

**Original Research Article****Evaluation of Peripheral Neuropathy in Chronic Hepatitis C Infection**

Authors

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Chingakham Arunkumar**Abstract****Background:** *Chronic Hepatitis C infection is very common in Manipur, a north eastern state of India. The study has been undertaken to assess peripheral neuropathy and find out any correlation of it with different parameters of chronic hepatitis C patients.***Materials and Method:** *This study was a cross sectional study of patients who were diagnosed as chronic HCV infected individuals in the Department of Medicine, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur. Comprehensive history, thorough clinical examination and all relevant routine investigation including HCV RNA quantitative and genotyping and nerve conduction velocity (NCV) were done for all patients.***Results:** *Among 31 patients of chronic HCV studied, peripheral neuropathy was more common in adults in the 4th decades. Peripheral neuropathy was observed in about 74.2% in which sensory involvement are more common. Axonal variety of neuropathy was maximum and most of the patients have lower limb involvement. Variables related to liver disease severity such as low platelet count, Child-Turcotte Pugh Score, presence of cirrhosis on ultrasound correlate well with the development of peripheral neuropathy. Presence of neuropathy is more common in group of patients whose viral is still detected in the blood.***Conclusion:** *Peripheral neuropathy affect 74.2% of patients of chronic HCV infection, most commonly involving sensory and axonal type of neuropathy in this study. There is positive correlation between the severity of neuropathy and increasing Child Class.***Keywords:** *Chronic HCV, peripheral neuropathy, sensory, axonal.***Introduction**

Hepatitis, inflammatory disorder of liver, dominates the clinical practice of hepatology. And the foremost hepatic infections are viral in origin. Unless otherwise specified, the term “viral hepatitis” is reserved for infection of the liver cause by a group of viruses having a particular affinity for the liver. They are – Hepatitis A virus

(HAV), HBV, HCV, HDV, HEV and HGV^[1].

Chronic hepatitis represents a series of liver disorder of varying causes and severities in which hepatic inflammation and necrosis continue for at least 6 month. Hepatitis C virus causes about 60—70% of cases, and 50—70% of acute hepatitis C cases become chronic. About 5—7% of hepatitis B cases, sometimes with hepatitis D

co-infection, become chronic. Complications of chronic liver disease and cirrhosis may eventually develop. Liver malfunction may lead to deterioration of brain function (hepatic encephalopathy), particularly in people with cirrhosis due to hepatitis C.^[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. Recognition of these symptoms will lead to early diagnosis and treatment of hepatitis C.^[3] Extrahepatic manifestation means diseases or conditions that affect organs other than the liver. Extra-hepatic manifestations of hepatitis C can be found in the skin, eyes, joints, immune system, nervous system and kidneys. Some of these conditions – cryoglobulinemia, for example – are somewhat more common and well documented, while others are infrequent or their association with hepatitis C has not yet been proven.^[4]

HCV-related neuropathies are usually associated with mixed cryoglobulinemia, although a few may be related to polyarteritis nodosa.^[5] The presentation of HCV neuropathy associated with mixed cryoglobulinemia ranges from mononeuritis multiplex to symmetric polyneuropathy that is typically painful with prominent sensory symptoms. The neuropathy caused by HCV-related polyarteritis nodosa is typically an asymmetrical polyneuritis with prominent motor symptoms. Polyarteritis nodosa can be life-threatening, and a combination of interferon treatment and immunosuppression in a sequential fashion along with plasmapheresis has been demonstrated to be highly effective.^[6] In general, HCV-related neuropathies are resistant to interferon treatment alone.^[7]

The mechanism of the extrahepatic manifestation seen with chronic viral hepatitis appears to be immune-mediated.^[8] Indeed, patients with chronic viral hepatitis commonly have immunologic manifestation including circulating auto antibodies and concurrent autoimmune disorders.^[9] Other

possible mechanisms include deposition of the circulating immune complex, induction of local immune complex formation by viral antigen, reaction with tissue antigen by viral-induced auto antibodies or a direct viral reaction to extrahepatic tissue sites.⁸

Peripheral neuropathy, one of the extrahepatic manifestations of chronic viral hepatitis, is characterized by numbness, burning, pins and needles sensations, crawling skin, and itching that occurs most often in the hands and feet, but can appear in other areas of the body. It is one of the rare phenomena in chronic HBV infection. But it is more commonly associated with HCV infection. In one study, it was found that 15.3% of people with HCV were diagnosed with PN. Treatment consists of treating the underlying disease (HCV) and avoiding any medications that cause or that can make PN worse.^[10]

In Manipur, the prevalence of injection drug user is high. It is because Manipur shares a 358-km porous border with Myanmar and have been associated with drug-trafficking routes.^[11] So, the prevalence of HBV and HCV infection is also high. So far there is no study conducted on the context of Peripheral neuropathy in the chronic HCV infection in Manipur.

