Hyponatremia and Zinc deficiency as a risk factor for Hepatic Encephalopathy in Cirrhotic Patients

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Abstract: Background: Cirrhosis is a gradually developing irreversible chronic disease of the liver which always involves the organ as a whole. It is the final stage of various chronic liver diseases or the result of long-term exposure to various noxae. This process distorts the normal liver architecture, interferes with blood flow through the liver and disrupts the functions of the liver . Majority of patients with cirrhosis die from one or more clinical complications especially ascites, hepatic encephalopathy, and variceal hemorrhage. The occurrence of the first episode of hepatic encephalopathy in a Cirrhotic patient confers an ominous prognostic sign and Constitutes a turning point in the evolution of liver disease.Estimated survival rates are 42% at 1 year, and 23% at 3 years . Zinc plays an important role in human physiologic processes being cofactor of many enzymes. Reduced serum and hepatic zinc levels correlated with reduced liver ornithine transcarbamylase activity and increased plasma ammonia level. Hyponatremia is a major risk factor of the development of overt HE . Several lines of evidence support the existence of a correlation between hyponatremia and hepatic encephalopathy. **Objectives of the work** To assess the level of hyponatremia and zinc deficiency in cirrhotic patients with hepatic encephalopathy. **Patients and materials:** Our study was a case control study conducted on 60 cirrhotic patients. **They were divided into 2 groups: Group A:** 30 cirrhotic patients without hepatic encephalopathy. **Group B**: 30 cirrhotic patients with hepatic encephalopathy in different grades admitted to Intensive Care Unit in the hospital of Theodor Bilharz Research Institute The aim of our work was assessment hyponatremia and zinc deficiency in cirrhotic patient with hepatic encephalopathy. All studied patients were subjected to complete medical history, detailed clinical examination, laboratory tests including CBC, serum creatinine, BUN, sodium, potassium, zinc, ALT, AST, albumin, total bilirubin, direct bilirubin, PT, PC and INR, in addition to MELD scoring and child classification. **Results:** Cirrhotic patients suffering from HE had lower serum zinc level when compared to those without HE. There was significant difference in serum zinc level according to the degree of decompansation as reflected by Child classifications in cirrhotic patients with and without HE. There was positive correlation between the serum zinc and serum albumin in both groups. There was highly significant negative correlation between serum zinc and (serum bilirubin, AST, ALT and PT)in both groups. There was highly significant negative correlation between serum zinc and MELD in both groups. Cirrhotic patients without HE had their serum level of sodium >130 mmol/L while patients with HE their serum level of sodium <130 mmol/L. There was significant negative correlation between serum sodium and grades of HE. There was negative correlation between Na and MELD in both groups. **Conclusion:** 1- Hyponatremia is a risk factor for Hepatic Encephalopathy. 2- Zinc deficiency is common in cirrhotic patients with and without Hepatic Encephalopathy according to the degree of decompansation as reflected by Child classifications and this deficiency is more severe in patients with hepaticencephalopathy.

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1.Introduction

Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of other known brain disease. It is characterized by personality changes, intellectual impairment and depressed level of consciousness **(Wolf, D.C.2008).**

Hyponatremia is common in patients with advanced liver disease **(Angeli, et al, 2006)** : dilutional hyponatremia results from reduction in solute-free water clearance despite increased total body water. the pathogenetic mechanism for hyponatremia in cirrhosis involves the antidiuretic hormone (arginine vasopressin). Conjugation of arginine vasopressin with its receptors (the so-called V2 receptors) located in the renal collecting duct induces production and translocation of water channel molecules (aquaporin-2), leading to reabsorption of water and reduction in excretion of free water **(Gine′s, et al, 1998).** Hepatic encephalopathy has recently been proposed that low grade cerebral edema is an important element in the pathogenesis of HE in cirrhotic patients **(Haussinger,D.2006).**

