

## Portal-systemic encephalopathy with hypermanganesemia: A case report and review of the literature

### *Hipermanganesemili portosistemik ensefalopati: olgu sunumu ve literatürün gözden geçirilmesi*

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#### ABSTRACT

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome of patients with chronic liver disease. In addition to ammonia levels, increased manganese levels in the brain are also considered as having role in the pathogenesis of HE. On cranial T1-weighted magnetic resonance imaging (MRI), hyperintense and symmetrical globus pallidi linked to the manganese deposition are characteristic for patients with cirrhosis of the liver. We presented here a case of portal-systemic encephalopathy demonstrated with typical MR images and increased blood manganese concentration.

**Key words:** Chronic liver disease, manganese, T1-weighted hyperintensity

#### INTRODUCTION

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome characterized by symptoms varied from mild personality changes to coma. Despite an increase in concentrations of more than 20 toxic compounds in the blood samples of the patients with liver dysfunction, ammonia and manganese are considered as the leading causes for HE.<sup>1</sup> Pallidal signal hyperintensity on T1-weighted magnetic resonance imaging (MRI) in patients with chronic liver disease was attributed to the manganese deposition.

Herein, we reported a case of chronic liver disease with recurrent HE episodes having typical cranial MR images attributed to high serum manganese concentrations and we discussed the review of relevant literature.

#### ÖZET

Hepatik ensefalopati (HE), kronik karaciğer hastalarında izlenen nöropsikiyatrik bir sendromdur. Amonyak düzeylerine ek olarak beyinde artmış manganez düzeyinin de HE patogeneğinde rolü olduğu düşünülmektedir. Karaciğer sirozlu hastalarda Manyetik Rezonans incelemenin (MRI) T1 ağırlıklı kesitlerinde globus palliduslarda simetrik hiperintens görünüm, manganez depozisyonuna ilişkin karakteristik bir bulgudur. Biz bu makalede porto-sistemik ensefalopatili bir vakayı, tipik MR görüntüsü ve artmış kan manganez düzeyi ile sunmaktayız.

**Anahtar kelimeler:** Kronik karaciğer hastalığı, manganez, T1 ağırlıklı hiperintensite

#### CASE

A 29-year-old man admitted to our emergency department with the complaints of general weakness, decreased appetite, progressive speech disturbance and sleep tendency developed within two days. In his history, he had diagnosed with chronic liver disease at 6 years of age. Sclerotherapy for the esophageal variceal bleedings and splenectomy due to hypersplenism were also noted. He had no HE episode up to the last 3 months. In this period, however, he developed HE for 5 times.

Physical examination revealed prominent tendency to sleep, slurred speech and flapping tremor at emergency room. Abdominal examination was normal without ascites, collateral veins or organomegaly. Child Pugh score was noted as B. Significant

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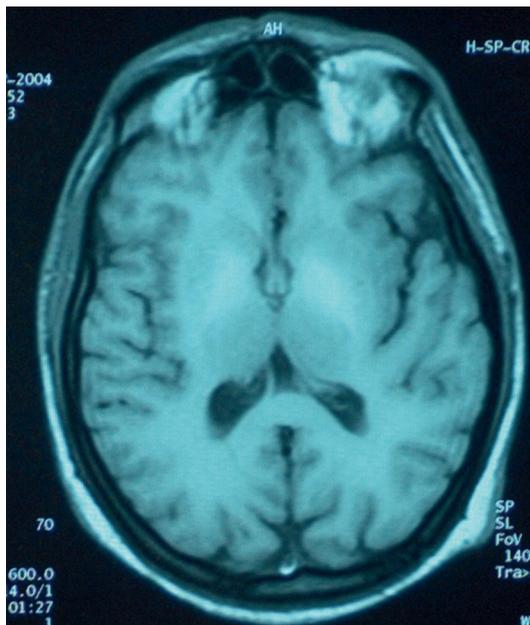
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laboratory findings were summarized in table-1. Serum creatinine level and electrolytes were in normal limits. Iron deficiency was detected with serum iron level; 27 µg/dl (50-175), transferrin saturation; 10 % and ferritin; 7.2 ng/ml (18-370). Peripheral blood smear revealed hypochromia and microcy-

tosis. Blood arterial ammonia level was 183µg /dl (45-80). Portal magnetic resonance imaging (MRI) venography showed an increased diameter of portal vein (27 mm), in addition to inferior and superior mesenteric veins. Splenic vein was in connection with renal vein via collateral veins.

