

Original Research

Assessment of peripheral neuropathy in untreated hepatitis c patients

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ABSTRACT:

Context: Peripheral neuropathy (PN) is one of the most common extrahepatic manifestations of HCV infection, affecting more than half of the infected patients. It can be clinical/sub-clinical. While clinical neuropathy presents with tingling, numbness, sharp pain, cramps, limb weakness, loss of balance or loss of reflexes; sub-clinical neuropathy is completely silent with the patient having no symptoms or signs of peripheral nerve involvement. Detection of sub-clinical neuropathy needs electrophysiological assessment in the form of nerve conduction study (NCS). **Aims:** To estimate the proportion of peripheral neuropathy among untreated hepatitis C patients and to assess the patterns of peripheral neuropathy in these patients. **Setting and Design:** This hospital based descriptive study was conducted in the Department of Medicine of a tertiary care teaching hospital. **Materials and Methods:** The study was conducted on 100 untreated HCV patients aged above 18 years, selected by consecutive sampling technique. The study subjects were then evaluated for the presence and patterns of peripheral neuropathy by nerve conduction study using NEUROSTIM NS2 NCV machine. **Statistical analysis used:** The data entry was done in Microsoft Excel spreadsheet and the final analysis was done with the use of Statistical package for Social Sciences (SPSS) software version 21.0. **Results:** PN was found to be present in 70(70%) of the 100 subjects; with 74.3% showing clinical neuropathy and remaining 25.7% showing sub-clinical neuropathy. The most common pattern of PN according to this study was a distal symmetrical axonal pattern of sensory polyneuropathy, mainly involving the lower limbs. The most common nerve affected was found to be CPN (common peroneal nerve) followed by median nerve. Among the effects of various variables on PN studied, advanced age (≥ 45 years), increased duration of infection (≥ 12 months) and high viral load (≥ 6 lakh) were found to have a statistically significant influence on the development of PN in HCV patients. Besides, it was found that infection by hepatitis C virus itself contributes to the development of PN, irrespective of the liver status (i.e; presence or absence of chronic liver disease). **Conclusion:** A significant proportion of HCV infected patients developed PN. Untreated HCV patients with advanced age, increased duration of infection and high viral load were at greater risk of developing PN. As peripheral neuropathy is a major contributor to morbidity and disability in HCV patients, early diagnosis and management of PN helps to improve the overall outcome of these patients.

Key words: HCV patients, Peripheral neuropathy, Electrophysiological testing.

Key message: Evaluation for PN should be a part of routine work-up for HCV infected patients, especially in the high-risk population. There is a need to expand the use of nerve conduction studies for the early diagnosis of PN in HCV patients. HCV treatment centers and tertiary care hospitals should be equipped with efficient system for evaluation and management of PN.

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INTRODUCTION

Chronic hepatitis represents hepatic inflammation and necrosis for at least 6 months. Hepatitis C virus accounts for 60-70% of the cases, and 50-70% of acute hepatitis C cases become chronic(1). Hepatitis C virus(HCV) is a parenterally transmitted hepatotropic and lymphotropic RNA virus belonging to the Flaviviridae family and it is a major public health

problem, affecting more than 185 million people worldwide. About 20-30% of these patients develop cirrhosis after 10 to 20 years of follow-up and some develop hepatocellular carcinoma (2).

Although most patients with chronic hepatitis C are asymptomatic, an appreciable number will experience symptoms that are due to the liver disease and /or extrahepatic manifestations of HCV

infection(1).Extrahepatic manifestations of hepatitis C can involve the skin, eye, joints, immune system, nervous system and kidneys. These associations include cryoglobulinemia, polyarteritis nodosa, sicca syndrome, membranoproliferative glomerulonephritis, lichen planus, thyroiditis and peripheral neuropathy (3).Clinical involvement of cryoglobulinemia(type II/mixed) seen in HCV is mainly characterised by purpura, arthralgia, kidney disease and peripheral neuropathy (PN)(2).

Peripheral neuropathy is the commonest and best established HCV-related neurological complication, affecting more than half of infected patients ,while central nervous system (CNS) involvement is rarely reported(5).Peripheral neuropathy affects the nerves in the legs and arms and it is characterised by numbness, burning, pins and needles sensation and cramps in the limbs.Usually involvement of feet and legs occur before the hands and arms(3).PN, though a major extrahepatic manifestation of chronic Hepatitis C ;it is often underdiagnosed, contributing more to the morbidity.

