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Neuropathies in relation to Serum Cobalamin in Chronic Hepatitis C Patients.

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ABSTRACT

This study aimed to investigate the incidence and characteristics of peripheral neuropathy in chronic hepatitis C patients and its relation to serum cobalamin. Fifty patients (32 males, 18 females) aged 22-26 years with HCV related chronic disease were divided into 2 groups: Group I - MELD<14, Group II - MELD>14, Group III control. Cardiovascular autonomic function tests were performed to assess presence or absence of autonomic neuropathy. All patients underwent nerve conduction studies (NCS). Patients with Diabetes Mellitus, chronic renal failure, malignancy, history of alcohol intake, receiving neurotoxic drugs as chemotherapy were excluded from the study. The abnormalities were sensory abnormalities (22%), motor abnormalities (18%), both sensory and motor abnormalities (10%). Moreover, 46% had evidence of neuropathy, 30% had dysautonomia, 36% had peripheral neuropathy and 20% had both peripheral and autonomic neuropathy. Neuropathy was seen irrespective of the cause of liver disease and there was a significant correlation of the severity of neuropathy to severity of liver disease suggesting that the metabolic dysfunction caused by liver disease is the primary determinant of polyneuropathy. It was found that serum B12 was above normal level and very high in liver cirrhosis. No relation was found between serum B12 and neuropathy in hepatic patients.

Keywords: neuropathies, chronic liver disease, HCV, serum cobalamin.

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INTRODUCTION

Peripheral neuropathy (PN) has been reported in association with chronic liver diseases including liver cirrhosis and hepatitis. However, reports vary regarding the incidence and characteristics of this neuropathy. The causal relationship of liver diseases with neuropathy has also been questioned [1]. Neurological examination showed distal sensory loss to pain or vibration or distal loss of reflexes. Sensory neuropathy is more common than motor axonal polyneuropathy according to nerve conduction studies [2]. Additionally, autonomic neuropathy (AN) has been reported in patients with alcoholic and nonalcoholic liver disease [2]. Due to its prevalence and clinical significance, it is important that hepatologists recognize dysautonomia and initiate appropriate investigation and management [3]. Other studies have addressed the relationship between autonomic neuropathy and chronic liver. They found frequent abnormalities of heart rate variation with deep breathing and with the Valsalva maneuver suggesting the presence of autonomic neuropathy with predominant parasympathetic dysfunction. Patients did not show orthostatic decreases in blood pressure suggesting relatively intact sympathetic function. This is consistent with previous observations that autonomic function was abnormal both in alcohol and nonalcoholic categories of chronic liver diseases [4]. It has also been found that the prevalence and severity of autonomic dysfunction was related to the severity of hepatic dysfunction and was independent of the cause of liver disease [5].

Six major genotypes and more than 50 subtypes of HCV have been described [6]. In general, HCV genotype 4(HCV4) is predominant in Africa and the Middle East. In Egypt where hepatitis C is highly endemic (up to 15% of the population), 91% of patients were infected with HCV4 [7]. HCV can invade Peripheral Blood Mononuclear Cells (PBMC); particularly macrophages. Infected leucocytes could cross the blood brain barrier in a process similar to that postulated for HIV-1 infection. Subsequently, there could be a secondary spread of HCV to permissive cells within the brain. The primary targets are brain microglia cells which are essentially tissue-resident macrophages of blood monocyte origin. Infected macrophages and macroglia cells could release pro-inflammatory cytokines such as IL-1 and IL-6, neurotoxins such as nitric oxide and viral proteins which could induce an alteration in brain function leading in turn to neurocognitive dysfunction and depression [8,9].

