Pallidal Signal Intensities on T1-weighted MRI are Highly Observed in Advanced Liver Cirrhosis

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ABSTRACT

Background: Manganese (Mn) has been found to increase the signal intensity of the globus pallidus (GP) on T1-weighted magnetic resonance images (MRI). We performed this study in order to determine the features of liver disease that correlate with pallidal signal intensities.

Methods: We assessed blood Mn levels and pallidal signals in T1-weighted MRI in 49 patients with liver cirrhosis and 23 healthy controls.

Results: Increased signal intensity in the GP was observed in 30 of 49 (61.2%) patients with liver cirrhosis, with the pallidal index (PI) in patients with Child-Pugh classes B and C differing significantly from the PI in controls. Multiple linear regression analysis showed that blood Mn concentrations and Child-Pugh scores in cirrhotics were significantly associated with increased PI after controlling for other confounders (p<0.05 each).

Conclusions: Pallidal signals on T1-weighted MRI are mainly observed in advanced liver cirrhosis. The present study suggests that advanced liver cirrhosis may be a human model for manganism.

Keywords: manganese, signal intensity, magnetic resonance, liver cirrhosis, pallidal index

I. Introduction

Manganese ion (Mn²⁺) has five unpaired electrons in the 3rd orbital, causing its large magnetic moment, which ultimately results in an increase in signal intensity on T1-weighted MRI, in particular, bilateral and symmetrical increases in signal intensity that are mainly confined to the globus pallidus (GP) and midbrain.¹,² However, Mn²⁺ does not affect T2-weighted MRI, which is most sensitive for detecting brain pathology such as brain tumor or bleeding. These phenomena can be specifically used for pinpointing Mn accumulation in brain tissues. High signal intensity in the GP has been observed during experimental Mn poisoning of non-human primates,³ in a patient with Mn intoxication,⁴ and in workers exposed to Mn.⁵ Chronic liver failure has been associated with increased pallidal signal intensities on T1-weighted MRI,⁶,⁷ with the correlation between MRI abnormalities in the GP and circulating Mn concentrations in patients with liver cirrhosis suggesting that these high signals are due to paramagnetic Mn.⁸,⁹ Several studies have examined the relationships among MR abnormalities, the severity of liver disease, hyperbilirubinemia and the degree of portal systemic shunting, but the results were inconsistent.¹⁰⁻¹⁵ Previous studies also showed wide variations in the prevalence of high pallidal signals (52-100%).¹⁵ It is not clear which features of chronic liver disease may affect pallidal signal intensities. We therefore examined pallidal signals in patients with liver cirrhosis and healthy
Pallidal signals are highly observed in advanced liver cirrhosis

II. Subjects and Methods

1. Subjects

Male patients with clinically confirmed hepatitis B-induced cirrhosis were selected from hospital inpatients and from patients attending an ambulatory hepatology care clinic. A diagnosis of hepatitis B-induced liver cirrhosis was based on the results of patient questionnaires, combined with clinical, laboratory, endoscopic and ultrasonographic findings. Of the 55 patients who provided informed consent and were recruited, 6 were excluded because they had received transfusions due to previous GI bleeding. Transfusion may confound iron deficiency-induced susceptibility to Mn. The control group consisted of 23 normal healthy men who visited a health promotion center. These subjects had no history of liver disease. Both patients and controls had no occupational exposure to Mn. After receiving a detailed explanation of the study design and potential risks, all participants provided written informed consent. The procedures used in this study were approved by the institutional review board of Ulsan University Hospital.

2. Questionnaires, laboratory testing, and analysis of Mn concentration

Samples of heparinized venous blood and urine were collected. Each subject filled out a questionnaire on basic demographic information, smoking history, alcohol consumption, medications, and a detailed medical history. Laboratory tests aimed at detecting liver dysfunction and anemia included liver function tests, blood cell counts, hemoglobin, hematocrit. The severity of liver disease was assessed using the Child-Pugh scoring system, which includes as variables the presence or absence of ascites and encephalopathy, serum albumin and bilirubin concentrations, and prothrombin time. Each variable is scored from 1 to 3 points for increasing abnormality, with total scores of 5–6, 7–9, and 10–15 defined as Child-Pugh classes A, B, and C, respectively, with C being the most severe.

