

Prevalence of Peripheral Neuropathy in Chronic Hepatitis C Patients

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Author's Contribution

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ABSTRACT

Objective: To determine the prevalence of peripheral neuropathy in chronic hepatitis C patients presenting at Tertiary Care Hospital, Karachi.

Methodology: This descriptive cross sectional study was conducted at Department of Medicine, Abbasi Shaheed Hospital, Karachi, from January 2021 to June 2021. Patients with chronic hepatitis C presenting with symmetric proximal and distal weakness (MRC scale ≤ 4) developing and reduced tendon reflexes in all extremities of either gender or aged 20 to 70 years were included. Medical history and clinical examination were performed, with motor strength graded using the Medical Research Council (MRC) scale, where a score of ≤ 4 in any muscle group was taken to indicate motor weakness suggestive of peripheral neuropathy. Relevant data was entered and analyzed using SPSS version 20.

Results: A total of 151 patients were studied; their mean age, duration of chronic hepatitis C, and BMI, were 57.14 ± 6.49 years, 8.72 ± 4.24 months, and 27.41 ± 2.56 kg/m² respectively. Overall peripheral neuropathy was found in 73 patients (48.3%). Based on post stratification analysis, advanced age of the patients, female gender, obesity and prolonged duration of disease were significantly associated with peripheral neuropathy ($p < 0.05$).

Conclusion: The prevalence of peripheral neuropathy was observed highly frequent among the patients with CLD, indicating an electrophysiological examination should always be done to avoid underestimating peripheral neuropathy, specifically among females, obese and older HCV patients.

Keywords: CLD, Hepatitis C, Peripheral neuropathy

Introduction

Hepatitis C virus (HCV) infection, with approximately 50 million infected individuals, and more than 240,000 annual deaths, remains a global public health concern.¹ Although, spontaneous clearance rate of virus is around 20 to 30% after acute infection, others will progress to chronic infection. Around 10 to 20% of these chronic cases will eventually progress to liver inflammation, cirrhosis, fibrosis, and hepatocellular carcinoma.^{1,2} Viral eradication rates now exceed 95% due to widespread availability of highly effective direct-acting antiviral (DAA) therapy.³ Yet, millions of individuals continue to live with chronic HCV infection and its hepatic and extrahepatic complications, with an annual burden of around 1 million fresh cases. The situation is even worse in low- and middle-income nations where diagnosis and treatment coverage remains suboptimal.^{3,4}

Extrahepatic manifestations occur in around 2/3rd of patients with chronic HCV infection. These manifestations involve multiple organ systems, including kidneys, skin,

endocrine glands, and peripheral nervous system, substantially contributing to reduced quality of life regardless of liver disease severity.⁵ Peripheral neuropathy is a frequently encountered extra hepatic manifestation in individuals infected with chronic HCV, with prevalence ranging between 26% and 86% in presence of cryoglobulinemia. However, peripheral neuropathy carries multiple pathogenic mechanisms and may occur with or without detectable cryoglobulins.⁶ Though exact cause of nerve injury in case of HCV infection remains to be explored, the multifactorial pathogenesis of HCV-associated peripheral neuropathy is considered to involve immune complex-mediated vasculitis secondary to mixed cryoglobulinemia, direct inflammatory injury, endothelial ischemia of the vasa nervorum, and chronic immune activation.⁶⁻⁸

The persistence of peripheral nerve abnormalities even when no mixed cryoglobulinemia is detected indicates

a direct association between subclinical nerve injury and chronic HCV infection. On the other hand, causal relationship between HCV infection and peripheral nerve dysfunction is supported by the improvement in nerve fiber density and electrophysiological parameters following successful direct-acting antiviral therapy.^{9,10} The prevalence of chronic HCV infection associated peripheral neuropathy considerably varies between studies from 15.3% to 90%. On the other hand, in patients without or with mixed cryoglobulinemia, the prevalence of peripheral neuropathy has been reported in the range of 43.5% to 86%, indicating a substantial burden of this subclinical disease.^{7,11,12}

Overall reported prevalence of peripheral neuropathy varies considerably across the studies among patients with chronic hepatitis C, depending on diagnostic method and the presence of cryoglobulinemia, as some studies identifying cryoglobulinemia and age as key factors, whereas others reported no significant role. According to this considerable inconsistency and very limited local evidence on this often under recognized complication, this study has been conducted to determine the frequency of peripheral neuropathy among chronic hepatitis C infection patients in our population.