Since liver plays an important role in the storage and transport of cobalamin, it is not surprising that liver pathology is associated with major changes in plasma cobalamin concentrations [10]. Elevated levels of serum cobalamin may be a sign of a serious, even life-threatening disease. Several liver diseases like acute hepatitis, cirrhosis, hepatocellular carcinoma and metastatic liver diseases can also be accompanied by an increase in circulating cobalamin. This phenomenon is predominantly caused by cobalamin release during hepatic cytolysis and/or decreased cobalamin clearance by the affected liver [11]. In liver cirrhosis, the increase of plasma cobalamin is also associated with tissue depletion. Several studies showed a significant decrease of intracellular cobalamin in liver biopsies. The increase of plasma cobalamin is related to the severity of cirrhosis. Theoretically, a significant elevated level of plasma cobalamin can be associated with a functional cobalamin deficiency [12].

The aim of this study was to evaluate peripheral and autonomic neuropathy in patients with HCV–related chronic liver diseases. Moreover, estimation of the relation between the severity of liver dysfunction was assessed by MELD score and the presence of peripheral and autonomic neuropathy as well as estimation of the relation between serum cobalamin and peripheral and autonomic neuropathy with chronic liver disease were also estimated during the study.

Patients and Methods

This is a prospective Case Control study including 50 patients (32 males and 18 females), 22-26 years old who attended the outpatient clinic and inpatient wards of Tropical Medicine Department of Ain Shams University hospital with stigmata of chronic liver disease based on clinical, laboratory and radiological data. The severity of each patient's liver disease was scored using the MELD score. Using as a cut-off the median value of the MELD score, patients were arbitrarily classified into two groups according to MELD score [13].

Group A: 25 Patients with MELD score < 14
Group B: 25 Patients with MELD score > 14.

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Controls: 25 healthy subjects with no history or manifestations of liver disease were included for assessment of serum cobalamin level.

Adult Egyptian patients with clinical, laboratory and radiological evidence of chronic liver disease being HCV positive and written informed consent, were included in the study. Patients with Diabetes Mellitus (DM), chronic liver failure, known malignancy with history of alcohol intake or receiving neurotoxic drug as chemotherapy suffering from liver disease due to any cause other than HCV were excluded from the study. All included patients were subjected to clinical examination with full history laying special stress on drug history, alcohol intake, DM, other causes of neuropathy as autoimmune diseases or heavy metal poisoning. Also, symptoms of hepatic decompensation, neurological manifestations including sensory symptoms, radiological investigations including abdominal ultrasonography and other modalities required for excluding any other cause of liver disease as well as neurological studies, were included. Assessment of orthostatic changes in blood pressure and heart rate are basic tests of cardiovascular autonomic functions. The beat-to-beat changes in heart rate in response to autonomic reflexes occur quickly, often too quickly for bedside assessment to be accurate. At the bedside, blood pressure and pulse were taken with the patient supine and after standing [14]. Nerve Conduction Studies (NCS), according to the American Academy of Neurology (Distal symmetric polyneuropathy: A definition for clinical research), a simplified NCS protocol was used for the purpose of defining the presence of distal symmetric polyneuropathy using the MEDTRONIC device. The simplified NCS protocol is as follows: Sural sensory and peroneal motor NCS's were performed in lower extremity. If both studies were normal it indicated no evidence of typical distal symmetric polyneuropathy. In such a situation, no further NCS's were necessary. If sural sensory or peroneal motor NCS's were abnormal, the performance of additional NCS's was recommended. This included NCS of at least the ulnar sensory, median sensory, and ulnar motor nerves in one upper extremity. A contralateral sural sensory and one tibial motor NCS was also performed according to demand. If a response was absent for any of the nerves studied (sensory or motor), a NCS of the contralateral nerve was performed. If a peroneal motor response was absent, an ipsilateraltibial motor NCS was performed [15]. Serum Cobalamin level was performed using Access Immune Assay system, competitive binding immune-enzymatic assay.

RESULTS

The patients and the control groups matched with respect to age and gender. There was statistically significant difference between both groups regarding symptoms of liver disease (Jaundice, Hepatic encephalopathy, Gastrointestinal bleeding and Lower limb edema) (Table 1).

