seven patients 3–12 months after, 11 patients 1–2 years after, and 18 patients more than 2 years after surgery. Eighteen patients were scanned repeatedly two or more times, but only nine of them within a period longer than 2 years.

For comparison, we scanned a group of 20 healthy volunteers, age of the controls varied from 20 to 65 years, mean age was 40 ± 13 years.

2.2. T_1 and T_2 measurement

We used a 1.5 T whole body imager Siemens Magnetom–Vision equipped with a commercial tuned and matched CP head coil. After a standard localization procedure by turbo spin echo sequences (5-mm transversal and coronal slices: repetition time TR = 5.4 s, echo time TE = 99 ms, flip angle = 180°, field of view FOV = 300 × 300 mm, matrix size: 154 × 256; 5-mm sagittal slices: TR = 700 ms, TE = 12 ms, flip angle = 180°, FOV = 260 × 260 mm, matrix size: 216 × 256) a 5-mm thick axial slice at the level of the basal ganglia was measured using the following sequences:

1. For T_1 measurement a series of T_1 weighted images (saturation recovery) with repetition time TR varying from 100, 200, 400, 600, 800, 1000 and 1500 ms, and an echo time TE = 22 ms was used with a field of view FOV 195 × 260 mm and a matrix 154 × 256;
2. For T_2 measurement a modified 16-echo CPMG sequence with TR = 2 s, TE = 22.5, 45, 67.5,..., 360 ms was used, the field of view and matrix size was the same as in T_1 measurement.

T_1 was evaluated using a three-parameter fitting (e.g., an equation $I = A*(1 - \exp(-TR/T_1)) + B$), similarly T_2 was calculated using a three-parameter fitting (fit to $I = A*\exp(-TE/T_2) + B$). Because of the error caused by imperfect pulses (CPMG compensates the cumulative error caused by imperfect pulses by phase shift of the refocusing pulses; however, it cannot compensate the first echo), the first point was omitted. Calculations and T_1 and T_2 maps were obtained using a homemade program written in Turbo Pascal [11]. Values of T_1 and T_2 were obtained from regions of interest (ROI) selected in the caudate nucleus (NC), putamen (Put), globus pallidus (GP), thalamus (Th), and frontal white matter (WM). The selected slice and regions of interest are displayed in Fig. 1. The size of the regions of interest was approximately: NC — 100 mm^2, Put — 190 mm^2, GP — 90 mm^2, Th — 240 mm^2, WM — 280 mm^2.

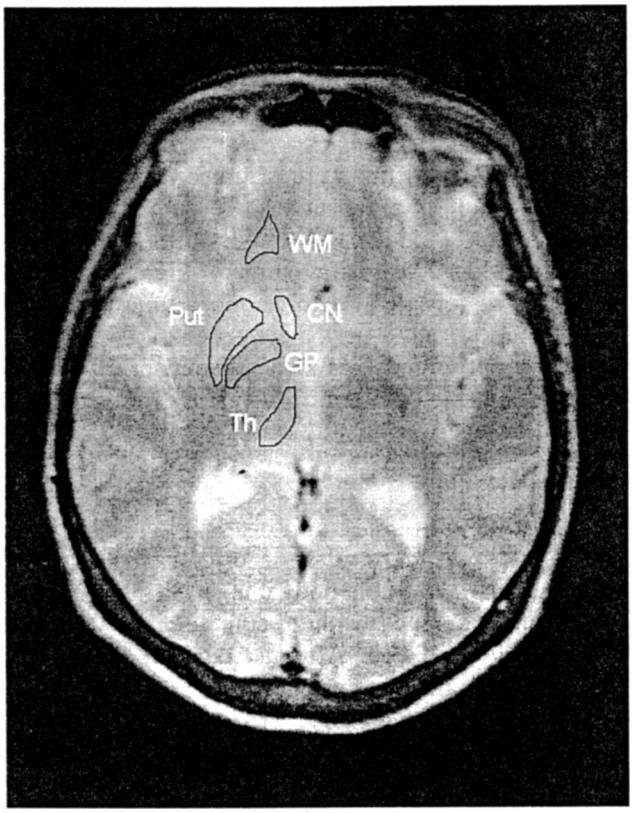

Fig. 1. Typical selected slice with marked regions of interest: caudate nucleus (CN), globus pallidus (GP), putamen (Put), thalamus (Th), occipital white matter (WM).