Methodology

This descriptive cross sectional study was conducted at Department of Medicine, Abbasi Shaheed Hospital, Karachi. Study duration was six months after approval of synopsis, from 07-01-21 till 07-06-21. The required sample size came out to be 151 patients. By taking prevalence of peripheral neuropathy to be 50.4%, margin of error = 8% and confidence level 'C.I'=95%. This sample size was calculated using the WHO software. Non-probability consecutive sampling technique was used. All the chronic hepatitis C patients presenting with symmetric proximal and distal weakness (MRC scale ≤ 4) developing and diminished tendon reflexes in all extremities ($\geq$ one month) assessed on clinical examination of either gender and aged 20 to 70 years were included. On the other hand patients with history of hypo or hyperthyroidism, vitamin B 12 deficiency, history of alcohol use, diabetes mellitus type II, history of SLE, patients with history of asthma, stroke, renal impairment, congestive heart failure, myocardial infarction and chronic obstructive pulmonary disease were excluded. Informed consent was obtained from all the patients for assigning them to the study and using their data in research. BMI was calculated of the all the cases. Brief medical history, demographic data (age, gender and residence status) and duration of chronic hepatitis C were taken. All patients were assessed for peripheral neuropathy, which was diagnosed on the basis of electrophysiological testing, with the presence of at least two of the following abnormal parameters in two or more nerves:

prolongation of motor distal latency by more than 50% above the upper limit of normal (ULN); reduction of motor conduction velocity by more than 30% below the lower limit of normal (LLN); prolongation of F-wave latency by more than 30% above the ULN (or more than 50% if distal compound muscle action potential [CMAP] amplitude was less than 80% of LLN); or abnormal temporal dispersion, defined as a greater than 30% increase in duration between the proximal and distal negative peak CMAP. All of the data was entered and analyzed using SPSS version 20.

Results

There were majority of males (58.3%) and belonged to the older age group of 46–70 years (64.2%). Mostly patients resided in urban areas (81.5%) and had a chronic hepatitis C duration of more than 12 months (67.6%). According to metabolic and lifestyle factors, dyslipidemia was the most prevalent comorbidity (62.9%), following by obesity (41.7%) and hypertension (39.7%), while the smokers were (33.77%). Around half of the participants were unemployed (51.7%), and had attained higher education (49.0%), reflecting a predominantly urban and educated study population, as shown in table I.

Table I: Clinical and demographic analysis (n=115)

Variable	Category	(n)	(%)
Peripheral Neuropathy	Yes	73	48.34
	No	78	51.66
Gender	Male	88	58.28
	Female	63	41.72
Age	20–45 years	54	35.76
	46–70 years	97	64.24
Residence Status	Urban	123	81.46
	Rural	28	18.54
Duration of Chronic Hepatitis C	≤ 12 months	49	32.45
	> 12 months	102	67.55
Hypertension	Yes	60	39.74
	No	91	60.26
Dyslipidemia	Yes	95	62.91
	No	56	37.09
Smoking Status	Yes	51	33.77
	No	100	66.23
Obesity Status	Yes	63	41.72
	No	88	58.28
Occupational Status	Employed	73	48.34
	Unemployed	78	51.66

Out of all 151 patients with chronic hepatitis C, peripheral neuropathy was present in 73 patients (48.3%), while the remaining 78 patients (51.7%) showed no evidence of peripheral neuropathy. Figure 1.

According to post stratification analysis, advanced age of the patients, female gender, obesity and prolonged duration of disease were significantly associated with

peripheral neuropathy ($p = 0.001$), as presented in table II.

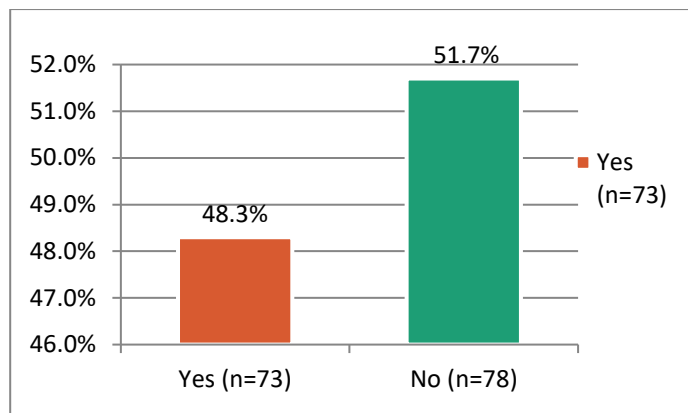


Figure 1. Peripheral Neuropathy Distribution among Study Participants. ($n = 151$)

(57.3%) like this study. The higher average age in this study compared to others may because differences in sample selection criteria across studies, along with variation in duration of disease.