Table1: Clinical symptoms and child classification of liver disease in both groups

Clinical Symptoms\classification		Group I		Group II		Total		X^2	P	Significance
		N	(%)	N	(%)	N	(%)			
Jaundice	No	24	(96)	1	(4)	25	(50)	42.3	<0.01	S
	sYe	1	(4)	24	(96)	25	(50)			
Hepatic Encephalopathy	No	25	(100)	14	(56)	39	(78)	14.1	<0.01	S
	Yes	0	(0)	11	(44)	11	(22)			
GI bleeding	No	24	(96)	18	(72)	42	(84)	5.4	0.02	S
	Yes	1	(4)	7	(28)	8	(16)			
LL edema	No	14	(56)	1	(4)	15	(30)	16.1	<0.01	S
	Yes	11	(44)	24	(96)	35	(70)			
Child	A	20	(80)	0	(0)	20	(40)	37.7	<0.01	S
	B	5	(20)	8	(32)	13	(26)			
	C	0	(0)	17	(68)	17	(34)			

*LL edema-lower limb edema

Table 2 shows that signs of liver cell failure are significantly more prevalent in group II than group I. This is compatible with our classification according severity of liver disease.

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Table 2: Signs of liver cell failure in the studied groups

Liver Failure Signs		Group I N %	Group II N%	Total N	X^2	P	Sig
Jaundice	No	20 (80)	0 (0)	2 (40)	33.3	<0.01	S
	Yes	5 (20)	25 (100)	30 (60)			
Ecchymosis	No	16 (64)	0 (0)	16 (32)	23.5	<0.0	S
	Yes	9 (36)	25 (100)	34 (68)			
LL edema	No	22 (88)	3 (12)	25 (50)	28.9	<0.01	S
	Yes	3 (12)	22 (88)	25 (50)			

Abdominal examination of our patients revealed that local signs of liver disease (palpable spleen and shifting dullness) are more evident in group II as compared to group I. Regarding palpable liver, all patients were cirrhotic with average size (36 patients, 72%) or shrunken liver (14 patients, 28%) (Table 3).

Table 3: Local abdominal signs in the studied groups

Local Abdominal Signs		Group I N (%)	Group II N (%)	Total N (%)	X^2	P	Sig
Palpable liver		0 (0)	0 (0)	0 (0)			
Palpable spleen		13 (52)	20 (80)	33 (66)	19.5	<0.01	S
Bilateral shifting dullness	No	19 (76)	4 (16)	23 (46)	18.1	<0.01	S
	Yes	6 (24)	21 (84)	27 (54)			

Table 4: Neurological symptoms in the studied groups

Neurological Symptoms		Group I N %	Group II N %	Total	X^2	P	Sig
Numbness	No	20 (80)	13 (52)	33 (66)	4.4	0.04	S
	Yes	5 (20)	12 (48)	17 (34)			
	yes						
Burning	No	21 (84)	19 (76)	40 (80)	0.5	0.48	NS
	Yes	4 (16)	6 (24)	10 (20)			
Prickling & paresthesia	No	22 (88)	21 (84)	43 (86)	0.17	0.68	NS
	Yes	3 (12)	4 (16)	7 (14)			
Motor weakness	No	20 (80)	19 (76)	39 (78)	0.12	0.73	NS
	Yes	5 (20)	6 (24)	11 (22)			

Table 4 shows the sensory and motor symptoms amongst the two groups. Thirty six percent of the patients complained of sensory manifestations with no statistically significant difference between the two groups. It was noticed that patients with liver cirrhosis complained more of negative symptoms (numbness) than positive symptoms (burning – bricking – dysthesia). There is statistically significant difference between the two groups regarding numbness.

