High Pallidal T1 Signal is Rarely Observed in Obstructive Jaundice, but is Frequently Observed in Liver Cirrhosis

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Abstract: High Pallidal T1 Signal is Rarely Observed in Obstructive Jaundice, but is Frequently Observed in Liver Cirrhosis: Sung-Jo BANG, *et al.* Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, South Korea—Although high signal intensities in the globus pallidus are frequently observed in T1-weighted magnetic resonance images (MRI) of patients with liver cirrhosis, it is unclear whether these increases are due to portal-systemic shunt or obstruction of biliary excretion. We therefore studied pallidal signals in 18 cancer patients with bile duct obstruction and marked jaundice (>10 mg/dl). Patients who had fever, leukocytosis or liver cirrhosis were excluded to ensure that jaundice was due to bile duct obstruction. All patients showed a dilated intrahepatic duct on computed tomography (CT) scan. A high pallidal signal was observed in one of 18 biliary obstructive patients whereas high signals were highly prevalent in liver cirrhosis. A portal-systemic shunt rather than an obstruction of biliary excretion may be responsible for the increased blood manganese concentrations and pallidal T1 signals in chronic liver diseases.

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Key words: Manganese, Signal intensity, Magnetic resonance, Liver cirrhosis, Biliary obstruction, Pallidal index

Symmetrical increases in signal intensities, mainly confined to the globus pallidus (GP) and midbrain, can be observed on T1-weighted brain magnetic resonance images (MRI) due to the paramagnetic property of

manganese (Mn), whereas T2-weighted images are not altered. Characteristic high signal intensities, mainly confined to the GP, have also been observed in T1-weighted MRI during experimental Mn poisoning of non-human primates¹⁾ and in a patient with Mn neurointoxication²⁾. A similar MRI pattern has been observed in patients receiving total parenteral nutrition, because of excessive Mn intake^{3,4)}. Chronic liver failure is also associated with increased T1-weighted signal intensities in the GP^{5,6)}. The correlation between signal intensities in the GP and circulating Mn concentrations of cirrhotic patients suggests that the high signals are due to paramagnetic Mn^{7–9)}. Although high signal intensities in the GP have also been reported to be highly prevalent in patients with liver cirrhosis (52–100%)^{10–12)}, it is unclear whether the increases in pallidal signals are due to portal-systemic shunt or obstruction of biliary excretion. Studying patients with biliary obstruction without liver cirrhosis may therefore clarify the role of biliary obstruction in increased pallidal T1 signals. We therefore assessed pallidal T1 signals in 18 cancer patients who had bile duct obstruction and marked jaundice without liver cirrhosis, and compared these findings with pallidal signals in patients with liver cirrhosis and healthy controls.

Subjects and Methods

Subjects

We selected 18 cancer patients, with biliary duct, pancreatic head, or gall bladder cancer, who had bile duct obstruction and marked jaundice (>10 mg/dl) without liver cirrhosis. Patients with cholangitis (fever and leukocytosis), anemia or liver cirrhosis were excluded to ensure that the jaundice was due to bile duct obstruction. Patients with calcification in the GP, which affects pallidal signals, were also excluded. All patients showed a dilated intrahepatic duct on computed tomography (CT) scan. We also selected 29 patients with clinically confirmed

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

	Healthy controls (n=16)	Liver cirrhotics (n=29)	Biliary obstructive patients (n=18)
Mean age (years)	53.8 ± 10.5*	47.5 ± 5.9*	66.8 ± 9.3
Proportion of males (%)	93.8	100	66.7 ^{&}
Proportion of drinkers (%) (premorbid)	56.3	72.4	38.9
Proportion of persons with high signal intensity on MRI (%)	0.0	86.2	5.6 ^{&}
Pallidal indices	101.84 ± 2.98 [†] (95.56 – 106.59)	125.63 ± 12.49 (100.45 – 153.05)	100.77 ± 4.30 [†] (94.51 – 109.82)
MnB (μg/dl)	1.20 ± 0.30 (0.58–1.59) [†]	2.05 ± 1.31 (0.78–6.66)	1.29 ± 0.59 (0.64–2.49) [†]
Hemoglobin (g/ dl)	14.9 ± 1.6 (13.0–19.0)	11.2 ± 2.0 (7.4–16.0) [§]	12.0 ± 1.5 (9.26–14.0) [§]
Total bilirubin (mg/ dl)	1.13 ± 0.39 (0.5–2.0)*	2.96 ± 2.31 (0.7–8.7)*	17.57 ± 8.60 (10–40)
Direct bilirubin (mg/ dl)	0.22 ± 0.08 (0.1–0.4)*	1.59 ± 1.48 (0.2–4.6)*	12.52 ± 5.60 (6.4–26)
AST (IU/l)	28.7 ± 9.1 (19–54)	76.6 ± 48.6 (27–264) [§]	101.0 ± 63.1 (35–231) [§]
ALT (IU/l)	32.5 ± 15.4 (14–60)	83.6 ± 119.3 (26–587)	140.1 ± 114.6 (36–432) [§]
GGT (IU/l)	37.1 ± 23.6 (12–84)*	107.7 ± 182.8 (13–879)*	687.3 ± 584.5 (33–1,850)
Child-Pugh score	–	9.0 ± 2.9 (6–14)	–
Proportion of persons with hepatic encephalopathy (%)	–	20.7	–

