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ROLE OF MANGANESE IN THE PATHOGENESIS OF PORTAL-SYSTEMIC ENCEPHALOPATHY

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ABSTRACT

Amongst the potential neurotoxins implicated in the pathogenesis of hepatic encephalopathy, manganese emerges as a new candidate. In patients with chronic liver diseases, manganese accumulates in blood and brain leading to pallidal signal hyperintensity on T_1-weighted Magnetic Resonance (MR) Imaging. Direct measurements in globus pallidus obtained at autopsy from cirrhotic patients who died in hepatic coma reveal 2 to 7-fold increases of manganese concentration. The intensity of pallidal MR images correlates with blood manganese and with the presence of extrapyramidal symptoms occurring in a majority of cirrhotic patients. Liver transplantation results in normalization of pallidal MR signals and disappearance of extrapyramidal symptoms whereas transjugular intrahepatic portosystemic shunting induces an increase in pallidal hyperintensity with a concomitant deterioration of neurological dysfunction. These findings suggest that the toxic effects of manganese contribute to extrapyramidal symptoms in patients with chronic liver disease. The mechanisms of manganese neurotoxicity are still speculative, but there is evidence to suggest that manganese deposition in the pallidum may lead to dopaminergic dysfunction. Future studies should be aimed at evaluating the effects of manganese chelation and/or of treatment of the dopaminergic deficit on neurological symptomatology in these patients.

Keywords: Manganese, portal systemic encephalopathy, Magnetic Resonance Imaging, globus pallidus, extrapyramidal disorders, portacaval shunt.

INTRODUCTION

The pathophysiology of hepatic encephalopathy is still not well understood despite many investigations that have been carried out during the last 50 years. Neurological manifestations are considered to result from a derangement of multiple neurotransmitter systems. Accumulation of several neurotoxic substances have been reported and it is likely that many of them contribute to the pathogenesis of HE. Manganese has been suggested recently as another candidate substance. There is increasing evidence to suggest that manganese deposition occurs in the brain (and more specifically in the basal ganglia) of patients with chronic liver disease and also in patients with spontaneous or surgically-induced portacaval shunt (PCS).

EVIDENCE FOR BRAIN MANGANESE OVERLOAD IN CHRONIC LIVER DISEASES

Pallidal signal hyperintensity on magnetic resonance imaging (MRI) has been observed in a majority of cirrhotic patients (Figure 1; Krieger *et al.,* 1996; Pujol *et al.,* 1993; Spahr *et al.,* 1996). Such images could theoretically be caused by lipid deposition, calcification, melanin, methemoglobin or manganese. Recent autopsy studies in cirrhotic patients demonstrated an increased manganese content in the brain and more specifically in the pallidum (Figure 2; Krieger *et al.,* 1995; Maeda *et al.,* 1997; Pomier-Layrargues *et al.,* 1995); in these patients, other causes for MRI pallidal hyperintensities had been ruled out.

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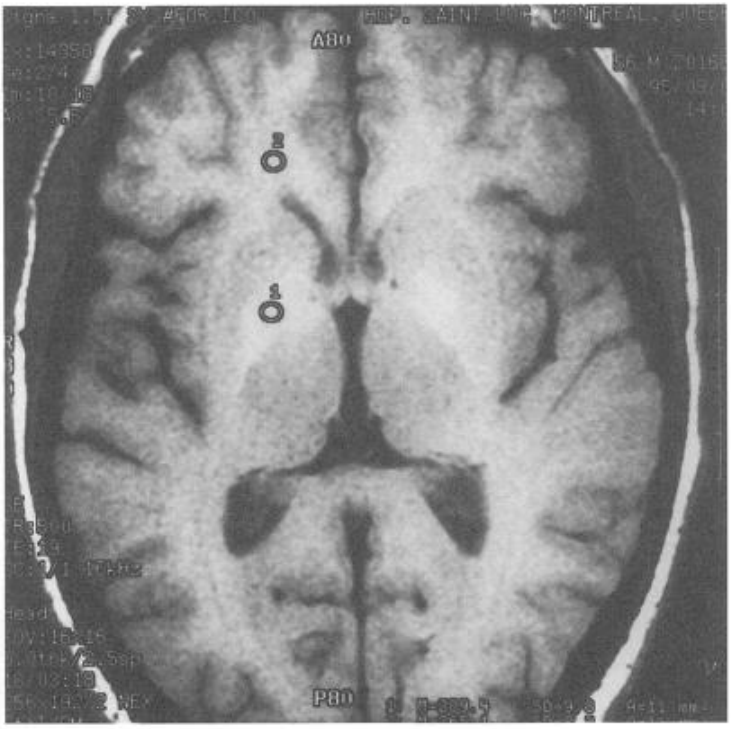