Table 5: Sensory examination in the studied groups

		Group I N %	Group II N %	Total	X^2	P	Sig
Pain	No	21 (84)	19 (76)	40 (80)	0.5	0.48	NS
	Yes	4 (16)	6 (24)	10 (20)			
Touch	No	21 (84)	20 (80)	41 (82)	0.14	0.71	NS
	Yes	4 (16)	5 (20)	9 (18)			
Vibration	No	25 (100)	24 (96)	49 (98)	1.0	0.31	NS
	Yes	0 (0)	1 (4)	1 (2)			

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Table 6: Motor examination in the studied groups

Motor Examination		Group I N %	Group II N %	Total	X^2	P	Sig
Atrophy	No	22 (88)	21 (84)	43 (86)	0.17	0.68	NS
	Yes	3 (12)	4 (16)	7 (14)			
Reflexes	Areflexia	2 (8)	1 (4)	3 (6)	1.4	0.1	NS
	Hypo	1 (4)	3 (12)	4 (8)			
	No	22 (88)	21 (84)	43 (86)			

Sensory examination of the studied groups showed that there is no statistically significant difference between both groups in sensory examination with abnormalities in pain, touch and vibration but no abnormalities occurred in hot, cold and proprioception (Table 5). Moreover, motor examination of the studied groups showed that there is no statistically significant difference between the two groups (Table 6).

Laboratory investigations revealed that anemia was more evident in group II than group I (hemoglobin 10.7±2.1 in group I vs 11.8±1.3 in group II). Also, liver functions were significantly impaired in group II than group I including ALT, total bilirubin, albumin and INR, while difference between white cell count, platelet count, AST and creatinine were insignificant in the two groups (Table 7).

Table 7: Clinical investigations of the studied groups

Clinical tests	Group I Mean ±SD	Group II Mean ±SD	T	P-value	Sig
WBC($x10^3$/ml)	6.2 ±2.1	5.9±2.1	0.44	0.66	NS
HGB (g/dl)	11.8±1.3	10.7±2.1	2.12	0.04	S
PLTs($x10^3$/ml)	110.4±48.6	94.5±39.5	1.27	0.21	NS
ALT(up to 40)	59.9±37.9	34.9±18.7	2.95	<0.01	S
AST(up to 38)	66.8±31.9	52.4±27.1	1.72	0.09	NS
T Bil (0.6-1.2)	1.3±0.5	5.9±3.6	-6.36	<0.01	S
Albumin(3.5-5)	2.98±0.39	2.2±0.42	6.48	<0.01	S
INR	1.28±.10	1.7±.37	-6.11	<0.01	S
Creatinine (up to 1.2)	1.2±1.4	1±0.22	0.85	0.4	NS

*ALT-alanine transaminase, AST-aspartate transaminase, HGB haemoglobin
INR- international normalized ratio, PLT – platelets, T Bil-total bilirubin,
WBC – White Blood Cell

Table 8: Abdominal ultrasound examination of the studied groups

Abdominal ultrasound examination		Group I N %	Group II N %	Total	X^2P	X^2P	Sig
Liver: size	Average	25 (100)	11 (44)	36 (72)	19.4	<0.01	S
	Shrunken	0 (0)	14 (56)	14 (28)			
Spleen size	Average	12 (48)	5 (20)	17 (34)	4.4	0.07	NS
	Large	13 (52)	20 (80)	33 (66)			
Ascites: Yes	Mild	3 (12)	5 (20)	8 (16)	28.2	<0.01	S
	Moderate	1 (4)	17 (68)	18 (36)			
No		21 (84)	3 (12)	24 (48)			

Abdominal ultra-sonographic examination indicated that there was a statistically significant difference between groups as regards the liver size and presence of ascites. All patients had echogenic liver (Table 8).

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Autonomic function tests in the patients revealed Dysautonomia in 6 patients (24%) of group I and 9 patients (36%) in group II, overall 15 patients (30%) of all patients suffered from dysautonomia. But there was no statistically significant difference between both groups (Table 9).

