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Original Article

Zinc Deficiency in Patients of Chronic Hepatic Encephalopathy

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Abstract

Background : To determine the zinc deficiency in patients with chronic hepatic encephalopathy

Methods: In this cross section study decompensated hepatic cirrhosis diagnosed patients (n=102) aged>16 years,both gender, with hepatic encephalopathy as per its grades were included. Blood samples were drawn and serum zinc levels were estimated.

Results: Mean-age of patients was 51.5±9.5 years. Men (64.7%) constituted the main. Zinc deficiency was noted in 68.6% patients. Hepatic encephalopathy grade II was most common (42.2%) . Hepatic encephalopathy grading, II, III and IV were found significantly associated with zinc deficiency (p-value= 0.007). No significant difference was found in zinc deficiency according to age p-value 0.739. Zinc deficiency was significantly higher among males (p-value 0.043).

Conclusion: Zinc deficiency was quite high (68.6%),with hepatic encephalopathy. Zinc deficiency was more common in males and middle age group patients.

Key words: Liver cirrhosis, Zinc levels , Encephalopathy.

Introduction

Hepatic encephalopathy is a neuropsychiatric complex syndrome, correlated with hepatocellular dysfunction and elevated porto-systemic shunting, noticed within 60% to 70% of hepatic cirrhosis patients.[1,2] This reversible, complex, metabolic encephalopathy syndrome is a major complication of hepatic cirrhosis.[3,4] Hepatic encephalopathy is distinguished via disruption within consciousness, instable neurological signs, personality and behavioral changes, asterixis and typical electroencephalographic variations. In severe cases irreversible coma and death can possibly as well take place. The two key mechanisms accountable for hepatic encephalopathy development are severe intrinsic liver failure or portosystemic shunts presence resulting in portal blood diversion towards systemic circulation earlier than removal of intestinal toxic substances.[1,5] Zinc is vital trace constituent which as well functions as antioxidant.[3] Low levels of zinc have been documented within patients with Hepatic encephalopathy and hepatic cirrhosis.[3,6] It was observed in 69% of hepatic cirrhosis patients.[7] A study reported that levels of blood ammonia are inversely correlated with levels of blood zinc in fasting. [8] Zinc accelerates the kinetics of formation of urea from amino acids and ammonia.[9] In agreement deficiency of zinc in hepatic cirrhosis seems to be because of low absorption and high excretion of urine for which administration of excessive diuretics is accountable to some extent.[7,1,8] It has been reported that Zinc improves the psychometric functioning in hepatic cirrhosis, very long-term supplementations improve severe encephalopathy and thus quality of life.[10,11]Supplementation is important in prevention of hepatic encephalopathy by activating glutamine synthetase.[8] Zinc supplements are also beneficial in urea cycle, protein, glucose metabolism, and neuro transmission[11]. Zinc supplementation in dose of 600 mg per day is recommended for 3 months period.[1,4] Considering the clinical proof, that zinc deficiency may have a contribution in pathogenesis of Hepatic encephalopathy and patients improve from it by replacing the zinc. Though, association between blood levels and state of mind in cirrhosis is not accurate. The permeability of blood-brain barriers to ammonia is raised within Hepatic encephalopathy patients consequently, blood levels weakly associate with brain values, however recurrent studies exhibit progress of this association by the correction ammonia value to blood pH.[12] Patients of chronic hepatic encephalopathy due to zinc deficiency is a critical condition resulting progressive worsening of encephalopathy and death, so careful observation and management are required.[13]

Patients and Methods

Following approval from hospital ethical committee, this study was carried out in Gastroenterology department of Isra University Hospital, Hyderabad. Study duration was 6 months from January to June 2011. All decompensated hepatic cirrhosis diagnosed patients aged >16 years, both gender, with hepatic

encephalopathy signs as per its grades were taken in study.All the patients with fulminant hepatic dysfunction, compensated hepatic disease, or without previous history of hepatic disorder were excluded, since, zinc deficiency was not noticed within patients of acute hepatic dysfunctions. Patients influenced by metabolic and neurological disorders like alcoholism, end stage renal disease, and diabetes mellitus, history of trans-jugular intrahepatic portosystemic shunt, history of intake of drug as tranquillizers or subjects with fresh head trauma were not included in study so as to prevent coexistent neuropathy or further brain failure. Patients were considered as suffering from hepatic encephalopathy according to the four grades of encephalopathy.[4] Grade 1 constituted euphoric or depression, disordered sleep, slurred speech, mild confusion, Asterixis may be present or absent.Grade II constituted moderate confusion, lethargy, and Asterixis. Grade III constituted sleeping but arousable, incoherent speech, marked confusion, and asterixis.Grade IV constituted coma, at first responsive to noxious inducements, and unresponsive later. Blood samples drawn from all patients and were sent to diagnostic laboratory of Isra University Hospital, for zinc levels estimation

