CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1487928

Available online at: http://www.iajps.com Research Article

FREQUENCY OF ZINC DEFICIENCY IN PATIENTS WITH HEPATIC ENCEPHALOPATHY

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Abstract:
Objective: *The objective of this study was to assess the frequency of zinc deficiency in patients with hepatic encephalopathy.****Study Design****: Cross Sectional Study.****Setting****: Study was conducted in Medical Unit-II, Jinnah Hospital Lahore.****Study Duration****: Present research was conducted from 03-02-2017 to 02-02-2018.****Material and Methods:*** *130 patients, whom were diagnosed with hepatic encephalopathy in Jinnah Hospital Lahore, were enrolled in the study. Verbal and written inform consent was taken from the patients. Data regarding Age, Gender and hepatic encephalopathy was taken. 5 ml of venous blood was taken from patients in red top vials within 24 hours of admission and was sent to the laboratory to check Zinc level using chromatographic technique. All the data was collected through a well-defined questionnaire. Patients having zinc deficiency were managed as per hospital protocol.****Results****: From 130 patients, it was observed that the minimum age was 40 years and maximum age was 65 years with mean and standard deviation of the age was 53.13± 7.17 years. The minimum duration of CLD was 1 years and maximum was 5 years with mean and standard deviation 3.16 ± 1.37 years. The minimum BMI was 28.50 and maximum was 37 with mean and standard deviation 32.44 ± 2.62. The minimum zinc level was 0.45 µg/dl and maximum was 0.96 µg/dl with mean and standard deviation 0.64 ± 0.13 µg/dl. Male patients were 69.2% while female patients were 30.8%. Diabetes mellitus was present in 59.2% patients while it was not found in 40.8% patients. Hypertension was present in 54.8% patients while it was absent in 45.2% patients. There were 60.8% smokers while 39.2% were not smokers. Zinc Deficiency was present in 71.5% while it was absent in 28.5% patients. Grade II of hepatic encephalopathy was found in 32.3%, Grade III was found in 36.2% and Grade IV of hepatic encephalopathy was found in 31.5%. Hypertension was found in 55.4% patients while Hypertension was not found in 44.6% patients.* ***Conclusion:*** *The frequency of zinc deficiency 71.2% in patients with hepatic encephalopathy. Effect modifiers have no significant influence except diabetes mellitus.*

Key words: *Chronic Liver Disease, Hepatic Encephalopathy, Zinc Deficiency, Hypertension Smoking.*

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Please cite this article in press Imran Bashir et al., ***Frequency of Zinc Deficiency in Patients with Hepatic Encephalopathy .,*** *Indo Am. J. P. Sci, 2018; 05(11).*

INTRODUCTION

Hepatic encephalopathy describes the spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of unrelated neurologic and/or metabolic abnormalities. The term implies that altered brain function is due to metabolic abnormalities, which occur as a consequence of liver failure. The full reversibility of symptoms after improvement of liver function is considered to be direct proof of this causal relation.

This definition is easy to apply in previously healthy patients presenting with acute liver disease and overt neuropsychiatric symptoms. It is more difficult to apply to patients with chronic liver diseases who have only mild to minimal signs of altered brain function, particularly in settings in which the underlying cause of the liver disease may be associated with neurologic manifestations (such as alcoholic liver disease or Wilson's disease). The problem in defining hepatic encephalopathy precisely is not just a matter of semantics, but has major implications in the design and evaluation of clinical studies on diagnosis and treatment of this syndrome.

A generally accepted nomenclature could provide a solution to this debate and provide a standard for clinical studies. To achieve this goal, the World Organization of Gastroenterology (OMGE) commissioned a Working Party to reach a consensus in this area. A group of experts proposed a consensus statement at the 11th World Congress of Gastroenterology in Vienna in 1998 [1]. A classification of hepatic encephalopathy has also been proposed.

Patients with hepatic encephalopathy (HE) usually have advanced chronic liver disease and thus have many of the physical and laboratory stigmata associated with severe hepatic dysfunction. Physical findings may include muscle wasting, jaundice, ascites, palmar erythema, edema, spider telangiectasias, and fetor hepaticus. Some of these findings (such as muscle wasting, spider telangiectasias, and palmar erythema) are usually absent in previously healthy patients with fulminant hepatic failure since their development requires a relatively longer period of hepatic dysfunction.

