IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 12 Ver. VI (December. 2016), PP 73-77
www.iosrjournals.org

Vitamin B12 Associated Peripheral Neuropathy in Cirrhosis of Liver–A Cross Sectional Study

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Abstract:
Introduction*-Peripheral neuropathy (PN) is commonly associated with cirrhosis of liver. Vitamin B12 is stored in liver and its storage is hampered in liver cirrhosis. Vitamin B12 deficiency appears to be the most common reversible cause for PN.*
Aims&Objectives*- We evaluated correlation between serum vitamin B12 levels and PN in patients of cirrhosis of liver. 2. To study prevalence and pattern of PN and its association with different etiology and severity in patients of cirrhosis of liver.*
Methodology*-Cross sectional study was conducted in which total 100 patients with liver cirrhosis were assessed clinically for PN and confirmed by nerve conduction studies.*
Results*-Out of 100 patients, only 5 patients showed clinical signs of PN. 75 patients were clinically asymptomatic with abnormal nerve conduction studies showing polyneuropathy(52%) and mononeuropathy(48%).Majority of patients(89.2%)of PN was present in Child Pugh C class. Serum vitamin B12 and homocysteine levels were elevated in 75% of patients. A significant & positive correlation was observed between vitamin B12 and homocysteine level. Raised serum vitamin B12 level due to hepatocellular damage and leakage of vitamin B12 into the circulation & raised serum homocysteine levels indirectly reflects hepatocellular vitamin B12 deficiency.*
Conclusion*: Vitamin B12 may be a causative or precipitating factor for PN in cirrhosis of liver.*
Keywords*: Cirrhosis of liver, homocysteine, peripheral neuropathy, vitamin B12.*

I. Introduction

Cirrhosis is an end-stage liver disease that invariably leads to death [1, 2, 3] It is a major global health problem and an important cause of morbidity and mortality. Liver plays an important role in the storage and transport of cobalamin, so any pathology of liver may be associated with major changes in plasma cobalamin concentrations. [4, 5] Inflammation-induced cell degradation hereby causes the release of stored cobalamin, which in the circulation predominantly binds to haptocorrin (HC). This later process becomes reinforced by a diminished concentration of TC II (Transcobalamin II), which is the result of an impaired synthesizing capacity of the liver. Several studies show a significant decrease of intracellular cobalamin in liver biopsies. The increase of plasma cobalamin is related to the severity of the cirrhosis, and can reach 4 to 5 times the upper limit of the reference values. It is therefore assumed that a diminished uptake of HC-bound cobalamin by the affected liver also contributes to the elevated levels of cobalamin in plasma. [6, 7, 8]

Peripheral neuropathy (PN) is an important complication of cirrhosis of liver that may seriously impair patient's routine daily activities and quality of life. Various studies revealed prevalence of PN varying from 19-80% in the cirrhotic patients on nerve conduction studies. PN is significantly more frequent in advanced liver disease as compared with early liver damage. Various literary works done regarding correlation between prevalence, type of PN and severity of liver disease and results are dubious and none of the studies compared its association with vitamin B12 levels. Some liver dysfunction can cause PN independently, hence, a cause and effect relationship between liver disease and neuropathy has been questioned. [9-15]So, despite various reports on the subject, there is still discordance regarding the type and extent of liver cirrhosis associated PN. Therefore, this study was planned to elucidate the prevalence and pattern of PN and its relation with severity as well as different etiology of liver cirrhosis and its association with serum vitamin B12 level.

II. Materials And Methods

This cross sectional, observational study was conducted in the Department of Medicine, King George's Medical University, Lucknow, India during 2014-2015. All patients with cirrhosis of liver, attending Gastroenterology and Medical outpatient department and admitted in indoor medical wards fulfilling the inclusion criteria were enrolled in the study.

III. Inclusion Criteria

Patient of cirrhosis of liver diagnosed by symptoms and signs of chronic liver cell dysfunction in association with evidence of portal hypertension (portal vein diameter >12mm and presence of oesophageal varices)

IV. Exclusion Criteria

Patient with overt hepatic encephalopathy, diabetic neuropathy, cerebrovascular disease, primary neurological disorder, chronic renal failure, surgical gastrectomy, malabsorption syndrome and human immunodeficiency virus disease.

V. Evaluation Of Patients

Detailed history and examination was done in all patients. Complete blood count, liver function tests(LFT), prothrombin time(PT), international nationalised ratio(INR), ultrasound abdomen focussing on liver echo texture, portal vein diameter, liver size ,spleen and ascites, upper gastrointestinal endoscopy for assessing varices, ascitic fluid analysis, viral markers (HBsAg, HCV, HIV), serum vitamin B12 ,homocysteine level and nerve conduction study was carried out in all patients.

VI. Statistical Analysis

Statistical analysis was done using unpaired t test, Chi Square test; Spearman Correlation coefficient test. The p-value of <0.05 was considered significant. Statistical analysis was carried out by using SPSS 22.0 version.