Figure 1: Pallidal hyperintensity on T_1-weighted MR image from a cirrhotic patient. Pallidal index calculated as the ratio of globus pallidus (1) to subcortical frontal white-matter (2) intensity was 133 (normal range: 96 - 103).

Further evidence suggesting that MR images result from manganese deposition is provided by observations in patients receiving long term parenteral nutrition where typical pallidal i mages disappeared after cessation of manganese supplementation (Mirowitz *et al.,* 1991; Mirowitz *et al.,* 1992). Prolonged inhalation of manganese dusts in miners produces similar MR images (Nelson *et al.,* 1993); furthermore exposure of monkeys to manganese administered either by inhalation or intravenously results in selective pallidal hyperintensities on MR imaging (Shinotoh *et al.,* 1995).

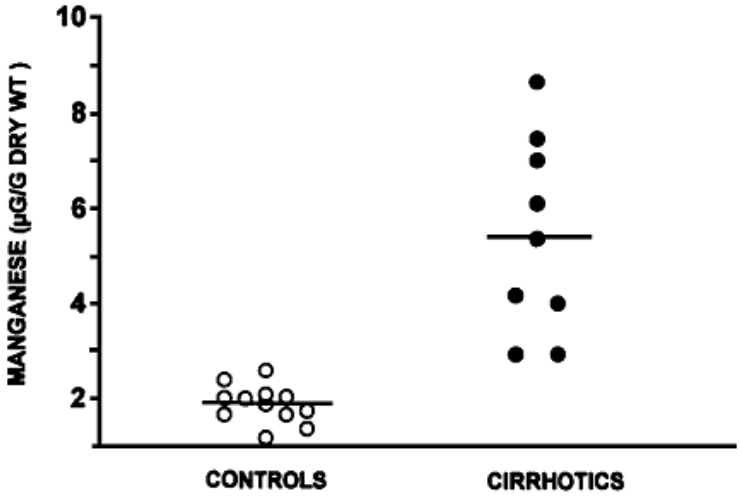

Figure 2: Manganese concentrations in globus pallidus of cirrhotic patients who died in hepatic coma (•) and age-matched controls (C). Mean values in the cirrhotics are significantly higher than controls, $p < 0.01$. (Adapted from Pomier-Layrargues *et al.,* 1995).

RELATIONSHIP BETWEEN BRAIN MANGANESE DEPOSITION AND CHRONIC LIVER DISEASE

Average daily oral manganese intake is 2.5 - 3mg. Only 1-3% of this normally reaches the systemic circulation because manganese is rapidly cleared by the liver and excreted into the bile (Papavasiliou *et al.,* 1966). Increases in blood manganese levels have been reported previously in cirrhotic patients (Spahr *et al.,* 1996; Versieck *et al.,* 1974; Hauser *et al.,* 1994; Hauser *et al.,* 1996) and it was shown that blood manganese correlated with brain MRI changes in patients with chronic liver disease (Figure 3).

Potential mechanisms responsible for manganese overload include a decrease in elimination via biliary excretion and an increased systemic availability due to portosystemic shunting.

