Study Of Peripheral Neuropathy In Chronic Hepatitis C Virus Infected Patients

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Abstract: Background:Hepatitis C is a serious worldwide problem, the WHO has estimated that, 170 million people worldwide are infected with hepatitis**,** while the prevelance in the general population ranges between 0.2 and 2%**. Aim of the work:** to study peripheral neuropathy in patients with chronic hepatitis C virus infection. **Patients and methods**: This study was conducted on forty patients selected from patients Of Tropical Medicine Department in Minoufiya University Hospital suffering from chronic hepatitis C virus infection. They were 23males and 17 females and their ages were ranging from 28 to 62 years, plus twenty healthy persons of matched age and sex. These patients will be classified into 3 groups:Group (1): Chronic HCV patients without liver cirrhosis, group (2): Chronic HCV patients with liver cirrhosis and group(3):Persons matching for age and sex as a control group. All Patients and control group will be subjected to Thorough history taking, Full clinical examination, Neurological examination, Laboratory investigations: Complete blood count, liver function tests, kidney function tests, random blood glucose level, Viral markers by ELISA, estimation of serum level of vitamin B12, estimation of serum level of cryoglobulins (immunoglobulin (Ig M)) and complement (C3), abdominal ultrasonography and nerve conduction studies. **Results:** peripheral neuropathy was diagnosed by electrophysiological examination in 14 patients (35%) of HCV positive cases and clinical peripheral neuropathy presented in 10 patients (25%). There is significant decrease of the amplitude of the median, ulnar and peroneal nerves in the group of HCV patients with cirrhosis than the control group but not between patients without cirrhosis and the cirrhotic or the control group. Also there was no statistically significant difference between the three studied groups as regard to the conduction velocity and distal latency of median, ulnar and peroneal nerves. Significant increase in serum cryoglobulin in peripheral neuropathy patients as 10 (71.43%) patients having peripheral neuropathy are positive CG. **Conclusion:** PN is present in HCV patients without cirrhosis and become progressively increased in HCV patients with cirrhosis, PN in HCV patients is polyneuropathy and axonal. PN may be clinically diagnosed or diagnosed by electrophysiological examination, Cryoglobulins significantly increased in HCV patients with peripheral neuropathy.

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Introduction:

Hepatitis C virus (HCV) is a parenterally transmitted, hepatotropic and lymphotropicRNA virus, it is a common cause of liver disease and a major health problem worldwide**.**[1]

Numerous extrahepatic manifestations have been reported in association with hepatitis C virus (HCV) infection including renal disease, lymphoma, sjogren syndrome, mixed cryoglobulinaemia, Porphyria cutanea tarda and peripheral neuropathy.[2] Most extrahepatic manifestations of chronic HCV infection are immunological and the chronic infection seems to be necessary for their development.[3]

It was generally believed that, hepatitis C virus can damage only liver and blood, however, other studies revealed that, hepatitis C virus also infects neurons and destroy the central nervous system**.** [4]

It has become clear that, most cases of so-called essential cryoglobulinaemia are in fact associated with HCV infection[5]**.** *Hepatitis C virus infection causes* peripheral neuropathy by performing an immune state which can elaborate three types of neuropathies, the first is cryoglobulinaemic neuropathy, the second is Guillian-Barre syndrome and the third is peripheral neuropathy without detectable cryoglobulins. In addition to these; HCV can cause neuropathy indirectly through induction of type 2 diabetes mellitus.[6] Aim of the work: This work aimed to study peripheral neuropathy in patients with chronic hepatitis C virus infection.

Patients and Methods

This study was conducted on forty patients selected from patients Of Tropical Medicine Department in Minoufiya University Hospital suffering from chronic hepatitis C virus infection in the period from Jan 2007 to March 2008. They were 23(57.5%) males and 17(42.5%) females and twenty healthy persons of matched age and

sex.These patients will be classified into 3 groups:
Group (1) comprised (20) chronic HCV patients without liver cirrhosis, **group (2)** comprised (20) chronic HCV patients with liver cirrhosis and **group (3):** comprised (20) healthy persons as a control group.

