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Is Peripheral Neuropathy a Part and Parcel of Chronic Hepatitis-C in South Asian Population?

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ABSTRACT

Introduction: Management of chronic Hepatitis C and its complications is a major concern for physicians. Peripheral neuropathy is a disease affecting the nerves, and is one of the complications of Hepatitis C. **Objective:** The aim of this study is to determine the prevalence of peripheral neuropathy in chronic hepatitis-C patients. **Study design and duration:** The type of study is a cross-sectional study, which was conducted over a period of one month from 01-11-2015 to 30-11-2015. **Setting:** The study was conducted at a tertiary care hospital in Karachi, Pakistan. **Sample size and procedure:** The study population consisted of a random sample group of 139 Hepatitis C positive patients who presented to the Internal Medicine Department either via out-patient clinic or via emergency. After due informed consent, variable such as demographic data and type and degree of neuropathy were recorded. All the Hepatitis-C patients who presented to us during that time were evaluated clinically, serologically and electrophysiologically. **Data Analysis:** Data was analyzed using SPSS version 20. **Results:** Out of the total study population of n= 139 patients peripheral neuropathy was present in n= 77 (55.39%) of the patient population; n= 3 (2.15%) had sensory type of neuropathy, n=13 (9.35%) had motor neuropathy and n= 61 (43.88%) had mixed type of neuropathy. **Conclusion:** According to the results of our study there is a significant association of peripheral neuropathy with hepatitis C in patients in South Asian population as more than hald of the participants had some form of peripheral neuropathy.

Keywords: Chronic liver disease; Hepatitis C; mixed type neuropathy; neurological disorders; peripheral neuropathy.

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INTRODUCTION

Hepatitis C is a RNA (Ribonucleic Acid) virus which is mainly transmitted through blood transfusions, tattooing, surgical procedures, intravenous drug abuse and sexual contact. It affects more than 170 million people worldwide and is one of the major causes for fatal diseases such as cirrhosis, chronic hepatitis and hepatocellular carcinoma.[1] The prevalence of hepatitis C virus among people of South Asian origin in Glasgow is 3.1%.[2] In Pakistan 5% of population is infected with hepatitis C out of which 80 % are infected with genotype 3a.[1] In Punjab 4.9 % patients have active hepatitis C.[3] Prevalence of hepatitis is high in intravenous drug abusers and is as high as 49%[4,5] Patient with hepatitis C infection are prone to develop both hepatic and extra hepatic complications. Hepatic complications mainly include cirrhosis, ascites and hepatocellular carcinoma. These complications are thought to be due to damage to the liver by inflammatory cytokines mainly tumor necrosis factor alpha released in response to the viral stimuli.[6] Extra hepatic associations include cryoglobulinemia, polyarteritis nodosa, sicca syndrome, membranoproliferative glomerulonephritis, lichen planus, thyroiditis, and peripheral neuropathy.

Neuropathy is a medical term for any disease of the nerves. There are four major forms of neuropathy – polyneuropathy, autonomic neuropathy, mononeuropathy and the most common form, peripheral neuropathy (PN). Peripheral neuropathy damages the nerves in the legs and arms. Usually the first area that PN affects is the feet and legs before the hands and arms.[7] Peripheral neuropathy in HCV (Hepatitis C virus) is mainly due to direct viral infection, inflammation of nerves mainly due to immune mediated response and deposition of cryoglobulins associated with HCV RNA.[8] It may present without cryoglobulinemia as well.[9] Sometimes peripheral neuropathy is associated with eosinophilic infiltration and granuloma formation which is evident by nerve biopsy.[10] According to some studies there have been incidences of finding HCV RNA in the nerve biopsy specimens, which suggest that there might be a direct role of HCV in the pathogenesis of polyneuropathy.[11,12] The nerve damage is either due to a direct cytopathic effect or due to immune mediated mechanisms such as immune complex mediated damage to the nerves and epineural vessels, which is also supported by finding HCV RNA in nerve biopsy specimens.[13] Studies reported different types of neuropathy in different part of world in hepatitis C population.[9,10] The aim of our study is to find out the prevalence of peripheral neuropathy and its different types in patients who are infected with hepatitis C at a tertiary care hospital in Karachi, Pakistan.

METHODOLOGY

Study design and duration: The type of study is a cross sectional study, conducted over a period of one month duration from 01-11-2015 to 30-11-2015.

Setting: The study was conducted at a tertiary care centre in Karachi Pakistan.

Ethical approval: Ethical approval covering all sites was obtained from the local research ethics committee.

Sample size: The study population consisted of a group of 139 HCV positive patients who presented to the Internal Medicine Department either via out-patient clinic or via emergency,

Sampling technique: The method of sampling that is utilized is cluster sampling. The sample size was calculated using OpenEPI sample size calculator using hypothesized frequency of 10%[2] and confidence interval of 95%.