Results

Most common age group was 40 – 59 years 49 (48.0%), followed by 60–80 years with percentage of 31 (30.4%) and 22-39 years age group was found in 22 (21.6%) patients. The mean-age and standard deviation was 51.5 ± 29.5 years. Men were more in number compared to females study participants as (64.7%) and (35.3%), respectively (Table 1).

Table 1: Patients distribution according to age and gender (n=102)

Variables	Frequency (%)
Age groups (years)	
22-39	22 (21.6%)
40 - 59	49 (48.0%)
60 - 80	31 (30.4%)
Total	102(100.0%)
Gender	
Male	66(64.7%)
Female	46(35.3%)
Total	102(100.0%)

Mean ± SD= 51.5 ± 29.5 years

Out of total 102 patients 70(68.6%) patients exhibited serum zinc deficiency compared to 32 (31.14%) non-deficient cases. According to the grading of hepatic encephalopathy grade II was most common 42.2%, grade I was 25.5% and grade III was found in 20.6% of the cases, while grade IV was found only in 11.8% of the cases (Table 2).Grade II, III and IV were found significantly associated with zinc deficiency (p-value 0.007), while grade I was found significant in normal cases(Table 3).No significant difference was found in zinc deficiency according to age groups in patients with hepatic encephalopathy p-value 0.739. Male gender was found mostly associated with zinc deficiency, while mostly female were found with normal zinc level(p-value 0.043) (Table 3).

Table 2: Zinc levels and grading of hepatic encephalopathy

Variables	Frequency	%
Zinc level		
Normal	32	31.4%
Deficient	70	68.6%
Total	102	100.0%
Hepatic encephalopathy		
Grade1	26	25.5%
Grade 2	43	42.2%
Grade 3	21	20.6%
Grade 4	12	11.8%
Total	102	100.0%

Table 3: zinc deficiency according to HE grading, age and gender

Variables	Zinc level		Total	p-value
	Deficiency	Normal		
Hepaticencephalopathy				
Grade I	10(14.9%)	16(45.7%)	26(25.5%)	0.007
Grade II	31(46.3%)	12(34.3%)	43(42.2%)	
Grade III	16(23.9%)	5(14.3%)	21(20.6%)	
Grade IV	10(14.9%)	2(5.7%)	12(11.8%)	
Total	67(100.0%)	35(100.0%)	102(100.0%)	
Age groups				
22-39	14(20.9%)	8(22.9%)	22(21.6%)	0.739
40 - 59	34(50.7%)	15(42.9%)	49(48.0%)	
60 - 80	19(28.4%)	12(34.3%)	31(30.4%)	
Total	67(100.0%)	35(100.0%)	102(100.0%)	
Gender				
Male	48(71.6%)	18(51.4%)	66(64.7%)	0.043
Female	19(28.4%)	17(48.6%)	36(35.3%)	
Total	67(100.0%)	35(100.0%)	102(100.0%)	

Discussion

Development of the hepatic encephalopathy is explained, to some extent, with effect of neurotoxic substances, which may occurr in cases with cirrhosis and portal hypertension. Zinc is essential for coenzyme synthesis, which mediate biogenic amine synthesis and metabolism. In this study Zinc deficiency noted within 68.6% of the chronic HE patients comparable to a similar study , by Soomro AA et al which noted zinc deficiency 69% of subjects among hepatic cirrhotic subjects.[7] Low levels of zinc have been documented within subjects with HE and hepatic cirrhosis.[3,6] In another study of Waheed A et al[13]Zinc deficiency among patients with hepatic encephalopathy was 71.9%. Inconsistently Kamani L et al reported that overall prevalence of zinc deficiency is 28.9%, which is low according to our findings. This difference may because in their study only cirrhosis patients were selected with chronic hepatic encephalopathy. [14] Consistently Prasad CK et al reported that zinc deficiency among cirrhosis patients is 70%. [15] These findings were confirmed by Kugelmans' study, who stated that lower level of zinc with lower ingestion due to protein reluctance, increased loss in gastroenterological system due to diarrhea or intestinal malabsorption and increased urinary losses.[16]

In our study the patients' mean age was 51.5 ± 29.5 years and males were most common (64.7%) as compared to females (35.3%). Similarly in the study of Waheed A et al[13]reported that patient's mean age was 47.8±7.5 years and 79(69.3%) patients were male while 35(30.7%) patients were female.Soomro AA et al also found mean of patients as 42.75± 15.88 years, and males were 55.7% and females were 44.3%.[7] According to the Siddique A et al mean age was 43.65+4.21 years.[17] Findings of these studies regarding mean age and gender distribution are consistent to this study.