The history may reveal a precipitating cause. These include:

- Hypovolemia
- Gastrointestinal bleeding
- Hypokalemia and/or metabolic alkalosis
- Hypoxia
- Sedatives or tranquilizers
- Hypoglycemia
- Infection (including SBP)
- Rarely, hepatoma and/or vascular occlusion (hepatic vein or portal vein thrombosis)

Disturbance in the diurnal sleep pattern (insomnia and hypersomnia) is common, and typically precedes overt neurologic signs. More advanced neurologic features include bradykinesia, asterixis (flapping motions of outstretched, dorsiflexed hands), hyperactive deep tendon reflexes, and, less commonly, transient decerebrate posturing.

Focal neurologic deficits may also be present in some patients. In one report, for example, a focal neurologic sign was detected in 17 percent of 38 hepatic encephalopathy episodes in 24 patients [2]. The most common was hemiplegia. None of the patients had abnormal findings on CT or CSF examination. Five of the eight patients also had a normal MRI and Doppler examination of the neck and vessels. The deficits resolved completely in seven of eight surviving patients after six months of follow-up.

Subtle changes of HE may be detectable by a number of specialized measures, particularly psychometric testing. Such patients have sometimes been referred to as having subclinical hepatic encephalopathy (SHE), although "minimal" hepatic encephalopathy is preferred.

Laboratory Tests

Laboratory abnormalities typically include evidence of hepatic biochemical and synthetic dysfunction, and electrolyte disturbances (such as hyponatremia and hypokalemia) that occur as a result of portal hypertension and use of diuretics. In addition, ammonia is the best characterized neurotoxin that precipitates HE. All other routine laboratory tests are only useful to exclude other causes of brain dysfunction (eg, hypoglycemia, uremia, electrolyte disturbances, and intoxication).

Ammonia

The gastrointestinal tract is the primary source of ammonia, which enters the circulation via the portal vein. Ammonia is produced by enterocytes from glutamine and by colonic bacterial catabolism of nitrogenous sources such as ingested protein and secreted urea. The intact liver clears almost all of the portal vein ammonia, converting it into urea or glutamine and preventing entry into the systemic circulation.

The increase in blood ammonia in advanced liver disease is a consequence of impaired liver function and of shunting of blood around the liver. Muscle wasting, a common occurrence in these patients, also

may contribute since muscle is an important site for extrahepatic ammonia removal.

For clinical practice determination of ammonia concentration remains controversial. It may be useful under certain conditions (eg, monitoring efficacy of ammonia lowering therapy), but is not required to make the diagnosis of hepatic encephalopathy or in the long-term follow-up of patients with advanced liver disease. The accuracy of ammonia determination is influenced by many factors (such as fist clenching, use of a tourniquet, and whether the sample was placed on ice). These factors should be considered when interpreting results. Furthermore, ammonia levels can be elevated in a variety of nonhepatic conditions.

Venous

Venous blood ammonia is not a useful screening test for HE since levels are inconsistently elevated [3]. Furthermore, HE is only directly related to ammonia levels up to about a twofold increase above normal. Any further increase of ammonia concentration does not contribute to the further evolution of HE [4]. However, ammonia can be measured in patients with clinically overt HE since it may assist in selecting the appropriate therapy and monitoring its efficacy.

Arterial

Compared to the venous blood ammonia concentration, the arterial ammonia concentration provides a more accurate assessment of the amount of ammonia at the blood-brain barrier. However, for the same reasons as discussed above, it is not more useful than the venous ammonia concentration. Furthermore, the grade of HE is more closely related to the partial pressure of gaseous ammonia (pNH3) than the total arterial ammonia concentration, since gaseous ammonia readily enters the brain [4]. The pNH3 can be calculated from the total ammonia and pH [5]. Determination of the pNH3 is mostly used for clinical studies.

Postprandial ammonia levels may be more closely related to minimal HE than fasting levels. Thus, in clinical trials, ammonia is often measured after a standard meal (or glutamine load) [6]. Induced hyperammonemia led to a significant increase in daytime subjective sleepiness and changes in the EEG architecture of a subsequent sleep episode in patients with cirrhosis, pointing to a reduced ability to produce restorative sleep [7].