Statistical significance test was done by Scheffe's test. *: $p < 0.05$ vs. obstructive jaundice, [†]: $p < 0.05$ vs. liver cirrhosis, [§]: $p < 0.05$ vs. control, [&]: $p < 0.05$ by chi-square test. Data are mean ± standard deviation (range).

MnB: blood manganese level. AST: aspartate aminotransferase. ALT: alanine aminotransferase. GGT: γ -glutamyltransferase.

cirrhosis from the hepatology clinic of the same hospital. A diagnosis of hepatitis B-induced liver cirrhosis was established using patient questionnaires combined with clinical, laboratory, endoscopic and ultrasonographic findings¹⁰. The 16 healthy controls were selected from healthy persons visiting our hospital for comprehensive health check ups; these subjects had no evidence of anemia or liver disease. None of the patients in the three groups had a history of exposure to Mn. All subjects provided their written informed consent, and the study protocol was approved by the Institutional Review Board of our hospital.

Questionnaires, laboratory testing, and analysis of Mn concentration

Samples of heparinized venous blood were collected from each patient. Each patient was administered a questionnaire that recorded basic demographic information as well as information about smoking history, alcohol consumption, medications, and recent medical history. Each subject was asked about his or her previous disease history in detail. Laboratory tests, designed to detect liver dysfunction or anemia, consisted of liver function tests as well as hematological investigations,

such as blood cell count, hemoglobin, and hematocrit. The severity of liver disease was assessed using Child/Pugh scores¹³, which included the variables of ascites, encephalopathy, serum albumin, serum bilirubin, and prothrombin time, with each variable scored from 1 to 3 points for increasing abnormality.

Blood Mn concentrations were determined by flameless graphite furnace atomic absorption spectrophotometry (AAS; Spectra AA880-GTA 100, Varian, Australia)^{14, 15}. Aliquots (0.1 ml) of blood were diluted 20 fold with 0.1% v/v Triton X-100, and 15-μl samples were injected into the graphite furnace.

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 and sagittal planes using the following parameters: 466/14 (repetition time (T_R)/echo time (T_E) ms] two excitations, a 22-cm field-of-view, a 256 × 256 matrix, and a slice thickness of 7 mm. T1-weighted sagittal

Fig. 1. Axial T1-weighted MR image of a patient with liver cirrhosis (A), a patient with biliary obstruction (B), and a healthy control (C). Black arrows show markedly increased signal intensities (A), and slightly increased signal intensities (B) at the globus pallidus.

images were also obtained using $T_R/T_E=466/14$ ms with the remaining parameters as listed above. Axial T2-weighted ($T_R/T_E=4,000/100$ ms) images were also obtained. The signal intensity of the GP relative to that recorded from frontal white matter was subjectively evaluated by a radiologist without prior knowledge of patient status. For quantitative evaluation of signal intensities, the region of interest (ROI) was placed in the regions of highest intensities in the GP and subcortical frontal white matter by visual assessment, and the PI was calculated as the ratio of signal intensity in the GP to that in the subcortical frontal white matter multiplied by $100^{(8)}$.

Statistical analyses

Mean values of continuous variables for the three groups 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. The differences in frequency distribution of males, drinkers, and persons with increased signals were ascertained by the chi-square test.