In this study HE grade II was most common 42.2%, followed by grade I was 25.5% and grade III was 20.6%, while grade IV was found only in 11.8% cases. While Waheed A et al grade III was most common as 47 (41.2%), 18(15.8%) patients were with grade-I, 32(28.1%) presented with grade-II, and 17 (14.9%) patients had grade-IV. [13] In our research middle aged males were in majority compared to women and deficiency of zinc was noted frequently in men like majority of other researches. Supplementation of zinc besides rifaximin, a modestly absorbed antibiotic, can possibly be further effective within refractory HE, because a fresh research exhibited the dominance of rifaximin over lactulose only treatment in severe recurrent HE subjects.

In this study, most subjects were from periphery / interior of Sindh province and this can possibly be due to improper counseling, motivational deficiency, lack of awareness and poor hygiene. Present study established that most patients were aged >40 years, though a study held in Balouchistan, Pakistanon spectrum of CLD, as well had similar findings.[18]Deficiency of zinc is frequent among cirrhotic subjects, specifically with alcohol-induced hepatic injury. Supplementation of zinc has been exhibited to lower the levels of serum ammonia and fluctuating neurotransmitters such as γ-aminobutyric acid and norepinephrine within brain. Just small studies have been carried out by supplementation of zinc with equivocal outcomes. Zinc, oral agent, is accessible over-the-counter and contributes for zinc deficient patients. Zinc is accessible in many forms besides zinc acetate, zinc sulfate, and zinc gluconate.[19,20]Many reports state that supplementation of zinc improve psychometric functioning with a decline in the level of blood ammonia within Hepatic encephalopathy subjects. Additionally, combinations of conventional therapies and zinc for example a protein-limited diet including lactitol or BCAA preparation have been stated as successful therapies for Hepatic encephalopathy.

According to this study supplementation of zinc besides standard treatment evidently exhibited improved hepatic functions, Hepatic Encephalopathy, Neuropsychiatric tests, and Health Related Quality Of Life especially Physical Component Status, in decompensated hepatic cirrhosis patients. Several reports report that supplementation of zinc improve psychometric functioning with a drop of level in blood ammonia among hepatic encephalopathy patients.[21,22] Furthermore, combination of conventional therapies & zinc for instance a protein limited diet together with lactitol or BCAA preparation have been documented as successful therapies for Hepatic encephalopathy. Hayashi et al.[23] documented that combination treatments with zinc supplements and BCAA diminish level of blood ammonia further than BCAA treatment only in cirrhotic subjects in the course of study period. They concluded from this finding that administration of zinc raised the hepatic ability for metabolizing ammonia contrasted to the nitrogen load via supplementation of BCAA. Katayama et al[24]documented that while either zinc or lactitol alone diminished levels of ammonia to around 70% of pre-treatment concentrations, combination treatment

lowered them to around 50%. Synthetic disaccharides effectively reduce blood ammonia via primarily preventing intestinal absorption of ammonia, and are believed to enhance NP tests.[25,26] This two agents' synergism to reduce ammonia resulting from various mechanisms appears to be useful in subjects who are non-responsive to standard treatments only. Supplementation of zinc besides Rifaximin, a moderately absorbed antibiotic, can possibly be further successful in refractory Hepatic encephalopathy, because a fresh research, exhibited the dominance of Rifaximin treatment over lactulose only treatment in severe recurring Hepatic encephalopathy subjects. [27]

Conclusion

1. Low levels of serum Zinc are frequent (68%) and it has higher effect on incidence of hepatic encephalopathy. A definite requisite for proper counseling and health education is needed of subjects diagnosed as hepatic cirrhosis regarding hepatic encephalopathy.
2. It is required to identify markers of exposure to deficiency of zinc in addition to effective approaches to diminish zinc deficiency as well as its consequences.
3. It is required to assess rule of zinc therapy in hepatic encephalopathy patients

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