In this cohort, peripheral neuropathy was detected in 48.3% of chronic hepatitis C patients. In line with our findings, in the study of Mapoure NY et al¹⁶ the prevalence of peripheral neuropathy was 49.6% of HCV infected individuals, which is slightly higher than our findings. Aligning with our findings, in the study carried out by Yoon MS et al¹⁴ prevalence of peripheral neuropathy in HCV infected patients without cryoglobulin was 43.5%, which is slightly lower than our findings. Consistently, in the study conducted by Seelro SH et al¹⁵ prevalence of peripheral neuropathy (59.8%) was higher than our findings. The wide variation in stated prevalence may reflect differences in diagnostic methods of the studies (clinical

Table II: Peripheral neuropathy according to age. ($n=151$)

Variables		PERIPHERAL NEUROPATHY		Total	p-value
		YES	NO		
AGE	20-45 years	17 (11.3%)	37 (24.5%)	54 (100%)	0.002
	46-70 years	56 (37.1%)	41 (27.2%)	97 (100%)	
Gender	MALE	31 (35.2%)	57 (64.8%)	88(100%)	0.001
	FEMALE	42 (66.7%)	21 (33.3%)	63(100%)	
Duration of disease	≤ 12 MONTHS	15 (9.9%)	34 (22.5%)	49(100%)	0.003
	> 12 MONTHS	58 (38.4%)	44 (29.1%)	102(100%)	
Obesity	YES	40 (63.5%)	23 (36.5%)	63(100%)	0.001
	NO	33 (37.5%)	55 (62.5%)	88(100%)	

Discussion

Despite advances in antiviral therapy, chronic hepatitis C remains an important global health burden as a leading cause of liver-related morbidity and mortality, with extrahepatic manifestations as peripheral neuropathy further contributing to impaired quality of life of patients. This study enrolled 151 chronic hepatitis C patients to observed peripheral neuropathy, with overall mean age of 57.14 ± 6.49 years, majority of males (58.3%), mean duration of disease around 12.72 ± 9.24 months and the smokers were 33.77%. Corresponding to these findings, in the study conducted by Khalek MA et al¹³ mean age of HCV infected individuals was less 40.08 ± 7.29 years, with male (60%) predominance, and mean duration of disease was 14.60 ± 10.29 months. The observed pattern is consistent with previously reported findings in the study carried out by Yoon MS et al¹⁴ where mean age of HCV patients was 48 ± 13 years, with mean duration of disease 9.1 ± 7.3 years for HCV infection, while inconsistently they found HCV infected females in majority (58.7%). Comparable demographic findings were documented in another study conducted by Seelro SH et al¹⁵ where middle-aged patients were predominant, with average age of 42.7 ± 18.2 years, mean disease duration of 10.2 ± 4.1 months and males in majority

assessment vs. formal electroneurography), the occurrence or absence of cryoglobulinemia in the study populations, diversities in age of the patients and disease duration, along with variation in HCV genotype across the regions, and differences in study setting and sample selection criteria, specifically whether confounding causes of neuropathy like diabetes were excluded. As well, this study possessed a remarkably higher mean age compared to other studies, which may itself partly explain its greater detected prevalence of peripheral neuropathy.

Additionally in this study, female gender and obesity were significantly associated with peripheral neuropathy ($p = 0.001$). In partial agreement with these findings, in the study conducted by Seelro SH et al¹⁵ gender showed a significant association with peripheral neuropathy ($p=0.021$). Although, association between peripheral neuropathy and obesity was statistically insignificant ($p=0.312$), they found that BMI was directly proportional to neuropathy, which indicates positive link between elevated BMI and neurological issues among HCV patients. Based on further post stratification analysis in this study showed advanced age of the patients and prolonged duration of disease were significantly associated to developed neuropathy ($p<0.05$). Similar trends have been

documented in studies from different populations like in the study carried out by Mapoure NY et al¹⁶ age $\geq$ 55 years and disease duration were significantly associated with peripheral neuropathy ($p < 0.05$). The observed pattern was also consistent with the study of Biasiotta A et al¹⁷ where age and disease duration (HCV infection) were significant predictors of peripheral neuropathy ($P < 0.01$). Our findings further validate by earlier report by Santoro L et al¹⁸ who showed significant association between age and peripheral neuropathy ($p < 0.001$). The similar trends have been documented in few other studies from different populations.^{15,19,20} However present study possesses certain limitations, like relatively limited sample size was, did not particularly analyzed the severity of peripheral neuropathy or stratify findings based on the severity of underlying CLD, both of which could expressively influence the strength and nature of the

relationships observed. Consequently, further large-scale studies, integrating detailed severity grading of both peripheral neuropathy and CLD, are suggested to validate the evidence.

Conclusion

The peripheral neuropathy observed to be a frequent finding among patients with chronic liver disease, with advanced age, extensive disease duration, female gender, and higher BMI being significant contributors for this frequently ignored extrahepatic complication. A substantial frequency emphasizes the requirement for routine neurological screening among HCV-infected CLD patients, empowering early detection and timely management of this frequently overlooked complication.

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