Other potential markers

Serum levels of 3-nitrotyrosine may be elevated in patients with minimal hepatic encephalopathy (mild cognitive impairment). One study found that using a cutoff of 14 nM, 3-nitrotyrosine was 93 percent sensitive and 89 percent specific for detecting minimal hepatic encephalopathy [8].

MATERIAL AND METHODS:

Study design:

It's a cross sectional study

Settings:

Medical Unit-II, Jinnah Hospital Lahore

Duration of study:

The present study was conducted from 00-00-2017 to 00-00-2017.

Sample Size:

Sample size of 130 cases with hepatic encephalopathy is estimated using 95% confidence level, 8% margin of error with an expected percentage of zinc deficiency I.e. 69%.

Sampling Technique:

Non probability, consecutive sampling.

Sample Selection:

Inclusion criteria:

1. Patients of both gender with age between 40 to 65 years
2. Patients with diagnosis of CLD for at least 1 year
3. Patients with diagnosis of Hepatic Encephalopathy Grade II to IV

Exclusion criteria:

1. Patients with uremic encephalopathy (on medical record)
2. Patients with evidence of brain infection i.e. meningitis, encephalitis or cerebral abscess
3. Patients with severe infection and disseminated intravascular coagulation (on medical record)
4. Patients with severe malnutrition
5. Patients with stroke, brain tumor or subdural/extradural hematoma

Data Collection Procedure:

130 patients, whom were diagnosed with hepatic encephalopathy in Jinnah Hospital Lahore, were enrolled in the study. Verbal and written inform consent was taken from the patients. Data regarding Age, Gender and hepatic encephalopathy was taken. 5 ml of venous blood was taken from patients in red top vials within 24 hours of admission and was sent to the laboratory to check Zinc level using chromatographic technique. All the data was collected through a well-defined questionnaire. Patients having zinc deficiency were managed as per hospital protocol.

Data Analysis Procedure:

All the collected data was entered into SPSS version 20. Numerical variables i.e. age, body mass index (BMI), duration of CLD, Zinc Level were presented by mean ±SD. Categorical variables i.e. gender, DM, grade of hepatic encephalopathy, hypertension, smoking and zinc deficiency were presented as frequency and percentages. Chi-square test was applied at p-value ≤0.05 as significant. Data was stratified for age, gender, BMI, duration of CLD, diabetes mellitus (random blood sugar level > 200mg/dl), hypertension (blood pressure > 160/90) and smoking status (> 5 pack years) to address the effect modifier. Post stratification Chi-square test was applied to check the significance with p-value ≤ 0.05 at significant.

RESULTS:

From 130 patients, it was observed that the minimum age was 40 years and maximum age was 65 years with mean and standard deviation of the age was 53.13± 7.17 years. The minimum duration of CLD was 1 years and maximum was 5 years with mean and standard deviation 3.16 ± 1.37 years. The minimum BMI was 28.50 and maximum was 37 with mean and standard deviation 32.44 ± 2.62. The minimum zinc level was 0.45 µg/dl and maximum was 0.96 µg/dl with mean and standard deviation 0.64 ± 0.13 µg/dl.

Male patients were 90/130 (69.2%) while female patients were 40/130 (30.8%). Diabetes mellitus was present in 77/130 (59.2%) patients while it was not found in 53/130 (40.8%) patients. Hypertension was present in 74/130 (54.8%) patients while it was absent in 61/130 (45.2%) patients. There were 79/130 (60.8%) smokers while 51/130 (39.2%) were not smokers. Zinc Deficiency was present in 93/130 (71.5%) while it was absent in 37/130 (28.5%) patients. Grade II of hepatic encephalopathy was found in 42/130 (32.3%), Grade III was found in 47/130 (36.2%) and Grade IV of hepatic encephalopathy was found in 41/130 (31.5%). Hypertension was found in 72/130 (55.4%) patients while Hypertension was not found in 58/130 (44.6%) patients.