Exclusion criteria :(1) Patients with diabetes mellitus, renal failure, vitamin B12 deficiency (2) the presence of other associated conditions that can cause neuropathy e.g. diseases such as, lymphoma and leprosy or medications such as, amiodarone, dapsone and isoniazide. (3) patients infected with hepatitis B virus or positive HIV, (4) patients with intravenous drug abuse and alcoholics, (5) patients already with hepatic coma or precoma and patients with extensive lower limb edema. (6) patients taking interferon therapy. (7) patients refusing to give a written consent,
All patients and control group were subjected to; (1) thorough medical history taking with stress on symptoms of chronic hepatic illness such as, fatigue, anorexia, nausea, pururitis, haematemsis, melena and jaundice. (2) general examination with stress on jaundice, ascitis, splenomegally and hepatomeglly. (3) Thorough neurological history and examination using standard neurological sheet.(4) laboratory investigations**; (a)** HCVinfection was assessed by ELISA and polymerase chain reaction(PCR), (b) complete blood count; (c) liver function tests(serum bilirubin;ALT, AST, albumin, prothrombin time and concentration), (d) kidney function tests**(**serum urea and creatinine**), (e)** random blood glucose level,(f) estimation of serum level of vitamin B12, (g) estimation of serum level of Cryoglobulins IgM and Complement 3 (5)abdominal ultrasound : for diagnosing liver cirrhosis, presence of portal hypertension and presence or absence of ascites(6)nerve conduction study of median, ulnar and peroneal nerves by using NIHON KODEN EMG machine**.**
Statistical analysis: Data was collected and analysed by SPSS version 11.quantitative data were expressed as arithmetic mean, standard deviation, paired t test and kruskal wallis test. qualitative data expressed as frequency and percentage and analysed by chi-square test. Level of significance was set as p-value<0.05.

Results:

Forty patients of HCV infection studied, they were 23males and17females and their ages were ranging from 28to62years.The mean age was47.45±8.47years in group(1)eleven of them were males and47.45±6.19 years in group (2) twelve were males. the mean age in control group was 48.5±8.26 years and there were no statistically significant difference between the three groups regarding demographic findings. Clinical manifestations of hepatic illness in patients groups include:fatigue, anorexia, dyspepsia, haematemsis, melena and jaundice. There was highly statistically significant difference between cirrhotic and non cirrhotic patients as regards to these symptoms. table(1)shows clinical, general and abdominal examination in patients groups and shows highly statistically significant difference between both groups regarding manifestations of liver decompensation. As regards ultrasonographic findings, there was statistically significant difference between both groups in splenomegally: liver size and ascites.Regarding peripheral neuropathy symptoms and signs, there was statistically significant difference between both groups as regards pain, numbness, weakness and superficial sensory loss but no statistically significant difference regarding deep sensory loss and absent tendon reflex. (table 2). laboratory measurements among the studied groups are summarized in table(3).There was statistically significant increase in the serum level of cryoglobulin in group (2) than group (1) and group (3) as positive cryoglobulin (IgM) found in seven patients (35%) of group (2) versus three patients (15%) of group (1) while negative in gropup (3).Serum level of complementC3 among the studied groups was1.39±0.46, 1.17±0.64 and1.72±0.46 in the three groups, respectively and there was statistically significant decrease in serum level of complement C3 in group (2) than group(1) and group (3). Tables (4, 5, 6) show median nerve, ulnar nerve and peroneal nerve conduction studies among studied groups, there was statistically significant decrease in the amplitude (motor and sensory) between group2 and3 and no statistically significant difference between the studied groups as regards the velocity and latency of the nerves.. peripheral neuropathy was diagnosed in 10 patients(50%) in group (2) of them in 8patients (40%) were symptomatic and 4 patients(20%) in group (1) of them 2 (10%) were symptomatic and this was of highly statistically significant difference. Among all patients of peripheral neuropathy(14patients in both groups), there was highly statistically significant increase in serum cryoglobulin in peripheral neuropathy patients as10 (71.43%) patients have positive cryoglobulin and the remaining 4(28.76%)patients have negative cryoglobulin. Peripheral neuropathy increased significantly with age, the mean age was 52.21±7.0yearsin peripheral neuropathy patients and 44.88±6.2 years in patients

without peripheral neuropathy and this was of highly statistically significant difference but not with sex, Also the serum level of Cryoglobulin increased significantly with age, of 10 patients with positive cryoglobulinaemia the mean age was 53.1±6.44 years while the mean age of 30 patients without cryoglobulinaemia was 45.57±6.67 years but not with sex.