Aim and Objectives

1. To assess clinical and electrophysiological pattern of peripheral neuropathy in chronic HCV infected patients.
2. To compare the pattern of neuropathy in chronic HCV.

Materials and Methods

This study was a cross sectional study of patients who were diagnosed as chronic HCV infected individuals. The study was carried out in the Department of Medicine, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur. The study was done during the period of two year period starting from September 2012 till October 2014. 31 patients whose ages were above 18 years irrespective of sex, religion and socio-economic

status with Chronic HCV infected were included in the study. Cases attending Medicine OPD, Liver clinic, Neurology clinic and inpatients in Medical ward who met the criteria of chronic HCV infection were included in the study. Patient with HBV and HCV co-infection, co-infected with HIV, diabetes, chronic alcoholic liver disease, history or laboratory evidence of other causes of neuropathy including vitamin B12, thiamine, familial, toxic or paraproteinemia and chronic renal disease, uremic neuropathy were excluded from the study. Comprehensive history, thorough clinical examination and all relevant routine investigation including HCV RNA quantitative and genotyping were done for all patients. Nerve conduction velocity (NCV) for sensory nerves (right sural and median nerve) and for motor nerves (right peroneal, ulnar, tibial and median) were carried out for all patients using standard techniques. Prior permission was taken from the Research Ethics Board RIMS, Imphal before the study was conducted. Informed consent of the participants of the study was taken as per ethical committee guidelines.

Statistics

Data from all the patients considered in the study were analysed using SPSS version 21. Chi square test and Fisher exact test were used as test of significance for finding if there is correlation between the severity of liver disease (Child class A, B and C) and peripheral neuropathy. P value less than 0.05 was considered to be significant.

Results

The present study was done on 31 patients with chronic hepatitis C recruited from the out-patient department as well as the in-patients of the department of Medicine, Regional Institute of Medical Sciences (RIMS)

Peripheral neuropathy was observed in 23(74.2%) patients. Sensory involvement was found in all of these 23 patients but motor nerve is involved only in 11(35.5%). Among the neuropathy, pure axonal variety was more in number accounting for

21(67.74%), demyelinating and mixed variety were found only in 1(3.2%) patient each.

Baseline parameters: Mean age of the study population was 42.58 ± 7.39 years. Males predominated the study population with 26(83.9%) while 5(16.1%) female was included. Genotype 3 is the most common followed by Genotype 1 (Table 1).

Symptoms: Patients presenting symptoms were assessed using a questionnaire and it was found that 14 (45.2%) patients do not have any neurological complaints or symptoms, 16(51.6%) complaints of mild symptoms in the form of tingling numbness or weakness and 1(3.2%) was having severe loss of sensation and weakness.

Table 1: Demographic, clinical and the laboratory features of the study population

Baseline Characteristic		Observation
Mean Age of the study population		42.58±7.39 years
Male : Female		26(83.9%): 5(16.1%)
Viral Genotype	1	11(35.5%)
	2	0
	3	18(58.1%)
	4	0
	5	0
	6	2(6.5%)
Anemia		14(45.2%)
TLC	< 3500	7(22.6%)
	3500- 9000	22(71.0%)
	>9000	2(6.5%)
Platelet Count	<1.6 Lacs	18(58.1%)
	>1.6 Lacs	13(41.9%)

Baseline NCV parameters: The results of the Nerve conduction study is given in the Table 2 below.

Table 2: Results of Nerve Conduction Study.

Nerves	No. Patients with Abnormal test (%)
Median Nerve Motor Latency	9(29%)
Median Nerve Motor Amplitude	2(6.5%)
Median Nerve Motor Conduction Velocity	1(3.2%)
Median Nerve Sensory Latency	8(25.8%)
Median Nerve Sensory Amplitude	12(38.7%)
Median Nerve Sensory Conduction Velocity	9(29%)
Peroneal Nerve Motor Latency	2(6.5%)
Peroneal Nerve Motor Amplitude	9(29%)
Peroneal Nerve Motor Conduction Velocity	8(25.8%)
Tibial Nerve Motor Latency	1(3.2%)
Tibial Nerve Motor Amplitude	10(32.3%)
Tibial Nerve Motor Conduction Velocity	2(6.5%)
Ulnar Nerve Motor Latency	0
Ulnar Nerve Motor Amplitude	1(3.2%)
Ulnar Nerve Motor Conduction Velocity	0
Ulnar Nerve Sensory Latency	5(16.1)
Ulnar Nerve Sensory Amplitude	9(29%)
Ulnar Nerve Sensory Conduction Velocity	1(3.2%)
Sural Nerve Sensory Latency	13(41.9%)
Sural Nerve Sensory Amplitude	22(71%)
Sural Nerve Sensory Conduction Velocity	13(41.9%)