VII. Results

We enrolled 100 patients of cirrhosis of liver. Of the 100 patients, 73 were males and 27 were females. Mean age of the study group was 49.78±11.33 years. Our study showed prevalence of 75% of PN in patients of cirrhosis of liver among which 24 were females (88.9%) and 51 were males (69.9%). PN was more common (79%) in lower socioeconomic status.

Polyneuropathy & mononeuropathy multiplex was seen in 52% and 48% of cirrhotic patients respectively. Sensorimotor demyelinating type of polyneuropathy was seen in 71.8% and sensorimotor axonal type of polyneuropathy was seen in 28.2% patients of cirrhosis of liver.

Table 1: Distribution of peripheral neuropathy in different etiologies of liver cirrhosis

Etiology of Cirrhosis of liver		Total no. of patients (N=75)	Type of neuropathy				p-value
			Polyneuropathy		Mononeuropathy Multiplex		
			No.	%	No.	%	
Alcoholic	Yes	26	12	46.2	14	53.8	0.46
	No	49	27	55.1	22	44.9	
HBsAg	Positive	23	12	52.2	11	47.8	0.98
	Negative	52	27	51.9	25	48.1	
HCV	Positive	26	15	57.6	11	42.3	0.32
	Negative	49	23	46.9	25	51.1	

Different etiology like Alcoholic liver cirrhosis, HBsAg and HCV related cirrhosis of liver had no significant association with PN.

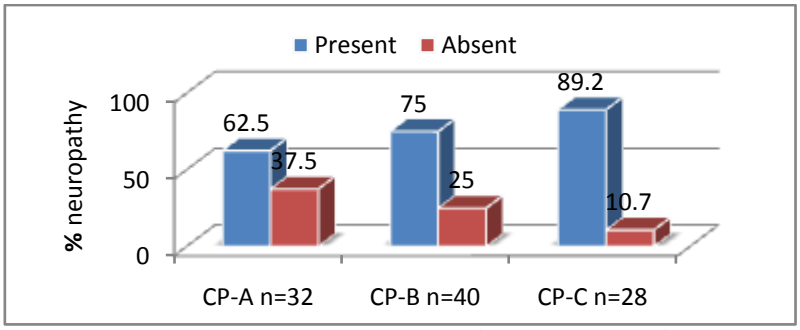

Fig 1: Distribution of peripheral neuropathy according to Child Pugh classification in patients of liver cirrhosis Our study showed the prevalence of PN has direct relation with severity of liver cirrhosis (p=0.02). PN was seen in 62.5%, 75% & 89.2% of Child Pugh class A, B &C patients of liver cirrhosis respectively.

Table-2: Comparison of biochemical parameters with the occurrence of peripheral neuropathy in liver cirrhosis

Variables	With neuropathy		Without neuropathy		p-value
	Mean	SD	Mean	SD	
S. Bilirubin total(mg/dl)	15.22	11.24	8.41	6.58	0.001*
S. Bilirubin direct(mg/dl)	11.30	9.21	5.52	4.95	0.001*
SGPT (IU/L)	422.26	404.48	238.07	180.99	0.002*
SGOT (IU/L)	402.31	346.10	224.08	164.18	0.001*
S. ALP (IU/L)	351.79	221.55	278.73	160.96	0.05
S. protein (g/dl)	5.12	0.48	5.57	0.72	0.001*
S. Albumin (g/dl)	2.25	0.38	2.40	0.61	0.17
Prothrombin time (Second)	29.54	9.26	22.12	7.75	0.001*
International Normalized Ratio (INR)	2.94	0.95	2.25	1.00	0.003*
Portal vein diameter (mm)	13.78	0.87	13.32	0.54	0.01*

PN had statistically significant association with deranged PT, INR and LFT. PN had statistically significant association with portal hypertension which suggests PN is common in portal hypertension.

Table-3: Distribution of Serum Vitamin B12 and Homocysteine levels in patients of liver cirrhosis with and without peripheral neuropathy

Patients of cirrhosis of liver	With peripheral neuropathy	Without peripheral neuropathy	P value
Serum Vitamin B12 (pg/ml) (mean±SD)	1953.73±301.40	887.48±492.67	0.0001*
Serum Homocysteine (µmol/L) (mean±SD)	13.54±1.30	11.00±1.21	0.0001*

