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CLINICAL STUDIES

Blood manganese levels in patients with hepatic encephalopathy☆

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ABSTRACT

Project: Hepatic encephalopathy is an increasingly common disease. Identification of prognosis risk factors in patients with liver damage may lead to preventive actions, towards decreasing its mortality. Manganese (Mn) levels are increased in basal ganglia of patients with hepatic encephalopathy as well as in cases of cirrhotic and liver failure patients. The present is a clinical, prospective, prolective and observational study developed at the Internal Medicine Service from "Dr. Darío Fernández Fierro" General Hospital, ISSSTE, Mexico City. The objective of this work was to report whole blood Mn levels and mortality in encephalopathic patients.
Procedure: Consecutive patients over 18 years of age, diagnosed with hepatic encephalopathy were recruited at the emergency room service. An informed consent, signed by their families was collected. Patients' clinical characteristics, biochemical tests of renal function, hemoglobin, glucose, bilirubins and albumin levels were obtained along with a blood sample to analyze Mn. Patients evolution was followed up for 6 months.
Results: Blood Mn in patients [median, (range)] [20.5, (10.5–39.5) μg/L] were higher than blood levels from a group of healthy volunteers [7.5, (6.1–12.8) μg/L] ($P < 0.001$). Among 9 patients studied four died, 2 women and 2 men, those patients showed higher ($P = 0.032$) Mn levels [28, (17–39.5) μg/L] than those alive [13.5, (10.5–32) μg/L] after the follow up period.
Conclusions: In this pilot study, Mn blood levels were higher in hepatic encephalopathy that died as consequence of the disease that those that survived in a 6 month follow up period. Blood Mn could be a potential prognosis factor for death in patients with hepatic encephalopathy.

Introduction

Hepatic encephalopathy is a serious complication of both acute and chronic liver failure. Precipitating factors of hepatic encephalopathy include gastrointestinal bleeding, oral protein load and the use of sedatives [1]. Although the precise pathophysiologic mechanisms are not completely understood, current available evidence suggests that the accumulation of neurotoxins, regularly disposed by liver function, is the primary cause of this condition, predisposing to neurotransmission changes.

The presence or severity of hepatic encephalopathy does not always show a consistent relationship with the severity of liver disease or portal hypertension, suggesting that other predisposing or precipitating factors may be involved. Recent studies reveal that exposure to ammonia and/or manganese (Mn) in liver failure results in altered expression of several genes [2]. Such alterations include decreased expression of the glutamate transporter GLT-1, and increased expression of monoamine oxidase, the "peripheral-type" benzodiacepine receptor, as well as constitutive neuronal nitric oxide synthase. These changes result in altered protein expression and increased extracellular brain glutamate, degradation of monoamine neurotransmitters, synthesis of neurosteroids with inhibitory properties and production of nitric oxide in the brain [3,4]. Other neurotransmitter systems implicated in the pathogenesis of hepatic encephalopathy include the synaptic deficit in the serotonin system, as well as the catecholaminergic and opioid systems along with increased presence of "endogenous" benzodiazepine-like compounds.

In patients with hepatic encephalopathy increased blood levels of Mn, a well-known neurotoxic metal, with biliary excretion has been described. Furthermore, the metal is found accumulated in basal ganglia of cirrhotic and liver failure patients [5–7]. Mn is a structural part of arginase, an important enzyme in the urea metabolism. Mn is a structural part of

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arginase, an important enzyme in the urea metabolism. Mn also acts as cofactor of numerous enzymes in Krebs cycle, particularly in the decarboxylation process. Magnetic resonance images (MRI) studies suggest the accumulation of Mn and the development of osmotic abnormalities in the brain of patients with cirrhosis [8–10]. The frontal cortex is also a site for deposition of Mn [11,12], and some cognitive functions related to this part of the brain and its connections with other cortical and subcortical areas could be affected by Mn [13].