Although the exact role of ammonia in the pathogenesis of HE remains completely understood, ammonia and other neurotoxins have been shown to act synergistically to induce a low-grade cerebral edema as a result of swelling of astrocytes (**Norenberg, M.D.,1996).**

Astrocytes are thought to be the primary handlers of brain ammonia, as they are the predominant cell types expressing glutamine synthetase**.**

Hyponatremia may represent a second osmotic hit to astrocytes, causing further aggravation of cellular swelling, which may result in alterations of neuronal function. this hypothesis seems to be borne out in clinical studies that have correlated hyponatremia with a higher incidence of clinically significant HE **(Angeli, et al, 2006).**

Zinc plays an important role in human physiologic processes being cofactor of many enzymes. With the rising of class of liver impairment and developing liver encephalopathy, level of zinc in blood drops. Treatment with diuretic therapy results in increase of discharge of zinc with urine and prevents recovery of its level in blood **(Shaposhnikova, et al, 2007).** Zinc concentration was significantly lower in patients with hepatic encephalopathy in comparison to cirrhotic patients without encephalopathy. The correction of trace elements concentrations might have a beneficial effect on complications and may be progression of liver cirrhosis. It would be recommendable to provide analysis of trace elements as a routine **(Dario,et al,2011).**

Cirrhosis is a gradually developing, chronic disease of the liver which always involves the organ as a whole. It is the irreversible consequence and final stage of various chronic liver diseases of different etiology. Majority of patients with cirrhosis die from one or more clinical complications especially ascites, hepatic encephalopathy, and variceal hemorrhage.

The occurrence of the first episode of hepatic encephalopathy in a Cirrhotic patient is a pejorative prognostic factor, and constitutes a turning point in the evolution of liver disease.

Estimated survival rates are 42% at 1 year, and 23% at 3 years. Hepatic encephalopathy is defined as a spectrum of serious progressive but potentially reversible neuropsychiatric abnormalities in patients with advanced liver dysfunction, after exclusion of other known brain disease. It is characterized by personality changes, intellectual impairment and depressed level of consciousness**.**

Zinc plays an important role in human physiologic processes being cofactor of many enzymes. With the rising of class of liver impairment and developing liver encephalopathy, level of zinc in blood drops (**Shaposhnikova,et al,2007).** Also, treatment with diuretics results in increase of loss of zinc inurine and prevents recovery of its level in blood.

Reduced serum and hepatic zinc levels correlate well with reduced liver ornithine transcarbamylase activity and increased plasma ammonia level **(Yang, et al, 2004).**

Zinc, a cofactor of urea cycle enzymes, may be deficient in cirrhotic patients, especially if associated, with malnutrition or encephalopathy **(Blei and Crdoba, 2001).** Hyponatremia is a major risk factor of the development of overt H.E. (**Guevara, et al, 2009).** Several lines of evidence support the existence of a correlation between hyponatremia and hepatic encephalopathy. Levels of serum sodium and ammonia determine the major electroencephalographic changes in cirrhosis **(Amodio, et al, 2001).** The novel theories suggest that low-grade cerebral edema (which can be induced by hyponatremia) may play a part in the pathogenesis of hepatic encephalopathy **(Haussinger,D.,2006)**.

In low-grade cerebral edema, hyponatremia plays an important role in increasing the osmotic pressure on the astrocytes. In this situation, only a small increase in ammonia level can induce clinically overt hepatic encephalopathy (**Kale,et al,2006).**

Our study was conducted on 60 patients they was classified into two groups.

Group A: 30 cirrhotic patients without hepatic encephalopathy.

Group B: 30 cirrhotic patients with hepatic encephalopathy in different grades admitted to Intensive Care Unit in the hospital of Theodor Bilharz Research Institute. All studied patients were subjected to complete medical history, detailed clinical examination, laboratory tests including CBC, serum creatinine, BUN, sodium, potassium, zinc, ALT, AST, albumin, total bilirubin, direct bilirubin,PT,PC and INR, in addition to MELD scoring

Aim of the work

To assess the level of hyponatremia and zinc deficiency in cirrhotic patients with hepatic encephalopathy.