Cirrhosis is associated with a variable degree of cholestasis that can diminish biliary manganese excretion. In addition, abnormalities of microcirculation (capillarization of the sinusoids and/or intrahepatic shunting) are present in a cirrhotic liver. Alternatively (or additionally) increased blood manganese in cirrhotic patients could result from the presence of portal-systemic collaterals produced either spontaneously or following surgical (portocaval anastomosis) or transjugular intra-hepatic portosystemic shunt (TIPS).

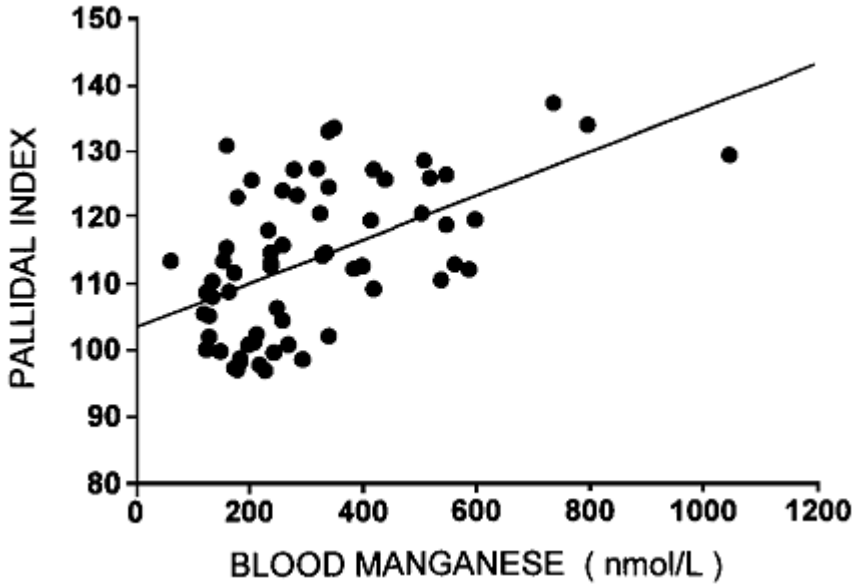

Figure 3: Correlation between pallidal index measured on T_1-weighted MR images and blood manganese concentrations ($r = .543$; $p < 0.001$). (Data from Spahr *et al.,* 1996).

Experimental and clinical observations provide some clues to the relative importance of these potential mechanisms. Portosystemic shunting plays a major role. We previously observed significant correlations between blood manganese, pallidal hyperintensity and the presence of portal-systemic shunting in cirrhotic patients (Spahr *et al.,* 1996). A significant increase of pallidal hyperintensity has been reported to occur after TIPS (Krieger *et al.,* 1997). Typical pallidal images were also described in a patient with patent ductus venosus (spontaneous portocaval shunt) in the absence of liver disease (Yanai *et al.,* 1995) and in 6 patients with portal vein thrombosis, portal-systemic collaterals and a normal liver (Nolte *et al.,* 1998). On the other hand, the important pathogenetic role of liver failure is illustrated by the disappearance of pallidal hyperintensity several months after liver transplantation (Pujol *et al.,* 1993). More recently, brain manganese accumulation was observed in a rat model of cholestatic cirrhosis as well as in rats with end-to-side portacaval shunt but with a normal liver (Rose *et al.,* 1997).

RELATIONSHIP BETWEEN BRAIN MANGANESE ACCUMULATION AND NEUROLOGICAL SYMPTOMS IN CIRRHOTIC PATIENTS

Manganese neurotoxicity had previously been reported in miners after a prolonged exposure to manganese dust, resulting in extrapyramidal symptoms resembling Parkinson's disease (Yamada *et al.,* 1986). In cirrhotic patients a high incidence of extrapyramidal symptoms is observed when a detailed and careful neurological evaluation is performed (Spahr *et al.,* 1996). Moreover, anatomical or functional lesions in the pallidum might induce cognitive deficits which are part of the clinical spectrum of neurological symptoms associated with hepatic encephalopathy (Iregren, 1994; Mergler and Baldwin, 1997).