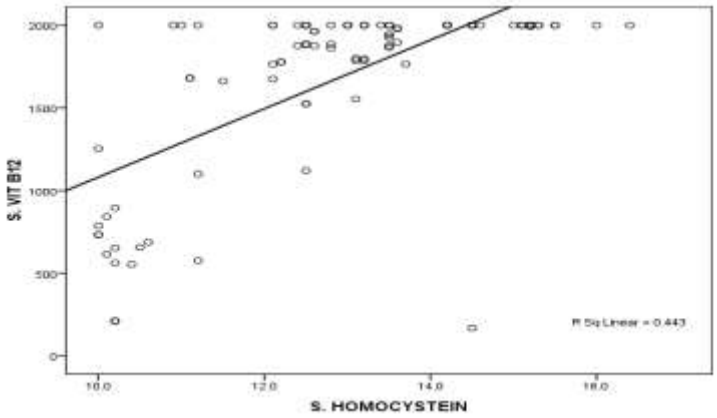

Fig 2: Correlation between Serum vitamin B12 and homocysteine

The mean serum vitamin B12& homocysteine levels in patients of cirrhosis of liver with PN was significantly higher than patients of cirrhosis of liver without PN (p=0.0001) depicted in table 3 and a significant & positive correlation was observed between vitamin B12 and homocysteine level(r=0.66,p=0.001) shown in scatter diagram Fig.2

VIII. Discussion

The study was conducted by us in which association of PN in 100 patients of liver cirrhosis and its correlation with Serum Vitamin B12 and Serum Homocysteine was assessed.

The demographic distribution in contrast to our study, a study done by Jain J et al[16] found that in patients of liver cirrhosis, higher magnitude of PN was seen in males and in patients with age group above 60 years and more among rural patients but in their study PN for age, sex, occupation were not significant.

75 patients of liver cirrhosis had PN out of which only 5 (6%) patients had clinical features of PN like absent vibration sense and position sense with diminished reflexes and remaining 70 were asymptomatic which was diagnosed by nerve conduction velocity test. These findings were supported by Chaudhry V et al. [11], Jain J et al.[16] and Kharbanda PS et al.[9]

In our study we observed that in 75 patients of PN, 39 (52%) patients had polyneuropathy and 36 (48%) patients had mononeuropathy multiplex .Further among 39 patients of polyneuropathy, 28 (71.8%) patients had sensorimotor demyelinating type and 11 (28.2%) patients had sensorimotor axonal type of polyneuropathy. Similar study done by Dayan et al. [17] and Chari V R et al. [10] concluded that a patient of liver cirrhosis with different etiology has demyelinating type of polyneuropathy. However, Kharbanda et al. [9] and Jain J et al. [16] found that sensory motor axonal type polyneuropathy was predominant. The probable reason may be as our study is cross sectional the patient which we included in our study may be in early stage of liver cirrhosis.

Different etiology of liver cirrhosis was evaluated according to PN the results of which are depicted in Table 1. Although statistically insignificant, we found that the incidence of PN was higher in hepatitis C related liver cirrhosis. Similar findings were also found by Kharbanda et al.[9]and Chari V R et al.[10]

To evaluate the association of PN with the severity of liver cirrhosis, we classified patients of liver cirrhosis on the basis of Child Pugh (CP) classification and we found statistically significant association of PN with the severity of liver disease. This data is depicted in Figure 1. These results are similar to study done by Fawi GH et al. [18] and Chaudhry V et al. [11]

Among the various biochemical parameters assessed in our study only LFT,PT & INR showed significant association with peripheral neuropathy which is depicted in Table 2.Portal vein diameter(PVD) of patients of liver cirrhosis was assessed ultrasonographically and it was found that mean value of PVD was 13.78±0.87 mm had significant association with peripheral neuropathy(Table 2).The probable cause may be that due to portal hypertension, collateral shunting develops and allows toxic factors, normally produced by colon and detoxified by the liver, access to peripheral nervous system.

Serum vitamin B12 and homocysteine levels were assessed and found to be elevated with a mean value 1953.73±301.40 and 13.54±1.30 respectively showing significant association with PN in patients of cirrhosis of liver. We also found significant & positive correlation between serum vitamin B12 and homocysteine which is shown in scatter diagram fig 2 and similar finding was observed in a study done by Essam F. Al-Jumaily et al. [19] and Ueland PM et al. [20] Deficiency of vitamin B12 leads to an increase in serum methylmalonyl- CoA, and its metabolic product, methyl malonic acid (MMA). The second reaction uses cobalamin as a cofactor in the synthesis of methionine from homocysteine. Homocysteine levels increase in vitamin B12 deficiency. The raised levels of Serum Vitamin B12 in liver cirrhosis with elevated levels of serum homocysteine signify hepatocellular Vitamin B12 deficiency. Raised levels of vitamin B12 in liver cirrhosis may be due to hepatocellular damage caused by liver cirrhosis leads to cellular leakage of vitamin B 12 in circulation with subsequent intracellular Vitamin B12 deficiency. Hepatocellular damage may also cause disruption of liver tissue vitamin B12 binding protein and storage of transcobalamin and causes raised levels of Vitamin B12 in circulation.

IX. Conclusion

From our study, we conclude that the prevalence of PN is 75% in patients of cirrhosis of liver. Predominantly sensorimotor demyelinating type polyneuropathy is common in such patients irrespective of etiology. Vitamin B12 deficiency seems to be a precipitating or causative factor for the development of peripheral neuropathy in patients of cirrhosis of liver.

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