2.Patients and methods

This study included 60 Egyptian cirrhotic patients, they was classified into 2 groups.

Group A: 30 cirrhotic patients without hepatic encephalopathy.

Group B: 30 cirrhotic patients with hepatic encephalopathy in different grades admitted to Intensive Care Unit in the hospital of Theodor Bilharz Research Institute

Inclusion criteria:

1-Patients aged 20-65 years old.

2-Patients suffering from cirrhotic liver with or without Hepatic encephalopathy.

Exclusion criteria:

1-Patients with hepatorenal syndrome

2-Acute Cerebrovascular accident (CVA) to be excluded by history, neurological examination and CT brain

3- Patients with diabetes mellitus.

4-Patients with renal impairment.

5-Patients with zinc supplements.

Each patient underwent:

(1) Full medical History

(2) Clinical Examination

(3) Laboratory tests: Liver functions tests, renal functions tests,

Serum Na, K and zinc

(4) Abdominal Ultrasongraphy

(5) Child Pugh and MELD score will be calculated

(6) CBC and coagulation profile.

Statistical Analysis

IBM SPSS statistics (V. 20.0, IBM Corp., USA, 2011) was used for data analysis. Data were expressed as Mean±SD for quantitative parametric measures in addition to Median Percentiles for quantitative non-parametric measures and both number and percentage for categorized data.

The following tests were done:

1. Comparison between two independent mean groups for parametric data using Student t test.
2. Comparison between two independent groups for non-parametric data using Wilcoxon Rank Sum test.
3. Comparison between more than 2 patient groups for parametric data using Analysis of Variance (ANOVA).

The multiple comparison (Post-hoc test or Least significant difference, LSD) was also followed to investigate the possible statistical significance between each 2 groups.

4. Comparison between more than 2 patient groups for non-parametric data using Kruskall Wallis test.
5. Ranked Sperman correlation test to study the possible association between each two variables among each group for non-parameteric data.
6. Chi-square test to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data. The probability of error at 0.05 was considered sig., while at 0.01 and 0.001 are highly sig.

3.Results

Table(1): Age and gender distribution in both groups:A and B.

Patients	No	Age	D.S.	Gender	
				Male	Femal
Group A	30	56.4	5.581	17	13
Group B	30	57.1	6.044	16	14

There was no statistical differences in age nor in gender in both groups.

Table(2): Distribution of Child classification

			Groups		
			A	**B**	Total
Child score	**A**	Count	8	0	8
		% within Groups	26.7%	.0%	13.3%
	B	Count	15	13	28
		% within Groups	50.0%	43.3%	46.7%
	C	Count	7	17	24
		% within Groups	23.3%	56.7%	40.0%
Total		Count	30	30	60
		% within Groups	100.0%	100.0%	100.0%

Chi-Square Tests			
	Value	*P*	Sig.
Pearson Chi-Square	12.310[a]	.002	HS

Table(3): Encephalopathy-distribution

Enceph.	**%**	**NO**
Grade 1	**26.7**	**8**
Grade 2	**26.7**	**8**
Grade 3	**33.3**	**10**
Grade 4	**13.3**	**4**