After studying the pattern in the Nerve Conduction Velocity test the result of the pattern of Peripheral neuropathy is shown here Fig. 1. Here, sensory axonal neuropathy is found to be present in 11(35.5%) patients, sensory motor axon seen in 10(32.3%) and sensory demyelinating & sensory motor mixed pattern in 1(3.2%) each.

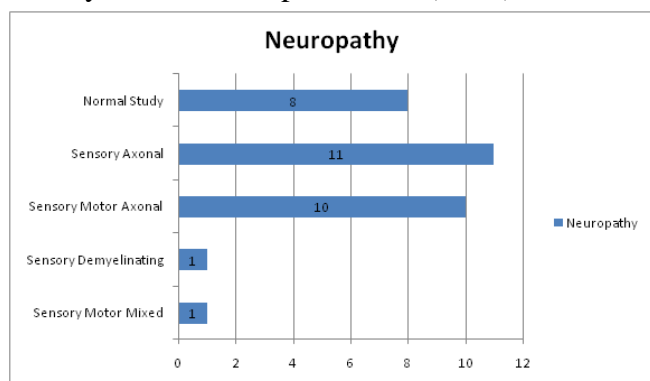


Fig. 1: Bar chart shown the pattern of peripheral neuropathy in the study population

Baseline cardiorespiratory parameters: Mean resting heart rate of the study group was 79.54±13.52 beats/minute. Mean resting systolic blood pressure was 122±14.4 mm Hg. Mean resting diastolic blood pressure was 78.58±9.93 mm Hg. Mean resting respiratory rate was 20.12±2.6 per minute. [Table 3]

Table 3: Baseline cardio respiratory parameters

Parameter	Mean± SD
Mean Resting Heart rate(beats/minute)	79.54±13.52
Mean Resting Systolic BP(mm Hg)	122±14.4
Mean Resting Diastolic BP(mm Hg)	78.58±9.93
Mean Resting Respiratory rate (per minute)	20.12±2.6

Laboratory parameters: Anemia was observed in 14(45.2%) of the study population. Thrombocytopenia (platelet count < 1.6 lakh) was observed in 18(58.1%). Liver disease severity was graded into Child class A, B and C. Patients belonging to child class A were 18(58.1%), class B in 11(35.5%) and class C in 2(6.5%) [Fig. 2]. Rise in SGOT and SGPT more than 5 times was considered significant and it was found in 3(9.7%) and 2(6.5%) respectively.

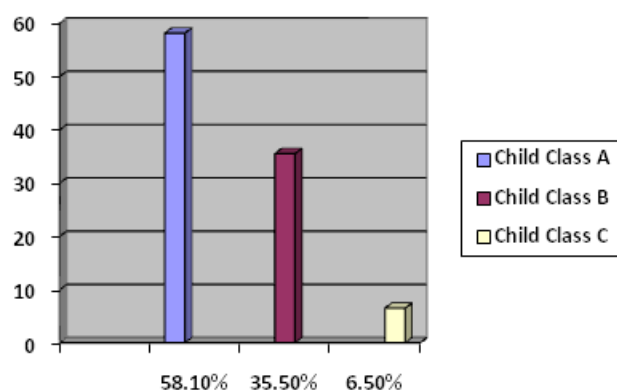


Fig. 2: Bar chart showing the prevalence of severity of liver disease in the study group according to Child Turcotte Pugh Scoring.

Imaging findings: Ultrasound findings of the study population are normal consisted of 7(22.6%) patients, fatty liver 11(35.5%) and hepatic parenchymal disease 13(41.9%)

Discussion

Viral hepatitis C causes chronic persistent infection with complex immune responses in the majority of individuals, which may have the potential to generate neurological illness through direct infection of neural cells or through immune-mediated mechanisms, including enhancement of autoimmune responses. Thus neurologists are increasingly faced with diagnosing or even predicting a wide spectrum of neurological complications of hepatitis viral infection and/or its treatment. Considering these factors in mind, our study aimed at studying the affection of nervous system in different spectrum of chronic Viral hepatitis C induced liver disease based on the Child-Turcotte Pugh score (CHILD A, B and C). Only few studies regarding this subject have been published. Similar study has not been conducted in Manipur population before.