Reproducibility of the relaxation time measurements was ensured by regularly performed quality control [12]. Quality control was performed using gelatine phantomes both for T_1 and T_2 measurements, similar results were obtained for repeatability and reproducibility. The dispersion of in vivo T_1 data may be slightly higher because the phantoms did not have the same T_1 relaxation times as those found in the brain, nevertheless our quality control excludes a systematic error.

2.3. Statistics

The values presented in the tables represent averages with standard deviations. For comparison between the patient and control groups, or between measurements performed at different times before/after transplantation, the Student's unpaired two-tailed t-test was used.

The protocol was approved by the ethics committee of our institution, and the patients and controls were informed in detail about the examination.

3. Results and discussion

No differences in the relaxation times were found related to the patients' original diagnosis (see the list in the Table 1). Therefore, for further evaluation we presumed that the liver failure itself is responsible for changes in the brain, independent of its specific etiology (this approach is validated by experiments performed on rats by Rose [8]).

We found a significant shortening of the T_1 relaxation time as reported earlier [3]. T_1 is shortened by approx. 20–25% (see Table 2) in all examined structures, i.e., the basal ganglia, thalamus, cortex, and white matter compared to healthy controls.

After liver transplantation the T_1 relaxation time gradually recovers and after approx. 2–3 years reaches almost normal values (see Table 2 and Fig. 2). This phenomenon can be observed in all evaluated structures.

The T_1 values before transplantation significantly differ from those in healthy controls and to those measured after one and more years after surgery in all examined structures ($P < 0.05$). After surgery, T_1 relaxation time gradually increases. One year after transplantation T_1 values in basal ganglia and thalamus are significantly higher than values obtained before transplantation and after one year there is no statistically significant difference when compared to healthy controls. In white matter the recovery of T_1 is somewhat slower: the statistically significant differences in T_1 values obtained before transplantation persist for almost 2 years after surgery. However, after 2 years there is no significant difference in T_1 in white matter compared to controls.

A small decrease of T_1 visible after 2 years in the globus pallidus, thalamus and white matter is not sig-

Table 2
T_1 values (average values with standard deviations, in ms) before and after liver transplantation compared to controls

	Globus pallidus	Putamen	Caudate nucleus	Thalamus	White matter
Controls	840 ± 60	1120 ± 100	1160 ± 140	980 ± 110	730 ± 60
Before transplantation	620 ± 140[a]	910 ± 160[a]	990 ± 190[a]	890 ± 140[a]	630 ± 130[a]
<3 Months after	660 ± 110[a]	960 ± 130[a]	1000 ± 90[a]	940 ± 100	670 ± 100[a]
3–12 Months after	830 ± 60	1090 ± 80	1110 ± 50	970 ± 90	690 ± 90
12–24 Months after	870 ± 140	1100 ± 130	1130 ± 140	990 ± 150	740 ± 150
>24 Months after	840 ± 110	1070 ± 100	1140 ± 100	960 ± 70	720 ± 70

[a] Significantly differs compared to controls, $P < 0.05$.