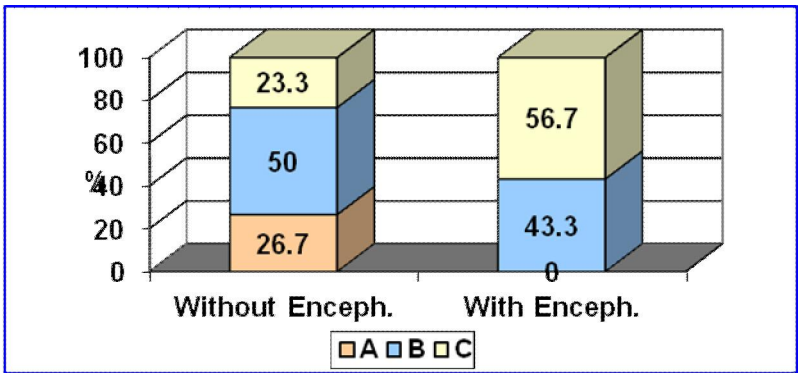


Fig. (1): Comparison between both groups as regards Child classification. There was a highly significant statistical difference between the two groups according to child classification(P=*0.* .002) being more advanced in group B.

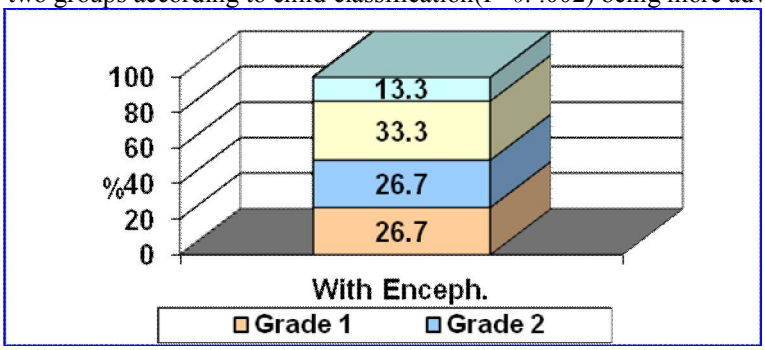


Fig. (2): Frequency distribution of different grades among patients with encephalopathy (group B).

Table(4): Lab. investigations of studied groups:

		n	Mean	±SD	t	*p*	Sig.
K	**Group A**	30	3.913	0.3748	3.255	0.002	HS
	Group B	30	3.54	0.5042			
Creat.	**Group A**	30	1.12	0.37083	-1.993	0.051	NS
	Group B	30	1.3343	0.45771			
BUN	**Group A**	30	26.93	10.68	-5.547	0	HS
	Group B	30	43.9	12.906			
Alb	**Group A**	30	2.573	0.4378	0.376	0.708	NS
	Group B	30	2.523	0.5823			
WBC	**Group A**	30	7.25	2.5597	-0.494	0.623	NS
	Group B	30	7.553	2.1804			
Hb	**Group A**	30	11.3	1.2889	2.547	0.014	S
	Group B	30	10.303	1.7121			
MCV	**Group A**	30	92.6	26.841	1.968	0.056	NS
	Group B	30	82.23	10.602			
INR	**Group A**	30	1.4913	0.40349	-1.779	0.081	NS

-There was highly significant statistical difference between serum K level between the two groups (*P*=0.002).
Serum BUN showed a significant statistical difference between both groups (*P* =0).An additional pre-renal condition may be the culprit.
HB showed a significant statistical difference between both groups (*P* =0.014).This may be due to bone marrow suppression or hypersplenism which can take place in advanced disease.

Na level in both groups:

Table(5): Na level in both groups:

		n	Min.	Max.	Mean	±SD	T	*p*	Sig.
Na	**Group A**	30	130	143	135.83	3.582	14.099	0	HS
	Group B	30	110	128	120.77	4.629			

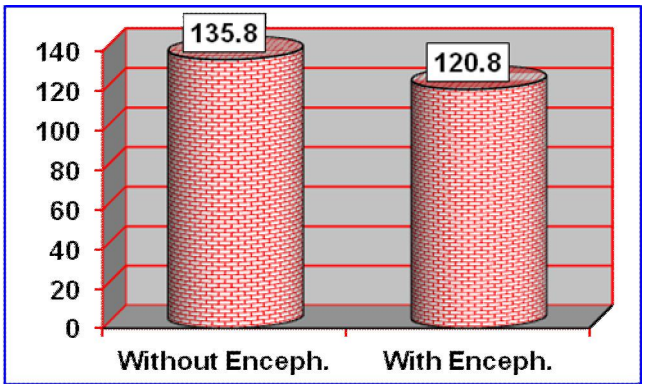


Figure (3): Comparison between both groups as regards mean values of Sodium
There was a highly significant statistical difference between serum Na level between the two groups (*P*=0).