**Table 1.** The results of laboratory tests

Variable		Patient's results	Normal limits
Blood Chemical Values	ALT (U/L)	71	10-35
	AST (U/L)	79	5-34
	GGT(U/L)	79	0-55
	ALP (U/L)	356	98-279
	Total Bilirubin (mg/dl)	1.3	0.2-1
	Direct Bilirubin (mg/dl)	0.4	0-0.4
	Albumin (g/dl)	3.3	3.8-4.4
	Total protein (g/dl)	6.9	6.4-8.3
Hematologic Values	Hemoglobin (g/ml)	9.4	14-18
	Haematocrit (%)	27	42-52
	MCV	77	80-94
	WBC (per/mm <sup>3</sup> )	7000	4800-10800
	Platelet (per/mm <sup>3</sup> )	130000	130000-400000
Coagulation Values	INR (seconds)	1.9	0.9-1.1
	aPTT (seconds)	36.5	25-35
	PT (seconds)	15.1	10-14



**Figure 1.** Symmetrical hyperintense lesions at bilateral globus pallidi, T1 weighted scan, cranial MRI

Cranial MRI was performed due to repeated encephalopathic states to rule out the organic pathologies. MRI demonstrated the symmetric hyperintense lesions at bilateral globus pallidi which were extending into the mesencephalome on T1 weighted scans (figure-1). Whole blood manganese concentration measured by atomic absorption spectrophotometry at admission was 593 nmol/L (72-110 nmol/L). We have started treatment for the HE and iron deficiency anemia. His symptoms improved progressively and during 10 months follow up, HE was not recurred.

## DISCUSSION

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome that may occur in such diverse clinical situations as acute or chronic liver diseases and spontaneous or iatrogenic portosystemic venous shunting.<sup>1</sup> It has recently been evidenced that,

in addition to ammonia, levels of manganese were also elevated in the brain<sup>2,3</sup> which may contribute to the pathogenesis of HE.<sup>4</sup>

Manganese is a trace element, which is primarily cleared by the liver. Inadequate elimination of manganese absorbed from the normal diet<sup>5</sup> and increased systemic availability due to portal-systemic shunting<sup>2</sup> may lead to manganese overload in the patients with liver disease. Kriger<sup>5</sup> et al have determined the whole blood manganese levels in patients with liver cirrhosis which were significantly increased as compared to controls and they have demonstrated the accumulation of manganese in the basal ganglia of patients with end stage liver diseases. Spahr and colleagues<sup>1</sup> have also demonstrated increased blood manganese concentrations in cirrhotic patients, especially with previous portacaval anastomoses or transjugular intrahepatic portosystemic shunts.

Our patient had the diagnosis of chronic liver disease for 23 years. Cranial MRI revealed bilateral symmetric T1 hyperintensities involving globus pallidi and extending into the mesencephalon. This was accepted as the characteristic finding of the manganese deposition.<sup>6</sup> Similar patterns of increased T1-weighted signal intensities can also be associated with lipid, hemoglobin breakdown products, melanoma, neurofibromatosis and calcification, which can be differentiated according to the clinical presentations and radiologic features. Signals induced by calcification can be ruled out by normal cranial computed tomography (CT) findings,<sup>7</sup> as performed in our case.

Whole blood manganese level measured via atomic absorption spectrophotometry was 593 nmol/L (72-110 nmol/L). Portal MRI venography established the spontaneous splenorenal shunt. We suggested that increased blood concentration of manganese was a result of impaired clearance of it, due to portal-systemic shunting developed because of hepatocellular dysfunction. In general, the transport of manganese across the intestinal tract is poorly understood. It is thought to occur through mechanisms similar to that regulating non-heme iron uptake.<sup>8</sup> Interdependence between manganese and iron on their transport has been demonstrated in some studies.<sup>9</sup> Malecki and colleagues<sup>9</sup> found that iron deficiency is an exacerbating factor, for increased intestinal absorption of manganese. In

our patient, iron deficiency anemia due to internal hemorrhoidal bleeding was detected. We speculated that increased absorption of manganese -in addition to decreased elimination- might have a role in its elevated blood concentration. We added oral iron replacement therapy to the treatment.