The question then arises as to whether pallidal manganese accumulation in cirrhotic patients might be related to the occurrence of neurological dysfunction in these individuals. Studies attempting to correlate neurological symptoms with MR imaging used as an index of brain manganese content have so far yielded conflicting results (Krieger *et al.,* 1996; Kulisevsky *et al.,* 1992; Spahr *et al.,* 1996; Spahr *et al.,* 1998; Taylor-Robinson *et al.,* 1995; Weissenborn *et al.,* 1995). This is not surprising because MRI provides only a semi-quantitative estimate of brain manganese concentration. Unfortunately, in vivo measurement of brain manganese is impossible to perform. An interesting alternative to evaluate the pathophysiological significance of brain manganese deposits would be to evaluate the influence of changes in liver function (before and after liver transplantation) or the degree of portosystemic shunting (before and after TIPS) on both neurological status and MR signal intensities. Accordingly it has been demonstrated that, several months after liver transplantation, neurological dysfunction improved or normalised and that MR pallidal hyperintensity disappeared (Devenyi *et al.,* 1994, Pujol *et al.,* 1993). More recently, it has been shown that, after the placement of an intrahepatic shunt, pallidal hyperintensity and neurological impairment worsened in a population of cirrhotic patients treated with this procedure compared to a control group (Krieger *et al., 1*997).

There are also similarities between the neuropathologic lesions observed in the brains of monkeys and humans intoxicated with manganese (Yamada *et al.,* 1996) and the brains of cirrhotic patients who died with hepatic encephalopathy (Butterworth *et al.,* 1987); Alzheimer type II changes have been observed in both circumstances and were predominant present in basal ganglia.

To summarize, increasing evidence supports a pathophysiologic link between brain manganese accumulation and the onset of neurological dysfunction in cirrhotic patients. However, the mechanisms of manganese neurotoxicity are still speculative.

It has been suggested that manganese might influence dopaminergic neurotransmission. Chronic inhalation of manganese in primates results in a 60-80% increase in pallidal manganese and in concomitantly reduced dopamine concentrations (Bird *et al.,* 1984). Other studies have demonstrated that manganese stimulates dopamine release from nerve endings (Drapeau and Machshev, 1984) and displaces dopamine from its storage sites (Lista *et al.,* 1986). Chronic manganese administration causes increased activity of the monoamine-degrading enzyme monoamine oxidase (MAO) in brain (Subhash and Padmashree, 1990, Leung *et al.,* 1986). Increased activities of both MAO_A and MAO_B isoforms have been described in autopsied brain tissue from cirrhotic patients who died in hepatic coma (Raghavendra Rao *et al.,* 1993) and a selective loss of binding sites for the dopamine D_2 receptor ligand ^3H spiperone has been observed in pallidum of cirrhotic patients (Bergeron *et al.,* 1989).

A number of other mechanisms for manganese neurotoxicity have been suggested (Aschner *et al.,* 1991): alterations of membrane fluidity, interference with enzymatic function in the CNS (such as glutamine synthetase, cytochrome P450-dependent drug hydroxylation activity, calmodulin-related Ca^{2+}-ATPase activity), inhibition of [H^3]-kainic acid, a glutamate receptor ligand, to forebrain membranes and the creation of oxidative stress following manganese accumulation within the mitochondria.

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CONCLUSIONS AND PERSPECTIVES FOR THE FUTURE

There is evidence to suggest that chronic liver insufficiency and portosystemic shunting results in accumulation of manganese in the brain and particularly in the basal ganglia. The pathophysiological significance of this region-selective manganese deposition remains to be established.

There is a poor relationship between cognitive abnormalities associated with hepatic encephalopathy and brain manganese overload; however the occurrence of extrapyramidal disorders is increasingly recognized in cirrhotic patients and there is a rational basis to hypothesize a relationship between manganese accumulation in basal ganglia and the presence of certain cognitive and motor symptoms. Clearly, further studies are needed to address these issues. If neurotoxic effects of manganese are clearly established in the future, chelation therapy could be tried in the hope of removing manganese and improving neurological dysfunction in patients with chronic liver diseases.

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