Table 9: Autonomic functions and nerve conduction studies in the studied groups

Nerve conduction/Autonomic * function		Group I N %	Group II N %	Total	X^2	P	Sig
AFT	Normal	19 (76)	16 (64)	35 (70)	0.86	0.36	NS
	Abnormal	6 (24)	9 (36)	15 (30)			
NCS	Normal	17 (68)	15 (60)	32 (64)	0.35	0.56	NS
	Abnormal	8 (32)	10 (40)	18 (36)			
Type NC	Axonal	5 (20)	4 (16)	9 (18)	9.2	0.03	S
	Demyelinating	3 (12)	0 (0)	3 (6)			
	Mixed	0 (0)	6 (24)	6 (12)			
	No	17 (68)	15 (60)	32 (64)			

* AFT- autonomic function test, NC- nerve conduction

Table 10: Comparison of B12 level in the studied groups:

level12Vitamin B		Group I	Group II	Group III	F	P	Sig
B12 (180-914pg/ml)	Mean±SD	1884±1834	1296±1007	242±105	11.8	<0.01	S
	Range	243-6580	391-5124	106-416			
	Median (IQR)	1059 (2368)	1086 (882)	212 (218)	▪44.6	<0.01	S

▪ x^2 value for Kruskal Wallis test.

NCS shows abnormality in 8 patients (32%) of group I and 10 patients (40%) of group II, overall 18 patients (36%) of the patients with peripheral neuropathy in NCS; but no statistically significant difference occurred between both groups (Table 9).Ten patients (20%) had both PN and AN. Overall, 23 patients (46%) had evidence of neuropathy, in agreement with peripheral NCS or cardio-vascular autonomic function test (Table 9).

Performing serum B12 (cobalamin) to all patients and controls, control group showed the least level as compared to the other two groups with statistically significant difference ($p<0.01$). This denotes that level of vitamin B12 is higher in cirrhotic patients than normal individuals (Table 10). Table 11 shows the comparison between vitamin B12 level and the results of neurological examination of the patients of the two groups. It was noticed that vitamin B12 level is significantly higher in patients with sensory examination abnormalities. The mean level of vitamin B12 was 2337±2097 while in patients without abnormality it was 1379±1230. No significant difference in vitamin B12 level in relation to motor examination and autonomic function tests occurred. Table 12 shows the comparison between vitamin B12 level and the results of autonomic function tests and NCS. There is no statistically significant difference between patients with and without peripheral neuropathy regarding vitamins B12 level.

Table 11: Comparison of serum B12 in relation to neurological examination in patients groups

Neurological examination		B12 Mean	B12 SD	P value	Sig
Sensory examination	No	1379.2	1230.7	0.05	S
	Yes	2337.7	2097.7		
Pain	No	1375.7	1215	0.2	NS
	Yes	2447.5	2177.7		
Touch	No	1371.9	1199.9	0.15	NS
	Yes	2583.4	2264.3		

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Neurological examination		B12		P value	Sig
		Mean	SD		
Sensory examination	No Yes	1379.2 2337.7	1230.7 2097.7	0.05	S
Motor examination	No Yes	1577.7 1646.4	1400.2 1968	0.9	NS
Atrophy	No Yes	1542.7 1880.6	1378.6 2196	0.6	NS

Table 12: Comparison of serum B12 levels in relation to autonomic function tests and NCS patients groups

Autonomic function tests		B12			
		Mean	Std Deviation	P value	Sig.
	Normal Abnormal	1384.4 2069.8	1257.9 1903.2	0.2	NS
NCS	Normal Abnormal	1464.9 1812.4	1305.8 1801.8	0.43	NS
Type of NCS	Axonala Demyelinating Mixed No	2296.4 2051.3 966.8 1464.9	2211.6 2122.4 311.6 1305.8	0.32	NS