Blood Mn concentrations were determined by flameless graphite furnace atomic absorption spectrophotometry (AAS; Spectra AA880-GTA 100, Varian, Australia) using a standard addition method. Aliquots of 0.1 ml blood were diluted 20-fold with 0.1% v/v Triton X-100, and 15 µl samples were injected into the graphite furnace.

3. Brain MRI

MRI examinations were performed using a 1.5 Tesla system (Signa Horizon LX; GE Medical Systems; Milwaukee, WI, USA). The spin echo (SE) technique was applied with two acquisitions in the T1 weighted sequence and one acquisition in the T2 weighted sequence. T1 weighted images were acquired in the axial plane using the following parameters: 600/20 (repetition time (TR)/echo time (TE) m sec) two excitations, a 22 cm field-of-view, a 256 × 160 matrix, and slice thickness of 5 mm. T1 weighted sagittal images were obtained with the same parameters, except that TR/TE was 466/14 ms. Axial T2-weighted (TR/TE = 4000/100 ms) images were also obtained. The signal intensity of the GP relative to that from frontal white matter was subjectively evaluated by a radiologist with no prior knowledge of patient status. High or increased signal intensity of GP was defined when pallidal signal intensity is higher than the intensity of frontal white matter. For quantitative evaluation of signal intensities, a region of interest (ROI) was placed in the region of highest intensities in the GP, as determined by visual assessment, and in the subcortical frontal white matter. Pallidal index (PI) was calculated as the ratio of signal intensity in the GP to that in the subcortical frontal white matter on axial T1-weighted MRI, multiplied by 100.

4. Statistical analyses

Univariate distributions of continuous variables were examined to evaluate normality using the Kolmogorov–Smirnov test. To better attain normal distributions, blood Mn, serum AST (aspartate aminotransferase), and ALT (alanine aminotransferase) concentrations, and Child-Pugh scores were natural log-transformed because their distributions were skewed, and the geometric means (GMs) were compared. In this case, p-values were calculated after logarithmic transformation. Mean values of continuous variables in patients and controls were compared using Student’s t-tests. Mean values of continuous variables for the four groups (controls to determine the features of liver disease that correlate with pallidal signal intensities.

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and patient subgroups by Child-Pugh classification were compared using one way analysis of variance (ANOVA). If the ANOVA showed significance at $P < 0.05$, Scheffe’s multiple comparison test was performed to identify the subgroup that was significantly different from the other subgroups. Multiple regression analysis was performed to verify any association between variables such as Mn, Child-Pugh class and AST/ALT (explanatory variables) and PI value (response variable) while controlling for the influence of other confounding variables such as age, smoking, and alcohol consumption.

### III. Results

The general and clinical characteristics of the subjects are shown in Table 1. The mean age of the 49 cirrhotic patients was 47.9 years, all were male, and all had hepatitis B-induced liver cirrhosis. The mean age of the 23 male control subjects was 52.7 years; none had been exposed to Mn or had any neurological disease, liver disease, or anemia. We found that the GM of Mn concentration (1.88 $\mu$g/dl vs. 1.45 $\mu$g/dl, $P < 0.05$) and mean PI (118.1 vs. 105.8, $P < 0.05$) were significantly higher in patients with cirrhosis than in controls. Increased T1-weighted MRI signals in the GP were observed in 30 of the 49 (61.2%) patients with cirrhosis, compared with 2 of 23 (8.7%) controls. AST (49.6 IU/L vs. 22.5 IU/L, $P < 0.05$) and ALT (50.1 IU/L vs. 24.6 IU/L, $P < 0.05$) concentrations were significantly higher, and hemoglobin concentrations (12.6 $\pm$ 2.5 g/dl vs. 14.8 $\pm$ 1.1 g/dl, $P < 0.05$) were significantly lower, in liver cirrhotics than in controls. The GM of Child-Pugh score was 7.5 in the cirrhotics.