Table (1) Clinical, general and abdominal examination in G1 and G2 :

	G1 (n=20)		G2 (n=20)		X2	P.value
	No	%	No	%		
Fatigue	4	20	10	50	14.16	< 0.001 **
A norexia	0	0	6	30	13.33	< 0.001 **
Dyspepsia	0	0	10	50	14.16	< 0.001 **
Haematemsis	0	0	6	30	13.33	< 0.001 **
Melena	0	0	6	30	13.33	< 0.001 **
jaundice	0	0	11	55	26.94	< 0.001 **
encephalopathy	0	0	0	0	----	----
Spider naevi	0	0	3	15	6.32	< 0.05 *
Palmer erythema	0	0	6	30	13.33	< 0.001 **
LL oedema	0	0	11	65	33.91	< 0.001 **
Flapping tremors	0	0	0	0	----	----
Peticheal Haemorrhage	1	5	9	45	17.52	< 0.001 **
Splenomegally	3	15	7	35	8.13	< 0.05 *
Shrunken liver	0	0	15	75	24	< 0.001 **
Hepatomegaly	7	35	5	25	0.48	> 0.05
Ascites : No	20	0	2	10	33.19	< 0.001 **
Mild	0	0	10	50		
Moderate	0	0	6	30		
Tense	0	0	2	10		

< 0.001 ** highly statistically significant < 0.05 * statistically significant.

Table (2): peripheral neuropathy symptoms and signs between G1 and G2.

	G1(n=20)		G2(n=20)		X^2	p. value
	No	%	No	%		
Pain	2	10	8	40	12.48	< 0.05*
Numbness	2	10	8	40	12.48	< 0.05*
weakness	1	5	3	15	3.75	< 0.05*
Superficial sensory loss	2	10	8	40	6.0	<0.001**
Deep sensory loss	1	5	2	10	1.58	> 0.05
Absent ten. Reflex of LL	2	10	4	20	2.72	> 0.05

< 0.001 ** highly statistically significant < 0.05 * statistically significant.

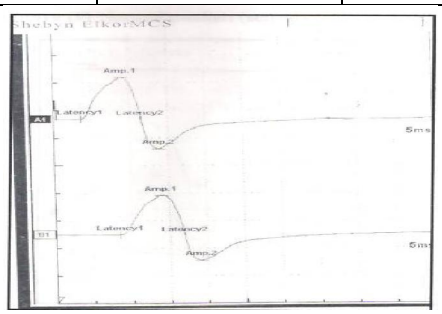
Table (3): laboratory measurements among the studied groups:

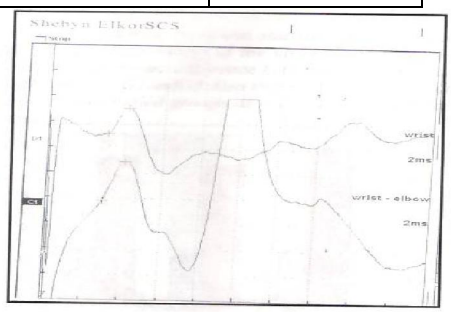
	G1(n=20) $\bar{x} \pm SD$	G2(n=20) $\bar{x} \pm SD$	G3(n=20) $\bar{x} \pm SD$	P. value of f-test
SGOT	39.3± 32.58	48.1 ± 32.36	17.1± 5.00	*Sig1, 3/2, 3
SGPT	40.9± 30.74	50.9 ± 31.60	17.6 ± 6.34	*Sig1, 3/2, 3
Albumin g/dl	4.05± 0.50	2.58 ± 0.45	3.91± 0.52	Sig1, 2/1, 3
Bilirubin	0.95 ± 0.07	2.01 ± 0.096	0.97± 0.08	Sig1, 2/1, 3
PT activity	89.15 ± 3.85	72.1 ± 11.12	93.65± 4.19	Sig1, 2/1, 3
Blood Urea	25.35 ± 4.16	28.45 ± 6.39	24.25± 3.08	Sig1, 2/1, 3
Serum creatinine	0.71± 0.22	1.12 ± 0.35	0.76± 0.29	*Sig1, 2/1, 3
RBCs /mm^3	3.78±0.47	3.62±0.49	4.30± 0.84	Sig1, 3/2, 3
WBCs/mm^3	6500±1572.80	6150±1598.52	6650± 1954.08	NS
Platelet/mm^3	250100±89103.66	133950±48407.78	257250± 76459.05	*Sig1, 2/2, 3
RBS g/dl	118.7±18.81	110.85±13.20	105.35± 9.02	Sig1, 3