By using chi-square test, significant association was not found between age group and Zinc Deficiency with p-value 0.712. There was no significant association between Zinc Deficiency and gender having p-value = 0.154. Significant association was not found between BMI and Zinc Deficiency with p-value 0.389. Significant association was not found between duration and Zinc Deficiency with p-value 0.985. Significant association was found between Diabetes mellitus and Zinc Deficiency with p-value 0.006. There was no significant association between Zinc Deficiency and Hypertension having p-value = 0.843. There was no significant association between Zinc Deficiency and smokers having p-value = 0.317.

Table 1. Descriptive Statistics
(n = 130)

	Minimum	Maximum	Mean	Std. Deviation
Age	40	65	53.13	7.17
Duration of CLD (Years)	1	5	3.16	1.37
BMI	28.50	37.00	32.44	2.62
Zinc Level	0.45	0.96	0.64	0.13

Table 2. Distribution of Gender

Gender	Frequency	Percent
Male	90	69.2
Female	40	30.8
Total	130	100.0

Table 3. Distribution of Diabetes mellitus

Diabetes mellitus	Frequency	Percent
Yes	77	59.2
No	53	40.8
Total	130	100.0

Table 4. Distribution of Hypertension

Hypertension	Frequency	Percent
Yes	72	55.4
No	58	44.6
Total	130	100.0

Table 5. Distribution of smokers

Smokers	Frequency	Percent
Yes	79	60.8
No	51	39.2
Total	130	100.0

Table 6. Distribution of Zinc Deficiency

Zinc Deficiency	Frequency	Percent
Yes	93	71.5
No	37	28.5
Total	130	100.0

Table 7. Distribution of Grade of Hepatic Encephalopathy

Grade of Hepatic Encephalopathy	Frequency	Percent
Grade II	42	32.3
Grade III	47	36.2
Grade IV	41	31.5
Total	130	100.0

Table 8. Stratification with respect to Age
(n = 130)

Age	Zinc Deficiency		Total	P-value
	Present	Absent		
< 50 years	32	14	46	0.712
≥ 50 years	61	23	84	
Total	93	37	130	

Table 9. Stratification with respect to Gender
(n = 130)

Gender	Zinc Deficiency		Total	P-value
	Present	Absent		
Male	61	29	90	0.154
Female	32	8	40	
Total	93	37	130	

Table 10. Stratification with respect to BMI
(n = 130)

Age	Zinc Deficiency		Total	P-value
	Present	Absent		
≤ 31 years	40	19	59	0.389
> 31 years	53	18	71	
Total	93	37	130	

Table 11. Stratification with respect to duration of CLD
(n = 130)

Duration of CLD	Zinc Deficiency		Total	P-value
	Present	Absent		
< 3 years	30	12	42	0.985
≥ 3 years	63	25	88	
Total	93	37	130	

Table 12 Stratification with respect to Diabetes mellitus
(n = 130)

Diabetes mellitus	Zinc Deficiency		Total	P-value
	Present	Absent		
Yes	62	15	77	0.006
No	31	22	53	
Total	93	37	130	

Table 13. Stratification with respect to Hypertension (n = 130)

Hypertension	Zinc Deficiency		Total	P-value
	Present	Absent		
Yes	51	21	72	0.843
No	42	16	58	
Total	93	37	130	

Table 14. Stratification with respect to smokers (n = 130)

Smokers	Zinc Deficiency		Total	P-value
	Present	Absent		
Yes	54	25	79	0.317
No	39	12	51	
Total	93	37	130	

DISCUSSION:

The objective of the present research was to assess the frequency of zinc deficiency in patients with hepatic encephalopathy. In this regard the present cross sectional study was conducted Medical Unit-II, Jinnah Hospital Lahore. So one hundred and thirty patients with diagnosis of Hepatic Encephalopathy Grade II to IV were included by fulfilling the inclusion and exclusion criteria by using non probability consecutive sampling.

From 130 patients, it was observed that the minimum age was 40 years and maximum age was 65 years with mean and standard deviation of the age was 53.13± 7.17 years. The minimum duration of CLD was 1 years and maximum was 5 years with mean and standard deviation 3.16 ± 1.37 years. The minimum BMI was 28.50 and maximum was 37 with mean and standard deviation 32.44 ± 2.62. The minimum zinc level was 0.45 µg/dl and maximum was 0.96 µg/dl with mean and standard deviation 0.64 ± 0.13 µg/dl.