Evidence suggests that neurosteroids synthesized in the central and peripheral nervous system, either from cholesterol or from steroid precursors, are involved in the pathogenesis of hepatic encephalopathy [14]. In the brain, neurosteroids are mainly produced in the mitochondria of astroglial cells. Translocator proteins are situated on the mitochondrial membrane in astrocytes and regulate neurosteroid synthesis. Ammonia and Mn are thought to enhance neurosteroid synthesis by activating these translocator proteins [15]. It has also been reported that Mn affects the glutamate N-methyl-D-aspartate (NMDA) receptors, which are involved in learning [16].

Toxic effects of Mn on central nervous system could also be mediated by its effects on the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH). It was also suggested that Mn-induced increases of "peripheral type" benzodiazepine receptors (PTBRs) could contribute to the pathogenesis of hepatic encephalopathy [17]. Mn is a potent dopamine oxidant, which could explain the toxic lesions in certain dopaminergic brain regions [18,19]. Another hypothesis for the toxic mechanism of Mn is the production of excess free radicals in the nerve cell, potentiating lipid peroxidation and resulting in tissue damage [20].

Three clinical syndromes attributed to Mn toxicity are described on the basis of the predominant symptoms and neurologic findings: (a) parkinsonism, (b) gait ataxia plus other features, and (c) cognitive impairment with psychiatric symptoms [21].

Orthotopic liver transplantation normalizes pallidal MRI signals, blood Mn levels in cirrhotic patients and clinical signs [22], suggesting that: (a) pallidal MRI signal hyperintensity is the result of Mn deposition and (b) alterations of dopaminergic function due to the toxic effects of Mn may contribute to the extrapyramidal symptoms in these patients [23].

The aim of this pilot study was to report whole blood Mn levels and mortality in encephalopathic patients at the "Dr. Darío Fernández Fierro" General Hospital, ISSSTE, Mexico City.

Methods

Subjects

This clinical, prospective, observational study included consecutive patients, males and females over the age of 18 years, with hepatic encephalopathy. Our exclusion criteria were: (a) portal bypass surgery, (b) cancer of any localization, (c) severe diseases that shorten life expectancy to less than 6 months, and (d) psychiatric illness. The withdrawal of any subject was based on the decision of patient's family, or due to life-threatening conditions. For comparison, blood samples from 11 healthy volunteers, five women and six men were collected.

Ethics approval was obtained from the ethics committee of the "Dr. Darío Fernández Fierro" General Hospital and was in accordance with the 1975 Helsinki Declaration on Human Rights, as revised in Edinburgh 2000. Patients were included after written informed consent was obtained from each patient's next of kin.

Patients' clinical characteristics were obtained and, after discharge, they were given an appointment to an external consultation every 2 months.

Clinical evaluation

The medical staff of the Department of Internal Medicine evaluated the patients, including their level of ascites and nutritional status.

Laboratory

Blood samples were collected into Vacutainer tubes. For Mn, a sample of blood was stored in metal-free Vacutainer tubes with EDTA as an anticoagulant until assayed. Biochemical tests of renal function, hemoglobin, glucose, bilirubins and albumin levels were measured according to standardized procedures in the Clinical Laboratory of the "Dr. Darío Fernández Fierro" General Hospital.

Manganese

From encephalopathic patients admitted at the Department of Internal Medicine after being stabilized in the Emergency Room, we took individual blood samples of 5 ml early in the morning, before breakfast, and refrigerated them until they were analyzed in the Neurochemistry Laboratory at the National Institute of Neurology and Neurosurgery "Dr. Manuel Velasco Suárez", Mexico City, with a graphite furnace atomic absorption spectrophotometer (GFAAS), according to the technique reported by Pleban et al. [24]. A Perkin-Elmer 3110 atomic absorption spectrophotometer and an HGA-600 graphite furnace with AS-60 autosampler were used. Calibration curves were constructed with a commercial standard solution (Merck Titrisol). Quality control was assured by analysing the biological matrix bovine liver (NIST 1577b) as external standard. The analysis was considered as analytically valid if values for Mn standard were in a 95% confident interval based on the certified concentration. An additional sample of blood was obtained from 10 healthy individuals with similar age and gender to serve as a reference of blood Mn value. Samples from patients and controls were analyzed in duplicate in all cases standard deviations were lower than 10%; if otherwise the sample was re-analyzed.