Vit B12 Pg/ml	539.05 ± 138.87	574.95 ± 149.46	533.95± 58.05	NS
Complement (C3)	1.39 ± 0.46	1.17 ± 0.64	1.72 ± 0.46	*Sig1,2/2,3

Table(4): Median nerve conduction study among the studied groups.

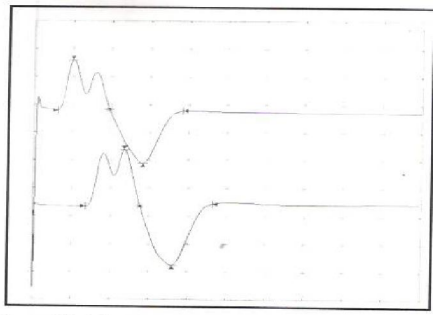
	G1**(n=20)** $\bar{x} \pm SD$	G2**(n=20)** $\bar{x} \pm SD$	G3**(n=20)** $\bar{x} \pm SD$	P.value of f- test
-motor				
Amp	4.85± 1.15	4.21± 1.58	5.61± 1.03	Sig 2, 3
velocity	52.5± 16.56	53.90± 3.29	55.60± 3.07	NS
Latency	3.55± 0.69	3.45± 0.78	3.39± 0.88	NS
-Sensory				
Amp	25.55± 8.31	20.85± 9.23	27.9± 8.01	Sig 2, 3
Velocity	55± 2.63	54.9± 2.75	57.8± 8.56	NS
Latency	2.91± 0.26	2.64± 0.38	2.70± 0.68	NS

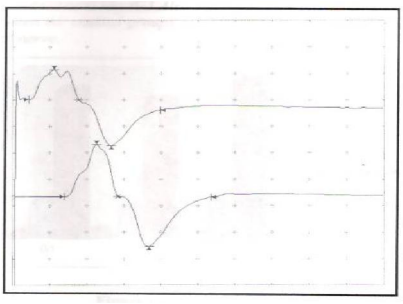




Table(5): Ulnar nerve conduction study among the studied groups

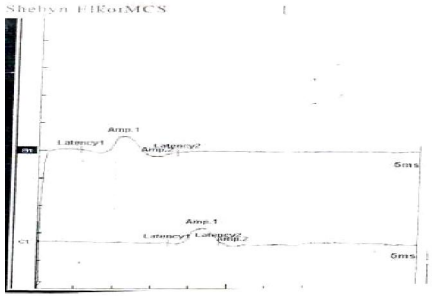
	G1**(n=20)** $\bar{x} \pm SD$	G2**(n=20)** $\bar{x} \pm SD$	G3**(n=20)** $\bar{x} \pm SD$	P.value of f- test
-motor				
Amp	6.48 ± 0.77	5.97 ± 1.26	6.82 ± 0.32	Sig 2, 3
velocity	55.19 ± 3.79	54.52 ± 2.56	55.75 ± 3.26	NS
Latency	3.08 ± 0.21	3.09 ± 0.32	3.01 ± 0.17	NS
-Sensory				
Amp	17.69 ± 3.24	16.76 ± 1.83	18.95 ± 0.89	Sig 2, 3
Velocity	56.71 ± 3.48	58.25 ± 5.16	56.25 ± 2.40	NS
Latency	2.63 ± 0.35	2.59 ± 0.38	2.54 ± 0.20	NS