The factors associated with neurological manifestations in HCV infection are cryoglobulinemia, advanced age and duration of illness. Peripheral neuropathy in HCV can be clinical/sub-clinical. Clinical neuropathy presents with tingling, numbness, sharp pain and cramps, loss of balance and co-ordination; some patients also present with muscle weakness, loss of reflexes and foot problems including sores and blisters(6).To define as peripheral neuropathy; mild loss of vibration sense in both great toes or absent/hypoactive ankle jerks bilaterally is needed. however, peripheral neuropathy can also manifest silently, with no symptoms, detected by electrophysiological studies(sub-clinical)(10).

Electrophysiological examination of nerves to detect peripheral neuropathy in hepatitis C is done by a simplified nerve conduction study (NCS)protocol. The most commonly described form of PN in HCV is distal symmetrical sensory/sensory-motor polyneuropathy with a predominantly axonal process, mainly affecting the lower limbs. Distal symmetrical peripheral neuropathy is diagnosed when all explored nerves or when both lower limb nerves are affected.

AIMS AND OBJECTIVES

- To estimate the proportion of peripheral neuropathy among untreated hepatitis C positive patients.
- To assess the patterns of peripheral neuropathy in these patients.

SUBJECTS AND METHODS

This hospital based descriptive study was conducted in the Department of Medicine of a tertiary care teaching hospital.100 untreated HCV patients who presented to the Internal Medicine Department either via outpatient clinic or emergency were enrolled. Permission was sought from IEC and written informed consent was taken from each subject before enrolling them for the study.

INCLUSION CRITERIA

1. Patients of any gender above 18 years of age who were willing to participate in the study.
2. Patients with positive HCV-RNA with or without chronic liver disease.(HCV RNA Quantitative) was done from any National accredited laboratory as per Punjab Govt. guidelines i.e; under MMPHCRF [Mukh Manthri Punjab Hepatitis C Relief Fund])

EXCLUSION CRITERIA

1. Patients already treated or were on treatment for Hepatitis C
2. Other confounding causes of peripheral neuropathy (like diabetes mellitus, alcohol use, renal failure, thyroid disorder, vitamin deficiency, neoplasm or drugs causing PN).

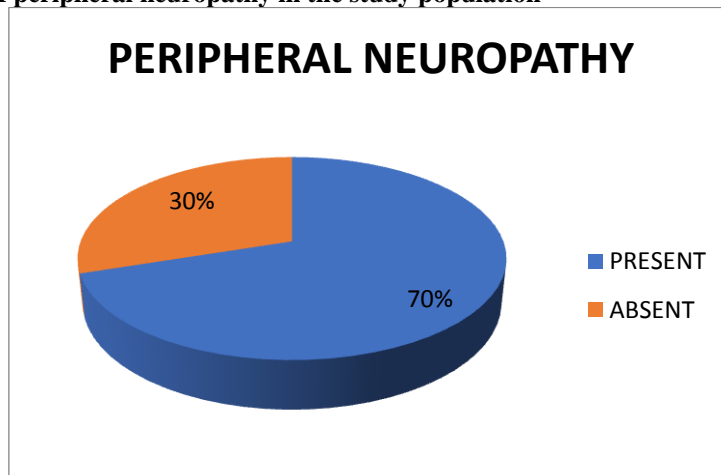
DATA COLLECTION PROCEDURE

All subjects underwent detailed history, complete neurological examination, serological testing and electrophysiological testing. The presence of HCV infection was assessed by the presence of anti-HCV antibodies by ELISA and quantitative assay by PCR. Electrophysiological testing was performed on median, ulnar, radial, sural, posterior tibial and peroneal nerves using NEUROSTIM NS2 NCV machine . Distal latency, amplitude (CMAP), F wave and conduction velocity for motor and sensory nerves were recorded and analysed. In this study, a peripheral nerve was electrophysiologically defined as affected when atleast 2 of these parameters were found to be abnormal for the nerve studied.

Patients were considered to have clinical neuropathy when clinical signs/symptoms of peripheral neuropathy(PN) co-existed with electrophysiological abnormalities in atleast 2 nerves examined; and subclinical neuropathy when they had electrophysiological abnormalities without any clinical signs or symptoms of PN. The results thus obtained were tabulated and analysed using appropriate statistical tools.