Zinc level in both groups:

Table(6): Zinc level in both groups.

		n	Min.	Max.	Mean	±SD	T	*p*	Sig.
Zinc	**Group A**	30	36	77	59.487	15.8746	3.367	0.001	HS
	Group B	30	32	66	47.867	10.2612			

There was a highly significant statistical difference between zinc levels in the two groups.

Correlation between zinc level and results of lab investigation in both groups:

Table(7): Correlation between zinc level and results of lab investigation in both groups.

Variable	**Zinc without HE group A**			**Zinc with HE group B**		
	R	*P*	Sig.	R	*p*	Sig.
Creat.	-0.181	0.338	NS	-0.317	0.088	NS
BUN	-0.09	0.635	NS	-0.525	0.003	HS
ALT	-0.007	0.972	NS	-.477	0.008	HS
AST	-0.094	0.62	NS	-.87	0.005	HS
T_Bil	-0.771	0	HS	-0.61	0	HS
D_Bil	-0.784	0	HS	-0.494	0.005	HS
Alb	0.67	0	HS	0.61	0	HS
WBC	0.328	0.077	NS	-0.406	0.026	S
Hb	0.149	0.431	NS	0.129	0.497	NS
MCV	-0.153	0.42	NS	0.083	0.662	NS
PLT	0.353	0.055	NS	0.123	0.516	NS
PT	-0.577	0.001	HS	-0.473	0.008	HS
PC	0.793	0	HS	0.277	0.138	NS
INR	-0.65	0	HS	-0.416	0.022	S
Na	0.389	0.033	S	0.174	0.359	NS
K	-0.025	0.895	NS	-0.048	0.802	NS

There was positive correlation between serum zinc and albumin in both groups.

- There was negative correlation between serum zinc and bilirubin in both groups.
- There was negative correlation between serum zinc and prothrombin time in both groups.
- There was negative correlation between serum zinc and AST and ALT in patients with HE (group B).

There was positive correlation between serum zinc and serum Na in patients without HE (group A).

Correlation between Na level and results of lab investigation in both groups:

Table (8): Correlation between Na level and results of lab investigation in both groups

Variable	Na without HE Group A			Na with HE Group B		
	r	*p*	Sig.	r	*p*	Sig.
Creat	-0.18	0.34	NS	-0.139	0.465	NS
BUN	-0.032	0.866	NS	-0.104	0.583	NS
ALT	0.105	0.581	NS	0.027	0.887	NS
AST	0.257	0.171	NS	0.04	0.833	NS
T_Bil	-0.377	0.04	S	-0.321	0.084	NS
D_Bil	-0.45	0.013	S	-0.146	0.442	NS
Alb	0.352	0.056	NS	-0.196	0.3	NS
WBC	0.274	0.143	NS	-0.045	0.814	NS
Hb	0.316	0.089	NS	-0.408	0.025	S
MCV	-0.202	0.284	NS	0.079	0.677	NS
PLT	0.546	0.002	HS	-0.113	0.551	NS
PT	-0.429	0.018	S	0.115	0.545	NS
PC	0.492	0.006	HS	-0.168	0.376	NS
INR	-0.484	0.007	HS	0.074	0.697	NS
Na	-0.154	0.416	NS	-0.299	0.108	NS
K	-0.18	0.34	NS	-0.139	0.465	NS

-Correlation between Child A,B and C regarding Na level in patients without HE(group A):

Table(9):- Correlation between child A,B and C regarding Na level in patients without HE (group A).