Statistical analysis

Results of numerical variables were expressed in median and range; group comparisons were made with the Mann–Whitney *U* test using the Statistical Package for Social Sciences (SPSS) program version 10 (SPSS Inc., North Carolina, USA).

Results

A total of nine patients fulfilled the inclusion criteria. The age [median, (range) years] in men ($n = 5$) was [61, (49–75)] and in women ($n = 4$) was [54, (49–67)]. The full description of the encephalopathic grade and liver enzymes is shown in Table 1.

As controls, we obtained blood samples from 11 healthy volunteers, with age [median, (range) years] in men ($n = 6$) [55, (40–70)] and in women ($n = 5$) [55, (38–62)].

According to our results, in patients, the age [median, (range) years] of those who died ($n = 4$) was [55, (49–67)], while for those alive after 6 months ($n = 5$) was [60, (53–75)]. Hemoglobin, glucose, creatinine and albumin showed similar values between these two groups. Blood Mn [median, (range) μg/L] levels found in patients [20.5, (10.5–39.5)] were higher ($P < 0.001$) than those from the group of healthy volunteers [7.5, (6.1–12.8)].

By gender, among women, there was a statistical difference ($P < 0.05$) in blood manganese between patients [29.2, (17–39.5)μg/L] and controls [9.1, (6.8–12.8)μg/L]; likewise, among men there was also a statistically significant difference ($P < 0.01$)

Table 1
Child-Pugh scores, liver enzymes and comorbidities.

	Males					Females			
	1	2	3	4	5	1	2	3	4
Bilirubin (mg/dl)	1	1.8	1.9	1.8	3.6	12	1.7	3.8	8
Albumin (mg/dl)	2	1.9	2.2	2.2	2.6	1.8	2.4	2	3
INR	1.02	1.6	1.9	1.6	2.2	2.5	0.84	3.8	1.9
Ascites	Mild-moderate	Absent	Absent	Absent	Mild-moderate	Mild-moderate	Absent	Mild-moderate	Mild-moderate
Encephalopathy	Mild (I–II)	Severe (III–IV)	Mild (I–II)	Severe (III–IV)	Severe (III–IV)	Severe (III–IV)	Severe (III–IV)	Mild (I–II)	Mild (I–II)
Child-Pugh score	9	9	9	9	13	14	9	13	11
ALT (U/L) male: 10–40 and female: 7–35	76	26	39	96	210	280	140	55	67
AST (U/L) male and female: 15–30	117	111	81	149	260	300	125	91	77
LDH (U/L) male and female: 100–190	406	406	304	400	460	450	290	407	340
ALP (U/L) male and female: 30–120	202	202	180	189	240	300	200	100	120
Precipitating factors	Urinary tract infection	Acute on chronic renal failure	Urinary tract infection, acute on chronic renal failure	Urinary tract infection. Death by gastrointestinal bleeding at day 80 after recruitment	Upper gastrointestinal bleeding, death at day 55 after recruitment	Death in less than 24 h by acute pulmonary edema	Urinary tract infection	Death in less than 24 h	Pneumonia
Chronic diseases	Alcoholism, hypertension	Chronic renal failure, alcoholism, hypertension	Alcoholism, hypertension	Alcoholism, hypertension	Alcoholism, esophageal varices	Hepatitis C	Hepatitis C, alcoholism, 2DM	Hepatitis C	Alcoholism, 2DM

ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; INR: International Normalized Ratio; 2DM: type 2 diabetes mellitus.

between patients [13.5, (10.5–35.5)μg/L] and controls [7.5, (6.1–9.2)μg/L].