Mean PI differed significantly among four groups of individuals, with liver cirrhosis (Child-Pugh classes A, B, and C) and the control group (Table 2). Mean PIs were significantly higher in patients with Child-Pugh classes B (125.7 $\pm$ 15.1) and C (130.9 $\pm$ 10.2) than in controls (105.8 $\pm$ 3.8) and was significantly higher in patients with Child-Pugh class C (130.9 $\pm$ 10.2) than in patients with Child-Pugh class A (109.9 $\pm$ 10.5). Mean blood Mn concentration

**Table 1.** Demographic, clinical and laboratory features of the studied male subjects

<table>
<thead>
<tr>
<th></th>
<th>Liver cirrhosis (n=49)</th>
<th>Controls (n=23)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>47.9 $\pm$ 6.4$^*$</td>
<td>52.7 $\pm$ 5.2</td>
</tr>
<tr>
<td>High signal intensity on MRI</td>
<td>30 (61.2%)$^*$</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>Pallidal index</td>
<td>118.1 $\pm$ 14.8$^*$</td>
<td>105.8 $\pm$ 3.8</td>
</tr>
<tr>
<td>Blood manganese ($\mu$g/dl)$^*$</td>
<td>1.88 (0.78-7.50)$^*$</td>
<td>1.45 (0.86-2.94)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)$^*$</td>
<td>12.6 $\pm$ 2.5$^*$</td>
<td>14.8 $\pm$ 1.1</td>
</tr>
<tr>
<td>AST (IU/L)$^*$</td>
<td>49.6 (5-260)</td>
<td>22.5 (12-32)</td>
</tr>
<tr>
<td>ALT (IU/L)$^*$</td>
<td>50.1 (15-581)$^*$</td>
<td>24.6 (10-51)</td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td>7.5 (5-14)</td>
<td></td>
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</tbody>
</table>

**Table 2.** Pallidal index (PI) and blood manganese (Mn) concentrations by Child-Pugh classification

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=23)</th>
<th>Child-Pugh classification</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>A (n=27)</td>
<td>B (n=11)</td>
</tr>
<tr>
<td>PI</td>
<td>105.8 $\pm$ 3.8</td>
<td>109.9 $\pm$ 10.5</td>
</tr>
<tr>
<td>Blood Mn ($\mu$g/dl)$^*$</td>
<td>1.45 (0.86-2.94)</td>
<td>1.73 (0.95-7.50)</td>
</tr>
<tr>
<td>Proportion with high pallidal signal</td>
<td>2 (8.7%)</td>
<td>9 (33.3%)</td>
</tr>
</tbody>
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NOTE. Data are mean$\pm$standard deviation or geometric mean (range). In the case of geometric mean, $p$-values were calculated by t-test after logarithmic transformation. $^* p < 0.05$ vs control.

AST; aspartate aminotransferase, ALT; alanine aminotransferase.
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Table 3. Multiple regression modeling of pallidal index (PI) in liver cirrhotics (n=47)

<table>
<thead>
<tr>
<th>Model</th>
<th>B Coefficient (95% CI)</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Log blood manganese 16.07 (9.07-23.07)*</td>
<td>0.354*</td>
</tr>
<tr>
<td>Model 2</td>
<td>Log blood manganese 14.39 (8.99-19.80)*</td>
<td>0.620*</td>
</tr>
<tr>
<td>Model 3</td>
<td>Log blood manganese 15.10 (9.78-20.41)*</td>
<td>0.653*</td>
</tr>
<tr>
<td>Model 4</td>
<td>Log blood manganese 14.94 (9.58-20.30)*</td>
<td>0.653*</td>
</tr>
</tbody>
</table>

Adjusted for age, alcohol drinking, and smoking. *: p < 0.05.