	Child_Class	N	MEAN	±SD	F	*P*	SIG
Na	**A**	8	137.5	3.381	2.778	0.08	NS
	B	15	136.07	2.987			
	C	7	133.43	4.158			
	Total	30	135.83	3.582			

-Correlation between Child B and C regarding Na level in patients with HE (group B)

Table(10): Correlation between child B and C regarding Na level in patients with HE (group B)

	Child_Cls	n	Mean	±SD	t	*p*	Sig.
Na	**B**	13	122.15	3.158	1.564	0.13	NS
	C	17	119.71	5.347			

there was no significant statistical difference between serum Na level between two groups according to child classification .

-Correlation between child A,B and C regarding Zinc level in patients without HE group A.

Table(11): Correlation between child A,B and C regarding zinc level in patients without HE (group A).

	Child_Class	n	Mean	±SD	T	*p*	Sig.
Zinc	**A**	8	72.625	2.7742	44.589	0	HS
	B	15	63.6	3.9605			
	C	7	35.657	15.411			
	Total	30	59.487	15.875			

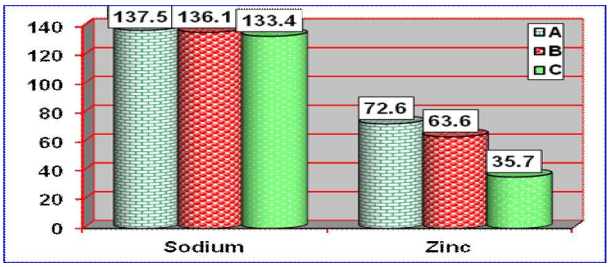
Correlation between child B,C regarding Zinc level in patients with HE(group B)

Table(12): Correlation between child B and C regarding zinc level in patients with HE (group B)

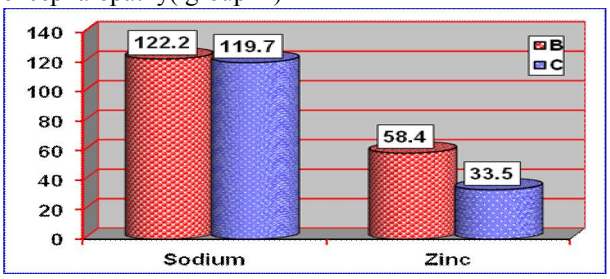
	Child_Class	n	Mean	±SD	T	*p*	Sig.
Zinc	**B**	13	58.385	4.1741	11.817	0	HS
	C	17	33.524	4.3766			

There was a significant statistical difference in serum level of zinc between patients with different child score in both groups. Child A patients has the highest level of zinc while Child C has the lowest level range.

There was a significant decrease in Serum zinc level in patients with HE (group B) in child B and C in comparison to patients without HE (group A) in child B and C.



Figure(4): - Comparison between Child classification scores as regards mean values of Sodium and Zinc among patients without encephalopathy(group A)



Figure(5): -Comparison between Child classification scores as regards mean values of Sodium and Zinc among with patients with encephalopathy (groupB).

4.Discussion

Cirrhosis is a gradually developing irreversible chronic disease of the liver which always involves the organ as a whole. The development of first episode of hepatic encephalopathy in a cirrhotic patient is a pejorative prognostic factor, and constitutes a turning point in the evolution of liver disease. Estimated survival rates are 42% at 1year, and 23% at 3 years **(Bustamante,et al,1999).**

Reduced serum and hepatic zinc levels correlated with reduced liver ornithine transcarbamylase activity and increased plasma ammonia level **(Yang,et al,2004).**

Zinc, a cofactor of urea cycle enzymes, may be deficient in cirrhotic patients, especially if associated, with malnutrition or encephalopathy **(Blei and Crdoba, 2001).**

Hyponatremia is a major risk factor of the development of overt HE **(Guevara,et al,2009).** Hyponatremia is acommon finding in patients with decompansated liver cirrhosis due to an abnormal regulation of body fluid homeostasis**(Gine′s,et al, 2006).** Hyponatremia in cirrhosis is defined as a reduction in serum sodium below 130 mmol/L **(Gine′s,et al,1998)**.