Inclusion criteria: The following points were kept in mind when including the patients in the study group: HCV-RNA positive patients by polymerase chain reaction or ELISA (enzyme-linked immunosorbent assay); the patients who did not receive any prior treatment for HCV infection (as large percentage of these patients came in from rural Sindh and Balochistan areas, and majority of them did not get treatment until very late because of inaccessibility to care centers and lack of finances). All the participants had to be above 18 years of age to be included in the study.

Exclusion criteria: The following points were kept in mind when excluding the patients from the study group: Patients with viral hepatitis other than hepatitis C; other diseases associated with neuropathy such as diabetes mellitus (abnormal HbA1c and fasting blood glucose test prior to enrollment), autoimmune disorder (Anti nuclear antibodies, Rheumatoid factor), renal failure, vitamin B deficiencies, thyroid disorders, malignant hematological disorders, alcohol consumption (drinking low percentage alcohol beverages more frequently than once per week), HIV infection or drug addiction, toxic agents, medications; impairment of the PNS (peripheral nervous system) other than neuropathy (example tunnelopathies, radiculopathies, and nerve trauma); impairment of central sensory pathways (e.g. multiple sclerosis); patients less than 12 years of age or those with any other risk factors to PN (peripheral nerves) or who refused to participate in the study were excluded; Patients receiving treatment for HCV.

Data collection and procedure: Various demographic variables were noted for all the patients including the patient's age, gender, the type of neuropathy in a specially designed proforma and all patients gave a written informed consent. Patients were evaluated clinically, serologically and electro physiologically. A complete neurological evaluation was done and symptoms (weakness, sensory disturbances) and signs (weakness, atrophy, sensation abnormalities, and diminished or absent tendon reflexes) of peripheral neuropathy were recorded. Clinical characteristics (motor or sensory or mixed type of neuropathy) were also noted. The presence of HCV infection was assessed by the presence of anti-HCV antibodies by ELISA and quantitative assay of HCV level by Polymerase Chain Reaction using PCR (polymerase chain reaction). All the patients underwent electrophysiological examination, nerve conduction studies were performed on the median, ulnar, posterior tibial and peroneal nerves. The temperature was maintained at 31 to 33 degree Celsius and amplifier setting was set at 10Hz to 2000Hz. Motor conduction study was performed for all the afore mentioned nerves, minimal F wave latencies were performed for the median, ulnar and posterior tibial nerves, Soleus H reflex study and sensory conduction study was done using an antidormic stimulation of the median, ulnar, radial, and sural nerves by applying the electrode on the second digit, fifth digit, tendon of the extensor policis longus muscle, lateral malloelus to 12 cm lateral from the midline of the calf muscle respectively. Patients were considered to have clinical neuropathy when they had one or more electrophysiological abnormalities in at least two nerves examined and subclinical neuropathy was considered when they had electro physiologic abnormalities without any clinical signs and symptoms of peripheral nerve involvement.

Data analysis: Data was analyzed using SPSS version 20 and rechecked by co-authors. Frequencies and percentages were used for quantitative data such as presence of peripheral neuropathy in HCV positive patients (chronic hepatitis, compensated and decompensated chronic liver disease) as well as for gender distribution. Chi square test was used for categorical variables and mean and standard deviations were used for continuous variables. P- Value of less than 0.05 was considered to be statistically significant.

RESULTS

In our study of n= 139 patients the number of males in the study are n= 78 (56.11%) with a mean age of 53.60 +/- 10.533 years, and the number of females in the study are n=61 (43.88%) with a mean age of 49.61 +/- 10.060 years.

Table 1: Characteristics of patients with Hepatitis C and its association with neuropathy and chronic liver disease

Characteristics	Patients	Compensated CLD	Decompensated CLD	p-value
GENDER				0.112
Male	78 (56.11%)	31	47	
Female	61 (43.88%)	34	27	
Type of Neuropathy				<0.001
Sensory	3 (2.15%)	3	0	
Motor	13 (9.35%)	13	0	
Mixed	61 (43.88%)	20	41	
No Neuropathy	62 (44.60%)	29	33	
AGE in years				0.131
15-35	13(9.25%)	5	9	
36-50	46 (33.09%)	28	18	
>50	80 (57.55%)	33	47	

Peripheral neuropathy was present in n= 77 (55.39%) of the patient population while no peripheral neuropathy was found in n= 62 (44.60%) of the patients. Out of the patients who showed signs of peripheral neuropathy n= 3 (2.15%) had sensory type

of neuropathy, n=13 (9.35%) had motor neuropathy and n= 61 (43.88%) had mixed type of neuropathy having features of both sensory and motor neuropathy. All the patients in the study population had been diagnosed with chronic liver disease, and out of those n= 65 (46.76%) had compensated cirrhosis and n= 74 (53.23%) had decompensated cirrhosis. When it comes to age group and peripheral neuropathy associated with CLD (chronic liver disease), there is no statistically significant difference p= 0.131. Further, presence of peripheral neuropathy and presence of CLD are related but there is no statistically significant difference p= 0.936. When it comes to type of peripheral neuropathy and type of CLD there is statistically significant difference p= <0.001.