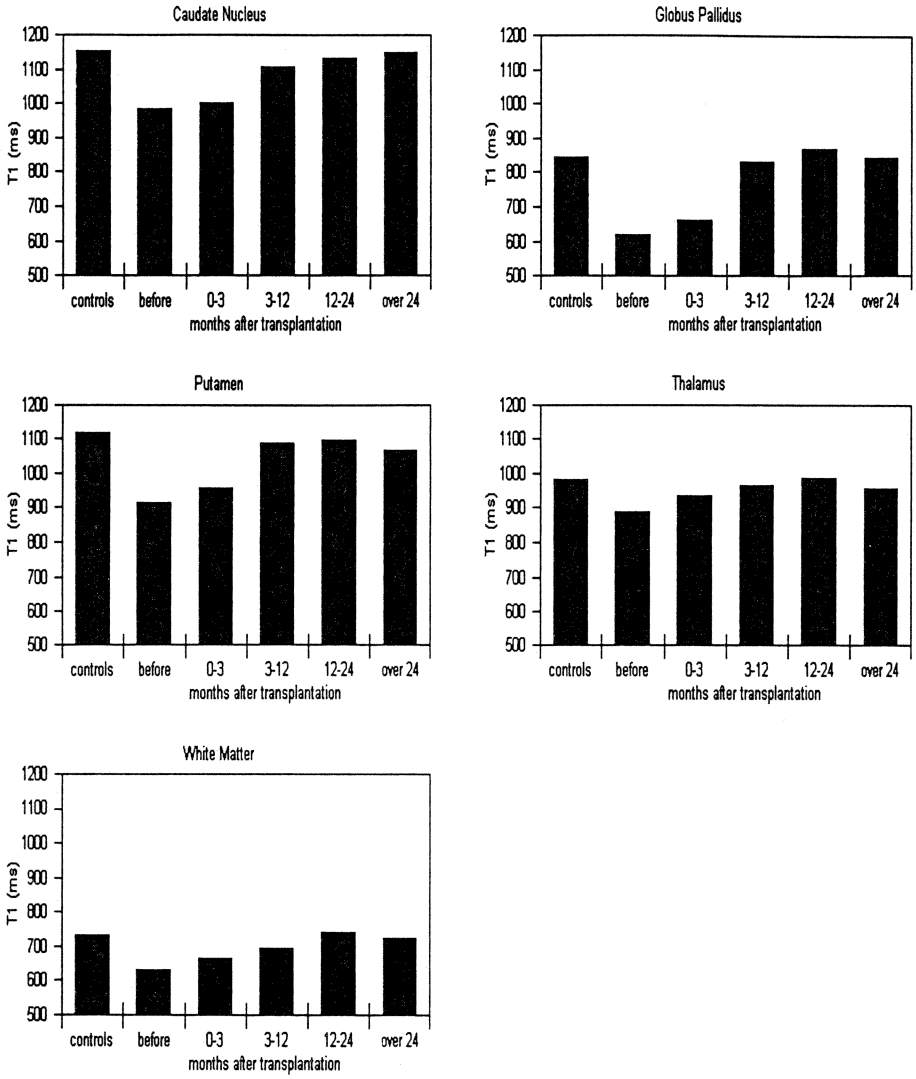

Fig. 2. T_1 values in different structures before and after liver transplantation compared to healthy controls.

nificant in comparison with the values obtained one year after liver transplantation. The decrease reached 2–3% and thus does not exceed experimental error.

We observed similar but not so pronounced results in the T_2 relaxation in the basal ganglia and thalamus. The evaluation here is more complicated because of the existence of age dependence of T_2 relaxation times in these structures. T_2 is much more susceptible to changes due to age. The concentration of paramagnetic iron (especially in the form of ferritin), which is also responsible for the relaxation time shortening, and which is deposited preferentially in the basal ganglia, increases in certain brain structures with age [13,14]. Thus, we had to divide both the patient and control groups into subgroups according to age. Such an approach makes the statistical evaluation more controversial. Two subgroups in each group were created: patients (or controls) between 20 and 40 years, and those over 40 years. However, the two groups (0–3 months) and (4–12 months) were too small for a meaningful analysis, we pooled them and created for each age category a subgroup of patients 0–12 months (scanned after transplantation).

We observed a significant decrease of T_2 relaxation times due to liver disease in both subgroups in the basal ganglia and thalamus, and a subsequent recovery of T_2 after transplantation both in younger and older subjects (see Table 3a and Table 3b). However, the recovery seems to be slower than in T_1, especially in younger (below age of 40) subjects. Also, a relative drop of T_2 due to cirrhosis seems to be greater in younger patients.

These findings were confirmed by *t*-test calculations. As expected, statistically significant differences of T_2 values, in the basal ganglia and thalamus between controls and patients before transplantation for both age categories, were found. Basal ganglia values obtained within 1 year of transplantation significantly differ from controls only in subjects below the age of

Table 3
(a) T_2 values (average values with standard deviations, in ms) before and after liver transplantation compared to healthy controls, subjects' age 20–40 years

	Globus pallidus	Putamen	Caudate nucleus	Thalamus	White matter
Controls	70.4 ± 2.4	82.8 ± 2.1	91.8 ± 2.7	82.1 ± 2.5	84.9 ± 4.2
Before transplantation	68.3 ± 6.3[a]	77 ± 1.7[a]	87.0 ± 2.8[a]	77.8 ± 2.2[a]	81.9 ± 6.6
0–12 Months after	67.1 ± 4.8[a]	78.8 ± 4.4[a]	86.5 ± 4.6[a]	79.5 ± 3.7	77.4[a] ± 6.2
12–24 Months after	71.0 ± 5.4	81.8 ± 3.2	91.4 ± 3.5	82.8 ± 2.3	78.6[a] ± 0.7
>24 Months after	71.4 ± 1.1	82.3 ± 1.8	89.2 ± 2.9	83.3 ± 0.5	80.1[a] ± 1.6