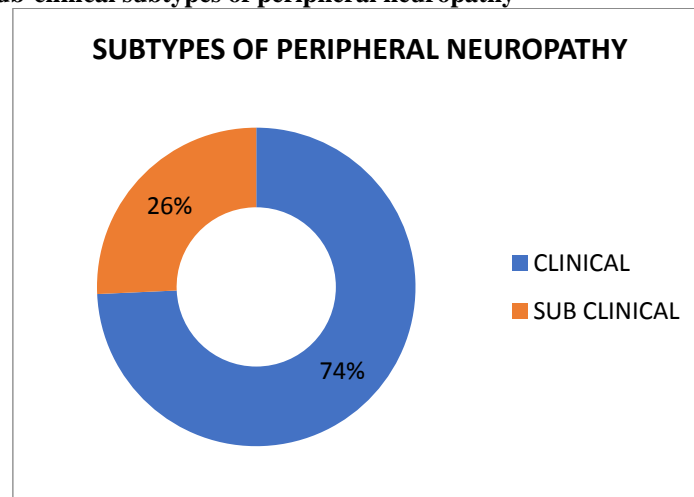
OBSERVATIONS AND RESULTS

FIG 1: Proportion of peripheral neuropathy in the study population



Out of 100 HCV patients , 70 patients(70%) had peripheral neuropathy and remaining 30 patients(30 %) did not have peripheral neuropathy.

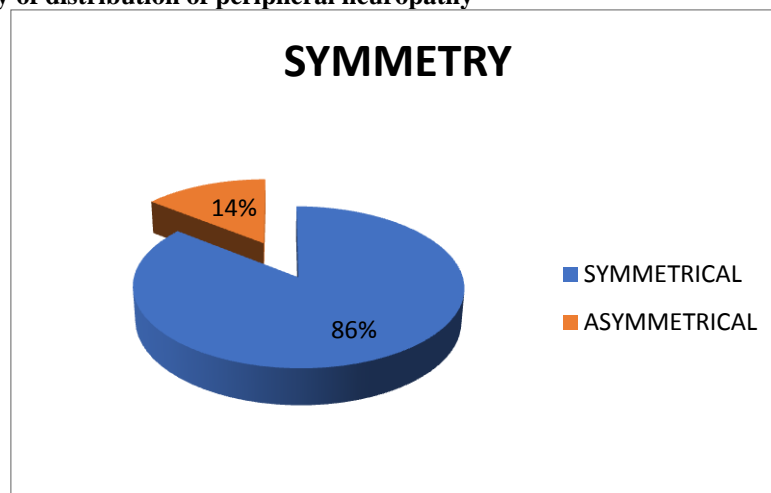
FIG 2: Clinical and sub-clinical subtypes of peripheral neuropathy



Among the 70 patients with peripheral neuropathy ;51/70 (74.3%) had clinical neuropathy and remaining 19/70 (25.7%) had sub-clinical neuropathy.