IV. Discussion

Characteristic increased signal intensities, mainly confined to the GP, have been observed on T1-weighted MRI after exposure to Mn. Chronic liver failure is also associated with increased signal intensities in the GP on T1-weighted MRI.1,2 Liver cirrhosis prevents Mn clearance via biliary excretion due to a portal systemic shunt, resulting in increased blood Mn and increased signal intensity in GP even in patients not exposed to Mn.1,2,3 Our findings, of increased T1 signal intensities in the GP in 61.2% of our patients with hepatitis B-induced liver cirrhosis1,2,3 and of a significant relationship between PI and blood Mn concentration1,2,3 were compatible with previous results. Moreover, we found that the severity of liver disease, as assessed by Child-Pugh score, was associated with the prevalence of increased T1 signals in the GP. PI was significantly higher in patients with Child-Pugh classes B and C than in the control group, and was significantly higher in patients with Child-Pugh class C than in those with Child-Pugh class B. According to multiple linear regression analysis as well, patients with Child-Pugh class C had higher PI than those with Child-Pugh class B as well as Child-Pugh class A after covariate adjustment. Furthermore, patients with Child-Pugh class B also had higher PI than those with Child-Pugh class A after covariate adjustment. Consistent with earlier results,1,2,3 we observed a significant relationship between PI and the severity of the liver disease, as determined using the Child-Pugh scoring system.16 Importantly, however, PI and blood Mn concentration did not differ in patients with early stage cirrhosis (i.e. Child-Pugh class A) and controls. We also found that pallidal signals were significantly associated with Child-Pugh score, but not with serum AST or ALT concentration. These results confirm and extend previous findings showing a correlation between increased pallidal signals and the severity of liver disease. The Child-Pugh scoring system includes the presence of ascites and encephalopathy, the concentrations of serum albumin and bilirubin, and prothrombin time.16

High pallidal T1 signals have been reported in children with congenital abnormalities of portal-systemic shunt due to dysgenesis of the portal venous system, but who showed almost normal liver function.1,2,3,4 High pallidal signals have also been observed in patients with long standing portal-
systemic shunt alone, due to portal vein thrombosis, without liver cirrhosis.\(^{20}\) Animal models of portal-systemic shunt without cirrhosis have higher concentrations of Mn in the basal ganglia than in animal models of cirrhosis.\(^{13}\) Moreover, high pallidal T1 signals were more prominent in patients with idiopathic portal hypertension than in patients with liver cirrhosis.\(^{20}\) Taken together, these findings support that pallidal signals is mainly affected by portal systemic shunt in advanced liver cirrhosis.

Pallidal signals have been reported to be highly prevalent in patients with liver cirrhosis (52-100%).\(^{9,16,19,20}\) Wide variation in the prevalence of high pallidal signals may be due to differences in the severity of liver diseases of the study subjects. The lower prevalence of high pallidal high signals among our patients than previously reported\(^{19-21}\) may have been due to our inclusion of subjects with less severe liver disease.

Our findings have implications regarding occupational health. First, individuals susceptible to high pallidal signal include patients with liver cirrhosis, but not patients with chronic liver disease without portal systemic shunt, such as those with fatty liver disease or chronic hepatitis. Second, PI may be a surrogate marker of exposure to Mn and thus advanced liver cirrhosis may be a human model for manganism because the prevalence of liver cirrhosis is high. Patients with advanced cirrhosis have been documented with a form of parkinsonism with clinical symptoms similar to those of Mn-induced parkinsonism.\(^{22,23,29}\) Our findings, however, are limited by our lack of information on subclinical neurobehavioral deficits in these individuals, because we did not perform neurobehavioral tests. In summary, we found that increased pallidal signals on T1-weighted MRI are mainly affected by the severity of liver disease.

Acknowledgments

This study was funded by Ulsan University Hospital (Biomedical Research Center Promotion Fund; UUH-07-14).

References


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Pallidal signals are highly observed in advanced liver cirrhosis (385).