The results show an increase in serum zinc levels, a decrease in plasma ammonia concentrations, and, in -55-60% of patients, an improvement in the HE states. The zinc levels decreased and the ammonia levels increased when the zinc supplementation was discontinued after normal-ization of the serum zinc levels. Renewal of zinc supplementation after a decrease in zinc levels affected an increase in zinc and a decrease in ammonia levels in most patients. This episodic behavior was noted over the whole observation time. [136]

Male patients were 69.2% while female patients were 30.8%. Diabetes mellitus was present in 59.2% patients while it was not found in 40.8% patients. Hypertension was present in 54.8% patients while it was absent in 45.2% patients. There were 60.8% smokers while 39.2% were not smokers. Zinc Deficiency was present in 71.5% while it was absent in 28.5% patients. Grade II of hepatic encephalopathy was found in 32.3%, Grade III was found in 36.2% and Grade IV of hepatic encephalopathy was found in 31.5%. Hypertension was found in 55.4% patients while Hypertension was not found in 44.6% patients.
In a previous study, from one hundred twenty seven cirrhotic patients with means age 42.7559 ± 15.8894 were evaluated and assessed. The serum zinc was low in 69% patients. According to Child-Pugh classification 72% zinc deficient cirrhotic subjects were in class C, 16% in class B & 12% in class A. 94% subjects had hepatitis C virus infection, 4% had hepatitis B virus infection and 2% had history of alcoholism. The serum zinc level was low in patients with liver cirrhosis. [137]

By using chi-square test, significant association was not found between age group and Zinc Deficiency with p-value 0.712. There was no significant association between Zinc Deficiency and gender having p-value = 0.154. Significant association was not found between BMI and Zinc Deficiency with p-value 0.389. Significant association was not found between duration and Zinc Deficiency with p-value 0.985. Significant association was found between Diabetes mellitus and Zinc Deficiency with p-value 0.006. There was no significant association between Zinc Deficiency and Hypertension having p-value = 0.843. There was no significant association between Zinc Deficiency and smokers having p-value = 0.317. Zinc supplementation significantly improved the PCS (P= 0.04), but not the MCS (P= 0.95). Zinc supplementation significantly decreased hepatic encephalopathy grade and blood ammonia levels (P= 0.03 and P= 0.01), and improved Child-Pugh score and NP tests compared with standard therapy (P= 0.04 and P= 0.02). In multivariate analysis, zinc supplementation was significantly associated with improvement in PCS (P= 0.03), whereas it was not significantly associated with change in MCS (P= 0.98). Zinc supplementation is effective in hepatic encephalopathy. [138]

CONCLUSION:

The frequency of zinc deficiency 71.2% in patients with hepatic encephalopathy. Effect modifiers have no significant influence except diabetes mellitus.

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PROFORMA
Frequency of Zinc Deficiency in Patients with Hepatic Encephalopathy
CASE NO: _____
Name of Patient: _____ S/D/W/O: _____
Reg. #: _____Age: _____ Sex: Male Female
Date of Admission: _____ Date of Discharge: _____
Address: _____BMI:_____
Study Variables:

Hepatic Encephalopathy: Yes No
Zinc Level: _____
Zinc Deficiency: Yes No
Previous History of Diseases:
Diabetes Yes No
Hypertension: Yes No
Smoking Status: Yes No

ANNEX-I
West Haven Criteria for Semi-Quantitative Grading of Mental State

Grade	**Criteria**
Grade I	Trivial lack of awareness (GCS 13-14/15)
	Euphoria or anxiety
	Shortened attention span
	Impaired performance of addition
Gtrade II	Lethargy or apathy
	Minimal disorientation for time or place (GCS 10-12/15)
	Subtle personality change
	Inappropriate behaviour
	Impaired performance of subtraction
Grade II	Somnolence to semi-stupor but responsive to verbal stimuli (GCS 6-9/15)
	Confusion
	Gross disorientation
Grade IV	Coma, unresponsive to verbal or noxious stimuli (GCS 3-5/15)