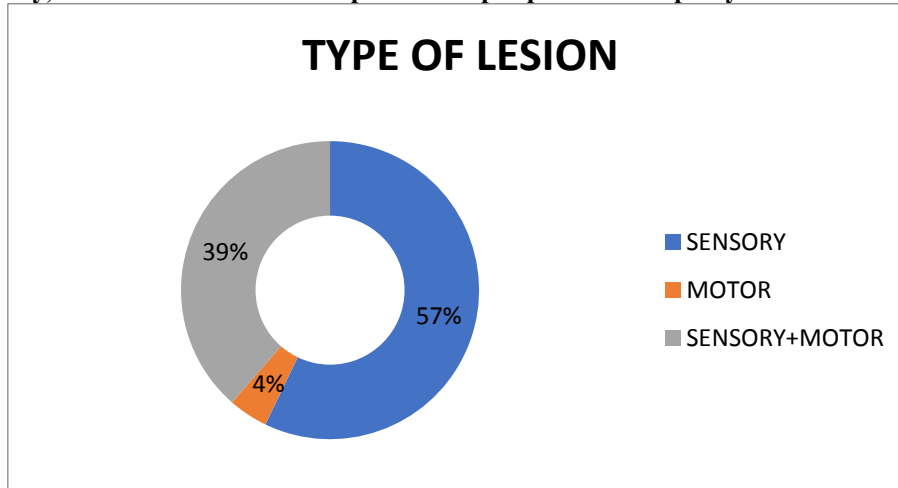
NCS FINDINGS

FIG 3a: Symmetry of distribution of peripheral neuropathy



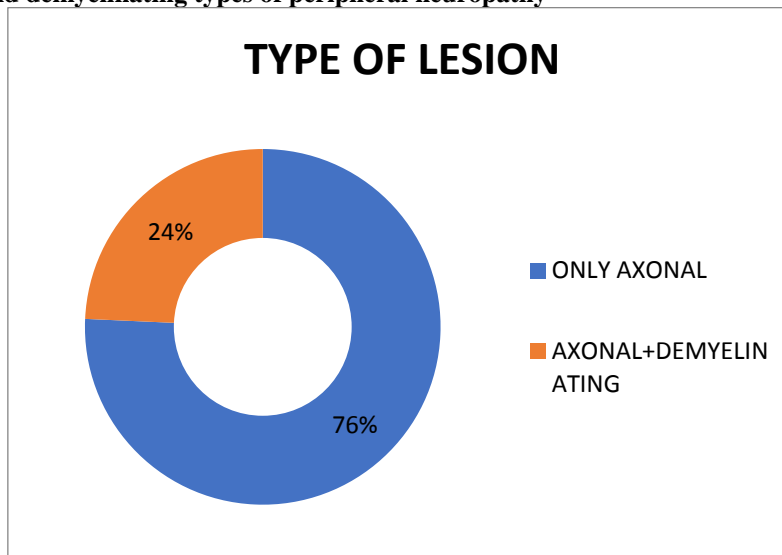
Among the 70 patients with peripheral neuropathy; 60/70 (85.7%) had symmetrical distribution of neuropathy and remaining 10 /70(14.3%) had asymmetrical distribution of neuropathy.

FIG 3b: Sensory, motor and sensori-motor patterns of peripheral neuropathy.



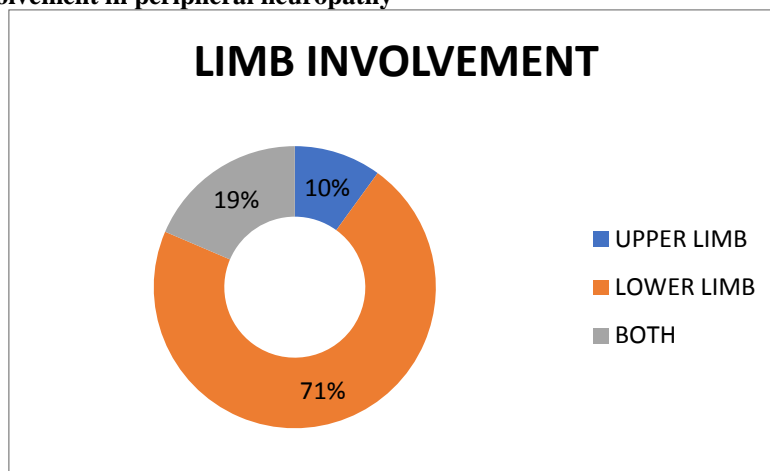
Sensory neuropathy was found in the maximum percentage of patients with peripheral neuropathy-40/70(57.1%) followed by mixed or sensori-motor type-27/70 (38.6%).Least common was pure motor neuropathy-3/70(4.3%).

FIG3c: Axonal and demyelinating types of peripheral neuropathy

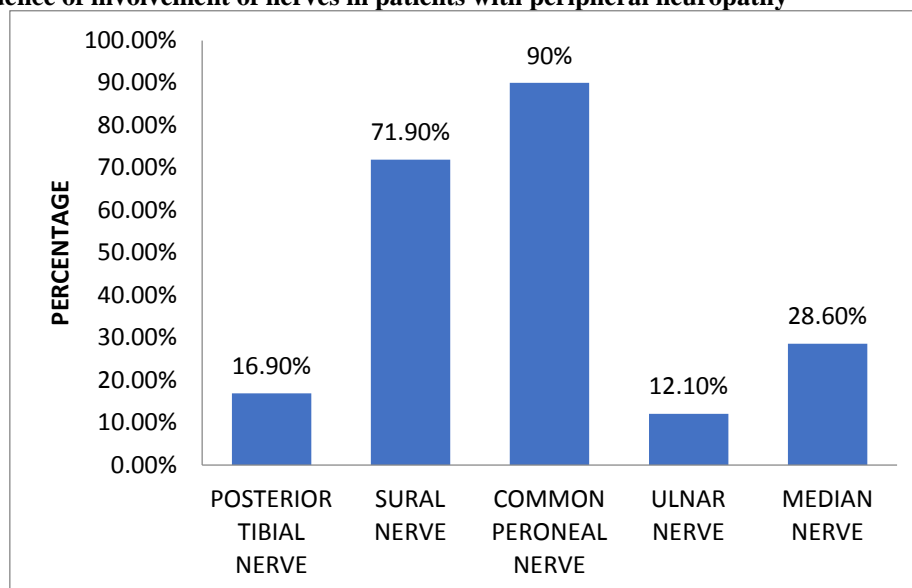


Axonal neuropathy was most common (76%) followed by mixed(24%).Only demyelinating type was absent.