In this cross sectional study conducted in 31 HCV infected patients were studied. Maximum cases were in the age group of 40-50 years with 17 cases (54.83%) followed by 30-40 years with 8 cases (25.8%). Mean ages of the study populations were 42.58±7.39 years. This data is comparable with previous studies by Vinay Chaudhry^[12] et. al., who studied autonomic function and peripheral

neuropathy in chronic liver disease, where mean age of study population of viral hepatitis group is 45years and O Lidove et. al⁵ where among the four cases, two of them were between 40-50ys. Males predominated our study group 26(83.9), with only 5 case being female (16.1%).

Before assessing the association between liver disease and Neuropathy, the effect of age on neuropathy was assessed. When we compared the mean age differences between the patients with and without neuropathy, there was no significant difference. However, the mean age of patients with peripheral neuropathy is lower by 2.42 years in the patients infected with HCV. The clinical significance may suggest that these patients with peripheral neuropathy is not age related rather may be due to the infection itself. Moreover, the association is not statistically significant though autonomic dysfunction seems to more with increasing age.

In our study, peripheral neuropathy was documented in 74.2% of patients in HCV infection. In most patients, the neuropathy was subclinical or mild with minimal symptoms. Examination showed distal sensory loss and loss of distal reflexes consistent with a length-dependent neuropathy. Electrophysiology confirmed this and suggested that the primary process is axonal degeneration. Only two patients, one with severe demyelinating and another with mixed axonal & demyelinating. The data is similar to Vinay Chaudhry¹² et al, where peripheral neuropathy involvement is found in 74% among the group of CLD due to viral hepatitis and primary pathology being axonal. In the study demyelinating was found only in one patient.

In the study conducted by Vinay Chaudhry¹² et al the number of patients according to Child-Pugh classification is A: B: C=13:6:4 which is comparable with our, that is, 18:11:2. The prevalence of peripheral neuropathy in HCV infection according to Child-Pugh Classification is 13 out of 18 (72.22%) in Child A, 8 out of 11 (72.72%) in Child B and 2 out of 2 (100) in Child C. These showed a significant clinical correlation

of the prevalence of peripheral neuropathy to the severity of liver disease. But the correlation was not significant statistically which may be due to non-uniform distribution of number of patient in each class of Child classification. Gonzalez-Reimer¹³ et al in their study of 33 alcoholics, 20 of them cirrhotic, found a weak correlation between liver function and both autonomic and peripheral neuropathy.

In our study, the variables related to liver disease severity that correlated with peripheral neuropathy significantly were low platelet count ((p = 0.029) for HCV group cirrhosis on ultrasound [(p =0.04) for HCV group. Thrombocytopenia & cirrhosis are directly related to the duration and severity of liver disease, thus can predict the occurrence of peripheral neuropathy in similar populations. Meanwhile total leucocyte count, the rise in liver enzymes (SGOT/SGPT), and spontaneous bacterial peritonitis correlated poorly with the peripheral neuropathy. Total leucocyte count and liver enzymes were not associated with the severity of liver disease in the present study. In cirrhotic, the liver enzymes can be normal, making it a poor predictor of neuropathy as evidenced by our study.

In our study, the electrophysiological study of nerves shows that sural nerve sensory amplitude was maximally involved in the population of the study, 22 (71%) patients of HCV. It is then followed by the involvement of the median nerve sensory amplitude. In the study by Chaudhry et. al. maximum number of abnormal test was also found in sural nerve sensory amplitude. Thus, in the present study we can conclude sensory involvement is more than the motor involvement and also lower limbs are more often involved than the upper limbs.

Abnormal sural nerve sensory amplitude were found in 68.4% of patients of class A, 80.0% of patients of class B and in 100% of patients of class C. Abnormal median nerve sensory amplitude was found in 31.6% of patients of class A, 50% of patients of class B and

50% of patients of class C. As regard to abnormal peroneal nerve motor conduction velocity, it was found in 26.3% of patients of class A, 20% of patients of class B and 50% of patients of class C. From our results, it is clear that peripheral neuropathy was common in patients with HCV and majority of abnormalities were related to patients of class C, followed by those of class B and lastly those of class a, and the differences were statistically significant. Similar results were reported by Fawi et al^[14]