The hyperintensity of the T1 signal is related to a high incidence of extrapyramidal dysfunction including rigidity, tremor, akinesia and athetosis in cirrhotic patients.<sup>4,10,11</sup> Extrapyramidal symptoms may result from a toxic effect of manganese on basal ganglia dopaminergic functions.<sup>12</sup> Spahr and colleagues<sup>1</sup> have reported that there was no significant correlation between blood manganese levels and extrapyramidal symptoms. In our patient, although the blood manganese level was elevated significantly, he only presented with flapping tremor without any other signs of extrapyramidal dysfunction.

Surgical obliteration of portal-systemic shunts or obliteration by interventional radiological techniques are fairly effective in reversing intractable portal-systemic encephalopathy, but it is often associated with ascites accumulation and/or formation of esophageal varices.<sup>13</sup> In our patient, in spite of the long duration of liver disease, he had never developed HE episode before to the last 3 months. The life threatening risks of intervention were taken into consideration and conservative therapy by removing exacerbating factors was initially planned for the patient. The treatment included preventive approaches for bleeding from the hemorrhoids, the iron replacement therapy for the anemia and recommendations of the diet poor from the manganese. The patient has remained stable and HE was not noted during 10 months follow up period.

In conclusion, the deposition of manganese in the brain of the patients with chronic liver disease may contribute to the pathogenesis of HE and should be considered especially for the ones having portal-systemic shunts. Manganese overload might be avoided with low manganese diet, removing factors promoting intestinal absorption and probably with chelating agents; which should be addressed in further studies.

## REFERENCES

1. Spahr L, Butterworth RF, Fontaine S, et al. Increased blood manganese in cirrhotic patients: relationship to pallidal

- magnetic resonance signal hyperintensity and neurological symptoms. *Hepatology* 1996;24(5):1116-20.
2. Riordan S.M, Williams R. Treatment of hepatic encephalopathy. *N Engl J Med* 1997;337 (7):473-9.
  3. Choi Y, Park JK, Park NH, et al. Whole blood and red blood cell manganese reflected signal intensities of T1-weighted magnetic resonance images better than plasma manganese in liver cirrhotics. *J Occup Health* 2005;47(1):68-73.
  4. Hauser RA, Zesiewicz TA, Rosemurgy AS, Martinez C, Olanow CW. Manganese intoxication and chronic liver failure. *Ann Neurol* 1994;36(6):871-5.
  5. Krieger D. Manganese may be of importance in the pathogenesis of chronic hepatic encephalopathy. *Biomed Pharmacotherapy* 1996;50(2):93-6.
  6. Gospe SM Jr, Caruso RD, Clegg MS, et al. Paraparesis, hypermanganesaemia, and polycythaemia: a novel presentation of cirrhosis. *Arch Dis Child* 2000;83(5):439-42.
  7. Rose C, Butterworth RF, Zayed J, et al. Manganese deposition in basal ganglia structures results from both portal-systemic shunting and liver dysfunction. *Gastroenterology* 1999;117(3):640-4.
  8. Krieger D, Krieger S, Jansen O, Gass P, Theilmann L, Lichtenacker H. Manganese and chronic hepatic encephalopathy. *Lancet* 1995;346(8970):270-4.
  9. Fitsanakis VA, Zhang N, Garcia S, Aschner M. Manganese (Mn) and iron (Fe): interdependency of transport and regulation. *Neurotox Res* 2010;18:124-31.
  10. Weissenborn K, Ehrenheim C, Hori A, Kubicka S, Manns MP. Pallidal lesions in patients with liver cirrhosis: clinical and MRI evaluation. *Metab Brain Dis* 1995;10(3):219-31.
  11. Pomier-Layrargues G, Spahr L, Butterworth RF. Increased manganese concentrations in pallidum of cirrhotic patients. *Lancet* 1995;345(8951):735-7.
  12. Ikeda S, Yamaguchi Y, Sera Y, et al. Manganese deposition in the globus pallidus in patients with biliary atresia. *Transplantation* 2000; 69(11):2339-43.
  13. Kashida H, Kondo M, Fukunaga T, et al. Reversal of portal-systemic encephalopathy by shunt-preserving disconnection of portal and systemic circulation. *Nihon Shokakibyo Gakkai Zasshi* 1996;93(2):96-103.