FIG 3d: Limb involvement in peripheral neuropathy



Involvement of the lower limb was seen in 50/70 (71.4%) patients with peripheral neuropathy. Both lower and upper limbs were involved in 13/70 (18.6%) patients. Only upper limb was involved in 7/70 (10%) patients.

FIG 4: Sequence of involvement of nerves in patients with peripheral neuropathy

Common peroneal nerve (CPN) was involved in the largest number of patients with peripheral neuropathy- 63/70(90%); followed by the sural nerve-23/32 (71.9%).

LOWER LIMB NERVE INVOLVEMENT

CPN(90%) > Sural nerve(23/32 or 71.9%) >PTN(11/65 or 16.9%).

UPPER LIMB NERVE INVOLVEMENT

Median nerve (20/70 or 28.6%) > Ulnar nerve (8/66 or 12.1%)

DISCUSSION

Peripheral neuropathy is one of the most common extrahepatic manifestation of chronic HCV infection. It can be clinical neuropathy exhibiting signs and symptoms; or sub-clinical(silent) neuropathy which can be detected only by electrophysiological examination. This study was aimed to assess the proportion and patterns of PN in untreated hepatitis C patients. The influence of age, gender, viral load and duration of infection on the incidence of PN was also observed in the study.

This study is one of the few studies where both clinical and electrophysiological assessment of HCV patients for PN was done ; hence a considerably large proportion of patients (70%) were diagnosed with PN. Only untreated HCV patients were enrolled in this study; as treatment alters the usual course and progression of PN. Also, patients with HCV infection can also be having other co-morbidities which can have a toll at the development of PN ; including diabetes mellitus , alcoholism, renal failure , thyroid disorders ,neoplasms ,vitamin B12/ folate deficiencies and HIV or hepatitis B co-infection. So, this study was focused to eliminate these confounding causes; excluding patients with any other co-morbidity other than HCV. This helped in establishing a one-to-one relationship of HCV infection and PN ; making chronic infection with HCV alone a significant risk factor for the development of PN.

PROPORTION OF PN IN HCV PATIENTS

Among the total of 100 HCV patients studied, 70 patients (70%) were found to have peripheral neuropathy (out of which 51 patients [74.3%] had clinical neuropathy; while remaining 19 patients [25.7%] had sub-clinical neuropathy). Manal et al. reported the prevalence of PN as 67.5% in a group of Egyptian HCV-infected treatment naïve patients (11); which supported the high prevalence of PN in this study. But another study done by Cacoub and colleagues (2) revealed a lower prevalence of PN (10.6% or 25/234 subjects). However they used only clinical assessment for PN ; which would have lead to underestimation of PN in the HCV patients. It was also pointed out by England and colleagues(59) that polyneuropathy occurs with a combination of symptoms , signs and abnormal electrodiagnostic studies ; whereas symptoms alone have relatively poor diagnostic accuracy in predicting the presence of PN.

PATTERNS OF PN IN HCV PATIENTS

The most common pattern of PN observed in this study was an axonal type of distal symmetrical sensory polyneuropathy with predilection for lower limb involvement. Silberbogen et al, conducted a study on HCV patients in 2007 with similar results (18). Also similar observations were obtained by Kafrawy et al.(100% sensory) in Egypt and Biasiotta et al.(96% sensory) in 2014(21); who demonstrated that sensory deficiencies are more common than motor loss ,and that sensory symptoms may persist for months to years before any motor deficit becomes clinically evident.

Furthermore, this study showed that symmetrical distribution of PN (60/70 or 85.7%) was significantly higher than asymmetrical distribution of PN (14.3%). The criteria for axonal and demyelinating

type of neuropathy revealed axonal neuropathy to be most common (53/70 i.e 75.7%), followed by combined (axonal + demyelinating) form (17/70 i.e 24.3%); whereas only demyelinating form of neuropathy was absent, in this study. Previous study conducted by Khalek et al (11) in 2012 also showed predominance of axonal pattern of neuropathy in HCV patients.