Results

The general, clinical and biochemical characteristics of the subjects are shown in Table 1. The mean ages of biliary obstructive patients, cirrhotic patients, and normal controls were 66.8 yr, 47.5 yr and 53.8 yr, respectively. Patients with biliary obstruction had mean total and direct bilirubin concentrations of $17.57 \mu\text{g/dl}$ and $12.52 \mu\text{g/dl}$, respectively, each of which differed significantly from those of the cirrhotic and healthy control groups. γ -Glutamyltransferase activity also showed a similar pattern. Levels of hemoglobin, aspartate aminotransferase, and alanine aminotransferase in

patients with liver cirrhosis and biliary obstruction were significantly different from those in healthy controls. Patients with biliary obstruction had a mean blood Mn of $1.29 \mu\text{g/dl}$, similar to that of healthy controls, but was significantly different from that of cirrhotic controls. The mean PI of patients with biliary obstruction was similar to that of healthy controls, but differed significantly from that of cirrhotic controls. A slight increase in pallidal signal was observed in one biliary obstructive patient, with a total bilirubin concentration of $40 \mu\text{g/dl}$, but in none of the healthy controls (Fig. 1). However, increased pallidal signals in the GP were observed in 25 of 29 (86.2%) patients with liver cirrhosis ($p<0.05$). In patients with liver cirrhosis, there was a significant correlation between blood Mn and PI ($\gamma=0.575$, $p<0.01$) and between Child/Pugh scores and PI ($\gamma=0.419$, $p<0.05$), but not between blood Mn and bilirubin concentrations. The correlations between PI and blood Mn and between PI and bilirubin were not statistically significant in the biliary obstructive patients.

Discussion

Increases in blood Mn levels and pallidal signals in cirrhotic patients are likely to be multifactorial. A significant relationship has been observed between pallidal T1 signal intensity and severity of liver lesions, as assessed by Child/Pugh scores^{10, 16–18}. However, Child/Pugh scores are a complex of heterogeneous variables, some of which are related indirectly to portal-systemic shunt (e.g. ascites and encephalopathy) and others to biliary excretion (e.g. bilirubin). Significant relationships have also been observed between pallidal T1 signal intensity and the presence of portal hypertension/portal-systemic shunt^{16, 17, 19, 20}, and between pallidal T1 signal intensity and the severity of liver lesions as well as portal-

systemic shunt^{10, 16, 17}).

To our knowledge, the present work is the first study of patients with bile duct obstruction, but without portal-systemic shunts. Mean blood Mn level and pallidal T1 signals were not increased in these patients, but were increased in patients with liver cirrhosis. Although patients with bile duct obstruction had concentrations of total and direct bilirubin much higher than those in patients with liver cirrhosis, almost all had incomplete biliary obstructions, suggesting that Mn might be excreted via the bile. One patient with biliary obstruction and a high pallidal signal had a total bilirubin concentration of 40 $\mu\text{g/dl}$, indicative of nearly total biliary obstruction. Our results suggest that incomplete biliary obstruction alone may not increase blood Mn and pallidal signals. Pallidal signals are significantly decreased after liver transplantation, even in patients with chronic graft rejection and severe cholestasis but no evidence of cirrhosis¹⁷. Moreover, there was no correlation between pallidal T1 signals and the presence of cholestatic liver disease¹⁷. Our findings, coupled with these earlier results¹⁷, suggest that the crucial mechanisms responsible for high pallidal signals are not linked to the impairment of bile excretion in liver cirrhosis.

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^{21, 22}. High pallidal signals have also been observed in patients with long standing portal-systemic shunt alone, due to portal vein thrombosis, without liver cirrhosis²³. Animal models of portal-systemic shunt without cirrhosis have higher concentrations of Mn in the basal ganglia than in animal models of cirrhosis²⁴. Moreover, high pallidal T1 signals were more prominent in patients with idiopathic portal hypertension than in patients with liver cirrhosis²⁵, showing that there is no correlation between pallidal T1 hyperintensity and the severity of liver dysfunction or hepatic encephalopathy. Taken together, these findings suggest that portal-systemic shunt *per se* may be a major determinant in the etiology of pallidal T1 signals. Since the liver plays an important role in regulating the distribution and excretion of Mn, portal-systemic shunt probably decreases the hepatobiliary clearance of Mn, resulting in increased blood Mn levels along with high pallidal T1 signals²⁶.

Our study had its limitation. Almost all patients had partial biliary obstruction of subchronic duration, although patients with acute obstructions, such as acute cholangitis, were excluded. Chronic and complete biliary obstruction may affect the intensity of the pallidal signal.

In summary, our findings indicate that portal-systemic shunt, rather than obstruction of biliary excretion, may be responsible for the increased blood Mn concentration and pallidal T1 signal observed in patients with chronic

liver diseases.

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