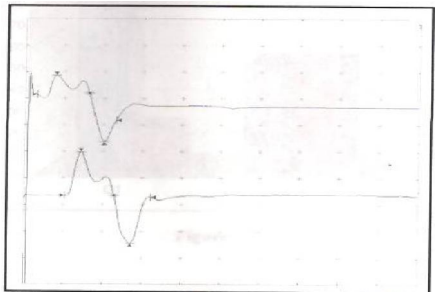




Table(6): Peroneal nerve conduction study among the studied groups

	G1**(n=20)** $\bar{x} \pm SD$	G2**(n=20)** $\bar{x} \pm SD$	G3**(n=20)** $\bar{x} \pm SD$	P.value of f- test
-motor				
Amp	4.8 ± 1.11	4.38 ± 1.16	5.36 ± 0.86	Sig 2, 3
velocity	48.42 ± 5.11	50.89 ± 5.87	49.9 ± 5.79	NS
Latency	3.77 ± 0.65	4.11 ± 0.38	3.9 ± 0.59	NS
-Sensory				
Amp	22.63 ± 4.18	21.08 ± 4.76	24.54 ± 4.88	Sig 2, 3
Velocity	57.31 ± 3.86	56.21 ± 3.49	57.71 ± 4.23	NS
Latency	3.68 ± 0.55	3.66 ± 0.30	3.87 ± 0.60	NS





Discussion:

Peripheral neuropathy has been reported in association with chronic liver disease, including liver cirrhosis and chronic hepatitisC.however, the reports have varied regarding the incidence and characteristics of this neuropathy and multiple studies were performed to study the peripheral neuropathy in hepatitis c virus and its relation to cryoglobulinaemia.[7]

In the present study peripheral neuropathy was diagnosed by electrophysiological examination in 14 patients (35%) of HCV positive cases and cryoglobulins found in 10 patients (25%), clinical peripheral neuropathy presented in 10 patients (25%).

These findings disagree with reports done by ***Cacoub et al., 2001*** [8] who diagnosed PN in (9%) of 321 HCV patients on the basis of clinical symptoms only and ***(Lucio et al., 2006)***[9] who diagnosed PN by electophy- siological examination detecting (15.3%) and clinical PN (10.6%), so, there are two points, **first**, there was a difference between the percentage of clinically diagnosed PN and the electrophysiologically diagnosed.This explained as that, polyneuropathy diagnosed by combination of multiple items, the symptoms, signs and abnormal electrophysiological studies, whereas, the symptoms alone have poor diagnostic accuracy in predicting the presence of polyneuropathy. **The second** is the percentage of neuropathy in HCV patients may vary significantly in different studies even if the same diagnostic tools are used (clinical, electrophysiological). This may be due to the fact that, HCV-associated neuropathy is a multifactor disease process, so that, for a given population of HCV patients, there will be mass of details that all can affect significantly the percentage of neuropathy in such patients [10]. the most important is the viral factors such as, viral genotypes as there is wide difference between the viral genotypes in Egypt and western countries [11].

Origgi et al., 2003 [12] found that, there was a significant difference in the frequency of peripheral nervous system involvement in cryoglobulinaemic HCV patients with different viral genotypes. Other environmental factors that may play a role in the pathogenesis may include the climate, since cryoglobulinaemic manifestations including neuropathy are more aggressive in cold weather. [12] The percentage of cryoglobulin in the present study(25%)agrees with the results of ***(Lucio et al., 2006)*** [9] who found the percentage of CG was (29.3%) close to the present study but disagrees with ***(Cacoub et al., 2001)*** [8] who reported a percentage of (56%). The explanation of this difference is not present except that, a wide variability of CG prevalence in HCV patients has been well documented.

In the present study, statistical analysis of peripheral neuropathy symptoms, neurological examination results and the results of nerve conduction study of the HCV patients shows that, PN appears in some HCV patients who do not have cirrhosis and become progressively increased in

patients with cirrhosis denoting that, cirrhosis has a role in the pathogensis of PN. This agrees with the report of ***(Parampreet et al., 2003)*** [7] who reported PN in patients with liver cirrhosis.