Given the information that we got, in patients, there was a statistical significant difference in Mn level between clinical evolution, death [28, (17–39.5) μg/L] vs. living [13.5, (10.5–32)μg/L] ($P = 0.032$) but not between gender ($P = 0.19$) (Table 2). Of particular concern, the blood levels of Mn were higher in patients with Child-Pugh C liver cirrhosis [29.2, (10.5–39.5) μg/L] in comparison to patients with Child-Pugh B [17, (12.5–35.5) μg/L].

We also noted that 75% of women had severe hepatopathy (Child-Pugh class C). Moreover, severe encephalopathy (grades 3 and 4) and mortality was at 50% in this group, whereas in men there was only one case with Child-Pugh class C, with both severe encephalopathy and mortality in 40% of male cases.

Among all patients urinary tract infection was the most common precipitating factor, while alcoholism was the main chronic disease, followed by hypertension. The only two cases without alcoholism died because of hepatitis C infection (Table 2).

Discussion

Mn is an essential metal that in excess can be toxic, especially to the brain. Taking into account that chronic exposure of to Mn results in extrapyramidal symptoms like tremor, rigidity, athetosis and psychological disturbances that resemble hepatic encephalopathy, it is suggested that cerebral Mn deposition is related to some signs and symptoms of hepatic encephalopathy, such as postural tremor [25]. Acute, high-level occupational Mn exposure causes "Manganism" characterized by progressive parkinsonism, dystonia and neuropsychiatric symptoms [26]. Other source of Mn accumulation in the brain, mainly in the basal ganglia, is due to biliary excretion deficiency [27]. In our patients, we have observed a critical prevalence of alcoholism, and as the actual statistics establish a continuous increase of this pathology even in pregnant women [28], it is expected to be the main cause of death attributed to liver disease in the coming years.

One difficulty in the study of Mn exposure is the lack of a well-recognized bioindicator of exposure. On an epidemiologic comparison basis, blood Mn levels may serve reasonably well as an indicator of recent Mn exposure. However, a relatively large variation in blood Mn among individuals, due to either diet or other unknown sources, suggests that this measure may not be the best parameter for the estimation of chronic exposure to this metal [29,30]. In this regard, Mergler and Baldwin showed a lack of correlation between blood Mn and neurological effects [31], while other authors think that the severity of motor dysfunction depends on the dose of exposure, and involves both the amount and the duration [32,33]. The assessment of Mn in hair has several advantages over other biomarkers. Hair averages off the variations of Mn levels found in blood or plasma, as it grows an average of 11 mm/month, thus representing a time-weighted average over the duration of exposure. To date, there have not been publications on hair Mn levels being useful to evaluate toxicity by this metal in liver failure, but it should be considered as suitable. In our study, a major drawback to the use of hair as a marker of internal dose of exposure was that most patients were bald.

Generally accepted methods for assessing the clinical status and severity of disease in cirrhotic patients are the Child-Pugh-Turcotte classification [34] and the Model for End-stage Liver Disease (MELD) [35,36]. Unfortunately, these systems do not include an assessment of nutritional status in spite of the fact that malnutrition plays an important role in morbidity and mortality in end-stage liver failure. The omission of nutritional assessment results no doubt from the heterogeneous nature of the nutritional deficits in this population.

Table 2
Child-Pugh classification, age and laboratory results in patients with hepatic encephalopathy at the moment of recruitment.

Gender	Child-Pugh	Age (years)	Leucocytes (mil/mm^3)	Hb (g/dl)	Glucose (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	Mn* (μg/L)
Male	B†	49	7700	10.6	78	128	2.8	35.5
	B†	61	2400	10.6	67	46	0.7	20.5
	B	75	5900	14.5	210	81	2.9	12.5
	B	60	6000	13.5	110	98	2	13.5
	C	70	6800	11.5	99	56	3.4	10.5
Mean		63	5760	12.1	112.8	81.8	2.4	18.5
SD		10	2013	1.8	56.9	33.0	1.1	10.2
Female	C†	49	8500	13	180	140	3	39.5
	B†	67	9900	9.3	78	152	1.3	17
	C	53	5500	11.8	161	41	0.8	26.5
	C	55	7200	12	200	80	1.8	32
Mean		56	7775	11.5	154.8	103.3	1.7	28.8
SD		8	1875	1.6	53.6	52.1	0.9	9.5