*NCS

Table 13: Correlation between vitamin B12 level and other parameters

Parameters	Correlation coefficient /valueP	B12			
		group I	group II	Total	Sig.
MELD	Correlation coefficient	0.4	0.006	-0.09	
	P value	0.05	0.9	0.5	S
Age	Correlation coefficient	0.6	0.27	0.47	
	P value	0.002	0.19	0.0	S
Hb	Correlation coefficient	-0.4	-0.1	-0.15	
	P value	0.046	0.6	0.3	S
TLC	Correlation coefficient	-0.1	-0.3	-0.16	
	P value	0.57	0.14	0.26	NS
Platelets	Correlation coefficient	0.26	0.3	0.3	
	P value	0.2	0.09	0.03	NS
ALT	Correlation coefficient	0.1	0.16	0.18	
	P value	0.6	0.44	0.2	NS
AST	Correlation coefficient	0.045	0.17	0.13	
	P value	0.83	0.39	0.37	NS
Bil.T	Correlation coefficient	0.270	-0.12	-0.15	
	P value	0.19	0.57	0.29	NS
Albumin	Correlation coefficient	-0.33	-0.19	-0.05	
	P value	0.1	0.3	0.7	NS
INR	Correlation coefficient	0.17	0.05	-0.08	

	P value	0.4	0.8	0.56	NS
Creatinine	Correlation coefficient	-0.12	0.03	-0.07	
	P value	0.55	0.89	0.58	NS

*TLC Total Leucocyte Count

Table 13 shows that vitamin B12 level is significantly directly correlated to MELD score and age (P= 0.05 and <0.001 respectively). However, it is inversely correlated to hemoglobin in group I (P= 0.046) with no significant correlation to any other parameter.

DISCUSSION

Clinical history of cases revealed that 36% of the patients had sensory manifestations of polyneuropathy. Patients with liver cirrhosis (groups I and II) complained more of negative symptoms (numbness) than positive (burning – bricking – dysthesia). Neurological examination of both groups showed that 22% of patients had sensory abnormality, 18% had motor abnormality while only 10% had both sensory and motor abnormalities. Autonomic function tests and nerve conduction studies revealed that overall 23 patients (46%) had evidence of neuropathy in agreement with peripheral NCS or cardiovascular autonomic function test. Also, 15 patients (30%) had dysautonomia and 18 patients (36%) had peripheral neuropathy in nerve conduction studies. Moreover, 10 patients (20%) had both peripheral and autonomic neuropathy. The results matched with a study where 83 patients were included with end-stage liver disease, and a higher prevalence of neuropathies (65%) was observed as compared to the general population [13]. Previous reports [16-20] stated that the incidence of neuropathy in chronic liver disease varies widely from 19% to 100%.

A difference in the prevalence of autonomic neuropathy (AN) and peripheral neuropathy (PN) could be due to the different sensitivity of the tests used to diagnose the two types of neuropathies or due to the different involvement of the two types of fibers. The high prevalence of association between autonomic and peripheral neuropathy in the patients (20%) showed that a mixed neuropathy is common. A number of hypotheses in the literature regarding the pathogenic role of liver failure in the genesis of neuropathy could explain the high prevalence of neuropathies in the present study. The pathogenesis is not well known but there could be different mechanisms of nerve damage, including the liver failure itself. One study posited the Porto systemic shunting and hepatocellular damage to be the two most important factors in the pathogenesis of hepatic neuropathy [21]. However, other studies found that undergoing a portocaval shunt made no such difference in patients with cirrhosis [22]. One study showed a mild depolarization of the resting axonal membrane potential, but did not confirm it as a pathogenetic factor of hepatic neuropathy [22]. Such depolarization likely results from poor nerve perfusion. The hypothesis of a nerve ischemia is supported by histopathological studies [23]. The mechanism which is thought to play a role in reduced microscopic vascular perfusion may be analogous to the one observed in hepatorenal syndrome, which is due to an imbalance of potent vasoconstrictors and vasodilators [24]. The ischemia of vasa nervosum and the changes in the axonal membrane excitability due to the metabolic and toxic modifications could be the primary pathogenic mechanisms of the nerve dysfunction.