The explanation of the role of cirrhosis in PN is porto systemic shunting [13]. ***(Hindfelt and Holmin, 2006)***[14] proposed hepatocellular failture as the main pathophysiological mechanism for neuropathy and the various mechanisms postulated for this hepatic neuropathy are metabolic inhibition of the axonal membrane function, metabolic damage to schwann cell and even a possible disordered insulin metabolism, something similar to diabetic neuropathy.

The present study shows significant decrease of the amplitude of the median, ulnar and peroneal nerves (sensory and motor) in the group of HCV patients, also there was no statistically significant difference between the studied groups as regard to the conduction velocity and distal latency of median, ulnar and peroneal nerves.

This denoting axonal type of PN and no evidence of demylinating PN in this study.

These findings agree with ***(Lucio et al., 2006)***[9] who reported axonal polyneuropathy affecting both motor and sensory parts of the nerves in HCV+ve cases and ***(Parampreet et al., 2003)***[7] who reported axonal polyneuropathy also, sensory and motor in cirrhotic patients.

Significant increase in serum cryoglobulin in peripheral neuropathy patients as 10 (71.43%) patients having peripheral neuropathy are positive CG and the remaining peripheral neuropathy 4 (28.76%) patients are negative CG.

This finding agrees with ***(Lucio et al., 2006)***[9] who reported an association between CG and PN but CG is not the only cause of PN.

But this findings disagree with ***(Cacoub et al., 2001)***[8] who found no significant association between PN and CG and ***(Lidove et al., 2001)***[15] who reported 4 cases with PN in HCV +ve cases without cryoglobulinaemia.

The explanation of PN in HCV patients is by different mechanisms, cryoglobulinaemic neuropathy which is (immune mediated, deposition of cryoglobulins causing ischaemic nerve injury and vasculitis- induced nerve damage)[16], HCV-associated guillian- barrie syndrome [17,] and the non cryoglobulinaemic neuropathy which can be explained by occurance of serum sickness- like state that leads to vasculitis in the vasa nervosum. [18]

The present study showed that, significant decrease of the amplitude of median, ulnar and peroneal nerves (motor and sensory) in cryoglobulinaemic patients denoting increase the incidence of axonal sensory motor polyneuropathy with cryoglobulin +ve patients.

These findings agree with ***(Lucio et al., 2006)***[9] who reported axonal sensory motor polyneuropathy in patients with cryoglobulinaemia

The explanation may be vasculitis induced nerve damage as there is vascular infiltrates in nerve tissue in vasculitis which are composed of T cells and macrophages and such cells are thought to play a role in vasculitic lesions, where these cells express certain molecules which may lead to neural vessel injury [19]. But **Kardel and Nielsen** [20] postulated the axonal neuropathy which is not related to the CG, to serum sickness like or direct effect of the virus.

Cryoglobulin was +ve in 3 patients of the first group versus 7 patients of the second group and significant lower level of C3 in patients of the second group than the first group.

These findings disagree with the reports done by ***(Parampreet et al., 2003)***[7] who reported that, there is no relation between CG and cirrhosis.

The explanation of the high percentage of CG in HCV with cirrhosis than HCV patients without cirrhosis may be the small number of patients taken and the CG present in the cirrhotic may be one of the extrahepatic manifestations of HCV which is the original cause of cirrhosis.

In the present study, statistical analysis showed that, significant increase in PN and cryoglobulins with the age of the patients while no significant relation between PN and CG to the sex of the patients.

This agrees with ***(Lucio et al., 2006)***[9] who reported a strong correlation between old age and peripheral neuropathy.

Some authors have already noted that, older age is a major risk factor for the clinical and biological extrahepatic manifestations of HCV patients [21].

Conclusion: This study concluded that, PN is present in HCV patients without cirrhosis and become progressively increased in HCV patients with cirrhosis, PN in HCV patients is polyneuropathy and axonal, both sensory and motor, PN may be clinically diagnosed or sub clinically diagnosed by electrophysiological examination in HCV patients, Cryoglobulins significantly increased in HCV patients with peripheral neuropathy, Peripheral neuropathy significantly increased in HCV patients with CG than in HCV patients without CG, PN and CG increased significantly with age .

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