SYMPTOM DISTRIBUTION OF PN IN HCV PATIENTS

The symptom wise distribution of the patients showed numbness to be the most common symptom (28.6%) followed by cramps (21.4%). Others in order were burning sensation and weakness (10% each), pain (4.3%) and tingling (2.9%). Among signs, impairment of vibration perception was found in 20/70 subjects (28.6%) and lost/diminished ankle jerks were found in 12/70 (17.1%). Similar data was also observed by Yoon et al. (23) in their study in Germany in 2011.

INVOLVEMENT OF NERVES BY PN IN HCV PATIENTS

The most studied nerves in our study were CPN in the lower limb and median nerve in the upper limb. 63/70 subjects with PN had CPN involvement (90%), whereas median nerve was involved only in 20/70 subjects (28.6%). Thereby, CPN was found to be the most affected peripheral nerve according to this study; followed by sural nerve (23/32 or 71.9%), with posterior tibial nerve involvement only in 11/65 (16.9%). Median nerve was found to be the most common nerve involved in the upper limb (28.6%) followed by ulnar nerve (12.1%). Radial nerve involvement was not found in any of the patients. Though much data is not available on the individual nerve involvement in HCV patients, a study done by Santoro et al. in 2006 concurred with these results (10).

RELATIONSHIP OF AGE WITH INCIDENCE OF PN

This study showed that increasing age was associated with increased prevalence of PN, with age \geq 45 years showing almost 100% involvement (11/12 patients in the 45-54 age group and all the 15 patients in the 55-64 age group and 14 patients in the >65 age group showed PN); whereas in the <35 age group which had the maximum number of subjects, only 16 of the 41 patients (22.9%) had PN. This is similar to a previous study conducted by Manpoure et al (4) in which age >50 years was significantly associated with neurological manifestations.

RELATIONSHIP OF GENDER WITH INCIDENCE OF PN

No significant gender difference in the incidence of PN was found in this study [38 out of 70 patients

(54.3%) with PN were males and remaining 32 were females (45.7%); with p value of 0.826].

RELATIONSHIP OF HCV VIRAL LOAD WITH INCIDENCE OF PN

According to this study, high viral load was found to have a significant influence in the development of PN. High viral load was defined as HCV RNA \geq 6 lakh IU/ml and low viral load as HCV RNA < 6 lakh IU/ml. In the PN positive group, 60% (42/70 patients) had high viral load and the remaining 40% (28/70 patients) had low viral load; or in other words, all the 42 (out of 100) patients with high viral load had PN. And in the PN negative group, all the 30 (out of 100) patients had a low viral load.

RELATIONSHIP OF DURATION OF HCV INFECTION WITH INCIDENCE OF PN

Like previous studies done by Luma and colleagues in 2016 and by Monaco et al. in 2015 (19); increased duration of infection was found to have a positive impact on the occurrence of PN. In our study also, among the PN positive group, 58.6% or 41/70 patients had duration of infection \geq 12 months; whereas among the PN negative group, 96.7% or 29/30 patients had duration of infection < 12 months; which had a statistically significant difference ($p < 0.001$).

STRENGTHS OF THE STUDY

Both clinical and electrophysiological evaluation of HCV patients for PN was done; hence this study was able to highlight the significance of electrophysiological testing to determine sub-clinical PN, which also contributes to significant morbidity in HCV patients. In this study, detailed NCS evaluation of upper and lower limb nerves was done; revealing different patterns of neuropathy. As multiple peripheral nerves were subjected to NCS in this study; percentage of involvement of all the major peripheral nerves could be documented in sequence. Symmetry of distribution of polyneuropathy was also analysed in this study.

By selecting only untreated patients, the effect of HCV treatment on neuropathy was eliminated. Also by excluding patients with diabetes mellitus, alcoholism, vitamin deficiencies, thyroid disorders and renal failure; the individualistic role of HCV infection in causing PN was established in this study.

LIMITATIONS OF THE STUDY

This was a single center study with a small sample size. And as there was a random selection of cases in this study; distribution of subjects according to age and gender was unequal. Severity of liver involvement was not a criterion in the study; hence distribution of PN according to the stage of liver disease could not be evaluated. Also, severity assessment of PN (or extent of nerve injury) was not done in this study.

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