SD: standard deviation; Hb: hemoglobin; Mn: manganese.
Control values: leucocytes: male and female: 5–10; Hb: male: 14–18, female: 12–16; glucose: male and female: 70–100; urea: male and female: 15–38; creatinine: male: 0.7–1.3, female: 0.6–1.1; Mn: male: 4.6–10.2, female: 4.3–13.9.
* $P = 0.032$ between "death vs. living".
† Death within 6 months.

In our study, two patients died in 24 h and two more in less than 3 months; of the two, both had blood Mn levels higher than 0.54 μmol/L (30 μg/L) and one higher than 0.36 μmol/L (20 μg/L); it is noteworthy that they died even though they were younger than those who were alive after 6 months. We cannot be certain of the role of high levels of Mn as a factor for the deaths in our study, although the overlap in these patients, and with other series, is noteworthy. For example, Krieger found significantly increased ($P = 0.0004$) whole blood Mn concentrations in patients with liver cirrhosis, median 0.62 μmol/L (34.4 μg/L) vs. 0.18 μmol/L (10.3 μg/L) in controls [5]. This result is in agreement with the present study, since we found higher values in patients [20.5, (10.5–39.5) μg/L] than in controls [7.5, (6.1–12.8) μg/L]. Even more, in our study, two patients died with Mn levels above 0.54 μmol/L (30 μg/L), suggesting that 0.54 μmol/L (30 μg/L) could be a value of prognosis. As Rahelic et al. [37], we found higher levels of Mn in patients with Child-Pugh C liver cirrhosis. Some authors discuss that as a result of a different metabolism between gender, women absorb more Mn than men [38–40] but we did not find this difference neither in patients nor in controls as being statistically significant.

Furthermore, it has been published that some factors may contribute to the presence and severity of hepatic encephalopathy independent of the severity of liver disease [41]. Based on the results from the present study, we suggest Mn could be a potential mortality prognosis factor in cases of hepatic encephalopathy, but further studies are warranted to investigate this hypothesis with more patients and complementary information, taking into account that measurement of Mn has limited prognostic value when other essential metals are likely affected as well, iron in particular. In this study we did not perform iron levels status as some patients received blood transfusion as soon as they arrived to the emergency room. We also believe that neuropsychological testing for the assessment of Mn neurotoxicity [42] should be useful in daily practice.

Finally, the treatment of hepatic encephalopathy is controversial. Empiric therapy is largely based on the principle of reducing the production and absorption of ammonia in the gut through administration of pharmacological agents such as rifaximin and lactulose, which are approved by the FDA. Future studies should be aimed at evaluating the effects of Mn chelation in these patients. Nonetheless with these evidences, liver transplantation might be the only option for some patients [43], even though the parkinsonian and the neuropsychiatric changes might persist even after this procedure [44]. A crucial issue, therefore, is that the workup of a patient who is eligible for liver transplantation should be initiated at the earliest opportunity after an acute episode of hepatic encephalopathy. Moreover, the severity of hepatic encephalopathy before liver transplantation is inversely correlated with the duration of survival after transplantation [45]. Surgical portosystemic shunting or tiPs placement worsens hepatic encephalopathy because ammonia in the gut circulation can then bypass metabolism in the liver and go directly to the brain. The best understanding of hepatic encephalopathy could derive in new therapeutic and even preventive alternatives to reduce relapses and hospitalizations.

Conclusions

Despite the low number of patients included in the present study, higher levels of Mn could be associated with increased mortality in patients with liver cirrhosis and encephalopathy. This finding may represent only more advanced grades of the disease or it can mean an independent prognostic factor. Studies with a larger number of patients could clarify these assumptions and even more determine whether Mn levels affect women differently than men.

Conflict of interest

None disclosed.

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All authors have made a significant intellectual contribution to the manuscript.

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