(b) T_2 values (average values with standard deviations, in ms) before and after liver transplantation compared to healthy controls, subjects' age 41 years and over

	Globus pallidus	Putamen	Caudate nucleus	Thalamus	White matter
Controls	68.9 ± 4.8	79.4 ± 2.7	88.5 ± 3.6	81.4 ± 2.1	84.5 ± 4.7
Before transplantation	66.2 ± 3.9[a]	77.1 ± 2.8[a]	86.2 ± 3.2[a]	79.5 ± 3.0[a]	83.6 ± 6.3
0–12 Months after	69.2 ± 6.0	78.3 ± 3.3	87.2 ± 3.3	81 ± 2.2	87.6 ± 5.1[a]
12–24 Months after	71.0 ± 3.2	79.9 ± 2.5	88.6 ± 3.7	82.4 ± 2.5	82.7 ± 4.2
>24 Months after	71.7 ± 3.1[a]	78.4 ± 3.4	88.4 ± 3.2	83.3 ± 2.7[a]	81.3 ± 3.6[a]

[a] Significantly differs compared to controls, $P<0.05$.

40, whereas the group of patients over 40 show no significant difference compared to controls. The values obtained after this period (i.e., 1 year or more after surgery) do not differ in any age category from controls. Most T_2 values remained stable, however, two patients exhibited another substantial increase in the relaxation time in the globus pallidus and thalamus more than two years after liver transplantation. There is no explanation for this observation, it may possibly be attributed to experimental error (it of course significantly affects the average values listed in Table 3b).

Unexpectedly, no recovery of T_2 relaxation time was found in white matter, although recovery was observed in T_1. Moreover, T_2 significantly decreased with time: although there is no statistically significant difference in T_2 between the group of patients scanned before transplantation and controls, values obtained a long time after surgery were significantly different from controls.

Manganese is considered a possible etiological agent for relaxation time alterations in basal ganglia and thalamus of patients suffering from liver disease [3]. It has been shown that mangenese is shunted away from the liver and its concentration increases in patients with a liver failure both in the brain and in blood [6–8]. Nevertheless, the unusual trend in T_2 in the white matter after liver transplantation leads us to hypothesize that manganese is not solely responsible for the alterations in relaxation times in the brain. If T_1 relaxation time shortening was caused solely by a paramagnetic form of manganese (or any other paramagnetic substance), it would also shorten T_2.

Alterations in T_2 in the white matter observed a long time after liver transplantation indicate that either manganese changes its form and becomes non-soluble (thus invisible in T_1 maps), or some other agent (phospholipids, suggested in [15], or unknown so far) is present, or perhaps some permanent morphological changes occur in the white matter.

Though, we must stress that patients are dependent on immunosuppresants after transplantation, which are potentially neurotoxic and could particularly influence white matter. Thus, T_2 relaxation could be affected by the immunosuppression.

Results obtained from repeated measurements of single patients roughly follow the general trends seen with average values. Seven patients from nine, scanned for a period of at least 2 years, showed an evident recovery of relaxation times in the basal ganglia and thalamus after liver transplantation, whereas the behavior of T_2 in the white matter is very ambiguous (see Fig. 3, a

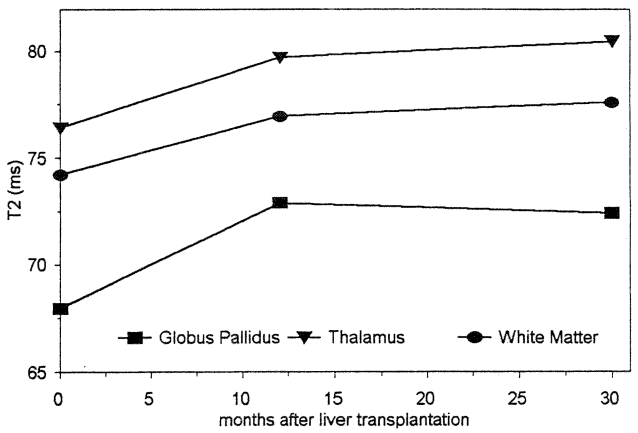

Fig. 3. T_2 evolution after liver transplantation, data from a single patient, 41 years old when transplanted, cirrhosis of hepatitic B and C etiology.

patient 41 years old when transplanted, cirrhosis of hepatitic B and C etiology). We can conclude that the results obtained from the gray matter in the brain of individual patients generally confirm the trends demonstrated in the pooled data.