In our study, the correlation between the prevalence of neuropathy and the severity of liver disease suggests that there is no significant difference between group I (MELD <14) and group II (MELD >14) in the prevalence of neuropathy. Our results did not match [13] who found that PN was more frequent in patients with more severe liver disease as compared to those with mild liver disease, and this difference was statistically significant. They concluded that liver dysfunction is the primary cause of neuropathy. This difference in our results may be due to the different sensitivity of the tests used to diagnose the two types of neuropathies, or to the different involvement of the two types of fibers. Moreover, patients with different causes of cirrhosis were used [13] and it is well known that some of these causes are independent cause of neuropathy as alcoholic liver disease. Moreover, they did not exclude the diabetic patients while we did.

In the present study, a hypothesis of relation between vitamin B12 level and neuropathy in HCV related chronic liver disease was assumed and studied. Vitamin B12 deficiency causes a wide range of neurological disorders. Neurological symptoms may occur in the absence of haematological abnormalities. The neurological syndromes associated with vitamin B12 deficiency include myelopathy and neuropathy [25].

In the present study, anemia was greater in group II with more severe liver disease, and that anemia was inversely related to vitamin B12 level in blood. The role of vitamin B12 in macrocytic anemia is well known due to its role in DNA synthesis. Since the liver plays an important role in the storage and transport of cobalamin, it is not surprising that liver pathology is associated with major changes in plasma cobalamin concentrations [10]. The high frequency of high serum cobalamin was exemplified in a retrospective study [26] which included 3702 hospitalized patients regardless the etiology in whom high levels of vitamin B12 were found in 12% of cases, whereas a deficiency was only observed in 10% of the cases. High serum cobalamin (vitamin B12) is a frequent and underestimated anomaly [27]. In the present study, assessment of serum cobalamin level was high in patients with liver disease; where 62% of patients had hypercobalaminemia with median 1059 pg/ml in group I and 1086 pg/ml in group II being significantly higher than the control group. Our results match with the study that in liver cirrhosis, high serum cobalamin can be found five times above the upper limit [10]. In this context, the degree of elevated cobalamin is thought to be correlated with the severity of cirrhosis. In cirrhosis, the decrease in tissue and cellular liver uptake of vitamin B12 and of haptocorrin (HC)–cobalamin complex are the main mechanisms involved and have been typified by biopsy studies performed in cirrhotic patients [12]. In acute hepatitis, elevated cobalamin levels in plasma have been found in 25 to 40% of the patients [11]. Inflammation-induced cell degradation hereby causes the release of stored cobalamin, which in the circulation predominantly binds to haptocorrin. This latter process becomes reinforced by a diminished concentration of Trans-cobalamin (TC) II, which is the result of an impaired synthesizing capacity of the liver.

During the present study, vitamin B12 level was directly related to MELD score which means that it is increasing with advancing liver disease. It has also been stated that in liver cirrhosis, the increase of plasma cobalamin is also associated with tissue depletion [11]. Several studies showed 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. However, hepatocytes are degraded to a lesser degree than is the case in acute hepatitis. 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. Our results matched with the study that the degree of elevated cobalamin is thought to be correlated with the severity of cirrhosis [27].

The relation between vitamin B12 and neurological examination revealed that high level of vitamin B12 was more associated with sensory abnormalities. The relation between serum cobalamin (vitamin B12) level and neuropathy revealed that there is no statistically significant difference between patients with peripheral neuropathy and patients without neuropathy. Therefore no significant relation between vitamin B12 level and neuropathy affecting patients with HCV related chronic liver disease occurred. As far as we are aware, the role of vitamin B12 level in the neuropathy of patients with HCV related chronic liver disease has not been studied.

CONCLUSION

It is concluded that liver disease causes multi-system manifestation and it is important to recognize its effect on other systems which may influence the outcome of liver disease. Peripheral and autonomic neuropathy has high prevalence in patients with HCV-related chronic liver disease. Serum vitamin B12 level is high in patients with HCV related chronic liver disease due to liver cell damage and improper uptake of vitamin B12 by diseased liver cells. There is no role of vitamin B12 in liver cirrhosis related neuropathy. This necessitates detecting neuropathy associated with chronic liver disease as it may affect the outcome, especially during post transplantation.

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