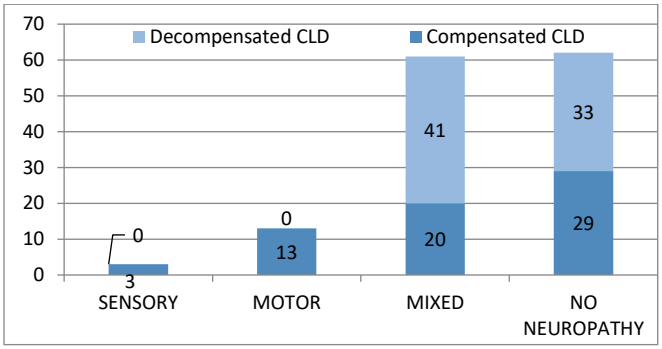

Figure 1: Types of neuropathy and their association with chronic Liver Disease

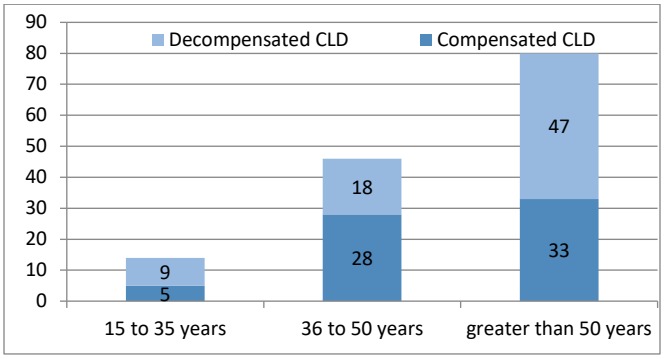

Figure 2: Association of age with chronic liver disease

DISCUSSION

Neurological involvement in chronic hepatitis C patients is a well known phenomenon. Though association of central nervous system symptoms with CLD is well established, association of peripheral nervous system with CLD is discussed with caution. Once considered rare, peripheral neuropathy in hepatitis C patients is now investigated routinely. According to the results of our study peripheral neuropathy was present in n= 77 (55.39%) of the patient population while it was not found in n= 62 (44.60%) patients, according to Santoro et al, they found the prevalence of peripheral neuropathy to be 15.3% by electrophysiological analysis, and 10.6% on clinical evaluation from a total patient population of 234, while Cacoub et al found the prevalence of peripheral neuropathy to be 9% of the 321 patients by clinical assessment.[14,15] In our study sensory neuropathy was found in n= 3 (2.15%) of patients while according to a study by Cacoub P et al, in their study they found the prevalence of sensory neuropathy to be 9% in patients with HCV infection.[15] Association of the type of neuropathy with hepatitis C could be an important factor in deciding the plan of treatment as the treatment of HCV-related neuropathy may differ depending upon how the nerve damage occurred.[16] Presence of CLD is not always associated with concomitant peripheral neuropathy. 44.60% of the CLD patients included in our research did not have any type of peripheral neuropathy. It is a possibility that these patients might eventually develop peripheral neuropathy over the course of the disease. However, the incidence of peripheral neuropathy in Hepatitis C patients increases with age. Peripheral neuropathy results from ischemic nerve changes secondary to vasculitis.[17] In our study mixed type peripheral neuropathy (that is both sensory and motor nerves involvement) was found to be the most common type of peripheral neuropathy found in chronic hepatitis patients with CLD. When present, peripheral neuropathy in decompensated CLD is more likely to be mixed type; however, peripheral neuropathy in compensated CLD can also present as isolated cases of sensory neuropathy or motor neuropathy. In the study by Koskderelioglu et al they also found optic nerve involvement (asymptomatic axonal type infection) which was independent of the interferon treatment in their patients of Hepatitis C.[18,19] This finding indicates that in a low resource health care system like that of Pakistan it is imperative that physicians utilize fundoscopy to screen patients for optic neuropathy. There were some limitations to our study such as old data of prevalence of peripheral neuropathy is used for comparison which might not reflect the current trends. The research is done in a setting where the patient population is typically of low socioeconomic class and are more prone to present to the hospital when the disease has progressed, which might not be the case for other hospitals and clinics.

CONCLUSION

According to our study there is a high prevalence of peripheral neuropathy among patients with chronic hepatitis C patients and Chronic Liver Disease. Accordingly, patients with hepatitis C should be worked up for the presence of peripheral neuropathy to ensure adequate treatment. However, because of the limitations of the study described above, the results should be interpreted with caution; moreover, a case control study with larger sample size over a longer period is recommended to confirm the findings of this study.

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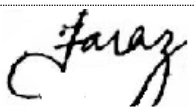
Dr. Muhammad Faraz Anwaar House Officer Civil Hospital Karachi	Design of study, preparation of synopsis, revision of final article	
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