4. Conclusion

No significant difference in brain relaxation times between the groups of patients with cirrhosis of different etiology was found.

We tracked the recovery of relaxation times T_1 and T_2 in the brain after liver transplantation. We proved that changes in the basal ganglia and thalamus are fully reversible within a period of 2 years. Nevertheless, results obtained in white matter indicate that permanent morphological and/or biochemical changes cannot be excluded.

Acknowledgements

We are grateful to Dr Sonya Stewart for reviewing the manuscript. This study was supported by grants GACR 309/97/K048 and IKEM 906, Czech Republic.

References

[1] Bernthal P, Hays A, Tarter RE, Van Thiel D, Lecky J, Hegedus A. Cerebral CT scan abnormalities in cholestatic and hepatocellular disease and their relationship to neuropsychologic test performance. Hepatology 1987;7:107–14.

[2] Moore JW, Dunk AA, Crawford JR, Deans H, Besson JAO, De Lacey G, Sinclair TS, Mowat NAG, Brunt PW. Neuropsychological deficits and morphological MRI brain scan abnormalities in apparently healthy non-encephalopathic patients with cirrhosis. J Hepatol 1989;9:319–25.

[3] Vymazal J, Babis M, Brooks RA, Filip K, Dezortova M, Hrncarkova H, Hajek M. T1 and T2 alterations in the brains of patients with hepatic cirrhosis. AJNR 1996;17:333–6.

[4] Hauser RA, Zesiewicz TA, Rosemurgy AS, Martinez C, Olanow CW. Manganese intoxication and chronic liver failure. Ann Neurol 1994;36:871–5.

[5] Krieger D, Krieger S, Jansen O, Gass P, Theilmann L, Lichtnecker H. Manganese and chronic hepatic encephalopathy. Lancet 1995;346:270–4.

[6] Butterworth RF, Spahr L, Fontaine S, Pomier-Layrargues G. Manganese toxicity, dopaminergic dysfunction and hepatic encephalopathy. Metab Brain Dis 1995;10:259–67.

[7] Pomier-Layrargues G, Spahr L, Butterworth RF. Increased manganese concentrations in pallidum of cirrhotic patients. Lancet 1995;345:735.

[8] Rose C, Butterworth RF, Zayed J, Normandin L, Todd K, Michalak A, Spahr L, Huet PM, Pomier-Layrargues G. Manganese deposition in basal ganglia structures results from both portal-systemic shunting and liver dysfunction. Gastroenterology 1999;117:640–4.

[9] Hockerstedt K, Kajaste S, Muuronen A, Raininko R, Seppalainen AM, Hillbom M. Encephalopathy and neuropathy in end-stage liver disease before and after liver transplantation. J Hepatol 1992;16:31–7.

[10] Ryska M, Trunecka P, Belina F, Spicak J, Peregrin J, Filip K, Vitko S. Liver transplant program in Prague. Results of consecutive first 100 orthotopic liver transplantations. Ann Transplant 2000;5:50–2.

[11] program CHROBAK, author: Vít Herynek, Institute for Clinical and Experimental Medicine, Prague, CZ

[12] Hajek M, Babis M, Herynek V. MR relaxometry on a whole-body imager: quality control. Magn Reson Imaging 1999;17:1087–92.

[13] Hallgren B, Sourander P. The effect of age on the non-haemin iron in the human brain. J Neurochem 1958;3:41–51.

[14] Schenker C, Meier D, Wichmann W, Boesiger P, Valavanis A. Age distribution and iron dependency of the T2 relaxation time in the globus pallidus and putamen. Neuroradiology 1993;35:119–24.

[15] Kucharczyk W, Lenkinski RE, Kucharczyk J, Henkelman RM. The effect of phospholipid vesicles on the NMR relaxation of water: an explanation for the MR appearance of the neurohypophysis? Am J Neuroradiol 1990;11:693–700.