Novel theories suggest that low-grade cerebral edema (which can be induced by hyponatremia) may play a part in the pathogenesis of hepatic encephalopathy **(Haussinger,D.,2006)**.

The existence of low-gradecerebral edema, hyponatremia plays an important role in increasing the osmotic pressure on the astrocytes. In this situation,only small increases in ammonia levels can induce clinically manifested hepatic encephalopathy **(Kale,et al,2006).**

Our study was conducted on 60 patients they were classified into two groups.

Group A: 30 cirrhotic patients without hepatic encephalopathy.

Group B: 30 cirrhotic patients with hepatic encephalopathy in different grades admitted to Intensive CarCare Unit in the hospital of Theodor Bilharz Research Institute. All studied patients were subjected to complete medical history, detailed clinical examination, laboratory tests including CBC, serum creatinine, BUN, sodium, potassium, zinc, ALT, AST, albumin, total bilirubin, direct bilirubin,PT,PC and INR, in addition to MELD scoring , West Haven grading for patients with hepatic encephalopathy and child classification.

Male predominance was found in our study(55%).This can be explained by the fact that males are more likely to get infected with HBV and HCV. Worth saying that Child classification, H.E. and ascites all showed significant differences between the two groups. Serum zinc was measured and compared in all patients. It was found to be low in both groups, being lower in group B with a significant statistical difference. Patients without HE had their serum levels of zinc ranging from 36-77 with mean of 59.487 ± 15.8746. On the other hand, patients with HE had their serum levels of zinc ranging from 32-66 with mean of 47.867±10.2612.

Many factors can explain this low zinc level: the decreased intake caused by anorexia in advanced liver disease, decreased absorption due to intestinal congestion caused by portal hypertension, decreased bioavailability of zinc as a great portion of zinc is bound to albumin and to α2 macroglobulin. Thus ,in advanced liver disease, where protein synthesis by the liver is impaired, zinc deficiency is augmented.

Serum sodium was measured and compared in all patients. There was significant difference in serum sodium level between both groups (*p* value 0). Patients without HE had their serum level of sodium range from 130-143 with mean 135.83± 3.582 while patients with HE their serum level of sodium ranged from 110-128 with mean 120.77±4.629 .

In one study, Angeli *et al.* found a high frequency of hepatic encephalopathy Among patients with hyponatremia.They also found the incidence of H.E. to be 15% when serum Na level >135 mmol/L , 24% when serum Na level 130- 135 mmol/L and 38 % when serum Na level <130 mmol/L **Angeli, et al, 2006)**.

Also, to assess the role played by hyponatremia as a risk factor leading to H.E.,Guavara *et al.* (2009)

in a prospective study, found that a low sodium level below 130 mmol/ L at the beginning of the study had been associated with an increased risk of developing overt hepatic encephalopathy during the follow up period (**Guevara,et al,2009).**

Our results indicate an association between the severity of hyponatremia and the risk of developing an advanced degree of hepatic encephalopathy.

Conclusion:

1- Hyponatremia is a risk factor for Hepatic Encephalopathy.
2- Zinc deficiency is common in cirrhotic patients with and without Hepatic Encephalopathy according to the degree of decompansation as reflected by Child classifications and this deficiency is more severe in patients with Hepatic Encephalopathy .

Recommendations

1.Routine estimation of serum zinc in cirrhotic patients
2. The correction of zinc deficiency would have a beneficial effect on some complications of liver cirrhosis and may halt the progression of the disease.
3- Treatment of hyponatremia may be a novel therapeutic approach to prevent the evelopment HE in cirrhosis.
4- Further studies are needed to evaluate the suggested role played by hyponatremia and zinc deficiency in other conditions e.g. hepatorenal syndrome.

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