In the study, we have also tried to find out the association of viral load and treatment with the presence of neuropathy. It has been observed that in a sub-population of patients who have not received any treatment, 9(81.8%) patients of HCV are found to have peripheral neuropathy. In the sub-population who were undergoing treatment, peripheral neuropathy were observed in 3(27.3%) patient whose HCV target is not detected & 9(100%) patients whose HCV target is still detected in the blood. Thus, we see that viral load is directly correlated to the presence of neuropathy the result is also found to be statistically significant ($p=0.001$) this may suggest that virus itself is causing the neuropathy as seen in other studies also. Moreover, we see that prevalence of neuropathy in HCV patients is highest in group undergoing treatment whose HCV target is still detected, even more than in group whose HCV treatment naive group with significant viral load. This observation also gives us a clue that the treatment of HCV, i.e. Pegylated Interferon may also act to cause certain degree of neuropathy in HCV.^[15, 16]

Peripheral neuropathy though usually found in mild form in these patients, very few of them might progress to severe disability. Therefore, any patient who complaints of any neurological symptom are needed to be examined and evaluated thoroughly. Hence, evaluation of peripheral neuropathy should be a part of routine work up for liver disease in the future.

Conclusion

Peripheral neuropathy was documented in 74.2% of patients in HCV infection. In most patients, the neuropathy was subclinical or mild with minimal symptoms. Electrophysiology confirmed that the primary process is axonal degeneration. And sural nerve sensory amplitude was maximally involved. There was a positive correlation between increasing Child Class and the severity of neuropathy in all the sub-group. Variables related to liver disease severity that correlated with neuropathy significantly were low platelet count, Child-Turcotte Pugh Score and presence of cirrhosis on ultrasound.

This study emphasizes the fact that identification of this subset of patients with neuropathy in HCV associated liver disease can possibly improve survival. Hence, evaluation of peripheral neuropathy should be a part of routine work up for liver disease in the future and preference should be given for early intervention in such a high-risk population.

References

1. James MC. Liver and Biliary Tract, In: Kumar R, Abbas A, Fausto, editors. Robins and Contran, Pathologic Basis of Disease. 7ed. Philadelphia: Elsevier; 2004: p. 890-895
2. Jules LD. Chronic Hepatitis. In: Longo DL, Fauci AS, Kasper DL, Hauser, Jameson JL, Loscalzo, editors. Harrison's principle of internal medicine. vol 2. 18thEd. New York: McGraw Hill; 2012. p, 2567-88
3. El-Serag HB, Hampel H, Yeh C, Rabeneck L. Extrahepatic manifestations of hepatitis C among United States male veterans. Hepatology 2002; 36:1439-45.
4. McKee DH. Et al. Neurologic complications associated with hepatitis C virus infection. Neurology 2000; 55: 459-459
5. Lidove O. et al. Hepatitis C virus infection with peripheral neuropathy is not always

- associated with cryoglobulinemia. Ann Rheum Dis 2001; 60:290-292
6. Lunel F, Cacoub P, Treatment of autoimmune and extrahepatic manifestations of hepatitis C virus infection. J Hepatology 1999; 31:210-216.
 7. Aman Ali, Nizar NZ, Hepatitis C infection: A systemic disease with extrahepatic manifestation. Cleveland Clinic J Med 2005; 72(11):1005-19.
 8. Wilson RA. Extrahepatic manifestation of chronic viral hepatitis. Am J Gastroenterol 1997;92:3-17.3
 9. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB. Immunologic feature and HLA associations in chronic viral hepatitis. Gastroenterology 1995;108:157-64
 10. Mckee DH. Et al. Neurologic complication associated with hepatitis C virus infection. Neurology 2000; 55: 459-459.
 11. Beyrer C Razak MH, Lisam K, Chen J, Lui W, Yu XF. Overland heroin trafficking routes and HIV-1 spread in south and south-east Asia. AIDS 2000; 14:75-83.
 12. Vinay C, Andrea MC, Rihcard O'B, David RC, Andrew SK, Paul JT. Autonomic and Perefheral (Sensorimotor) Neuropathy in Chronic Liver Disease: A Clinical and Electrophysiologic Study. RJ hepatology 1999; 29; 6:1698-1703.
 13. Gonzalez-Reimers E, Alonzo-Socas M, Santolaria-Fernandez F, Hernandez-Pena J, Conde-Martel A, Rodriguez-Morena Moreno F. Autonomic and peripheral neuropathy in chronic alcoholic liver disease. Drug Alcohol Depend 1991; 27(3):219-22
 14. Fawi GH, Khalifa GA, Abo Dahab LH. Autonomic and peripheral neuropathies in chronic liver diseases: Clinical and Neurophysiological study. Egypt J Neurol. Psychiat. Neurosurg 2005;42(1);187-200
 15. La Civita L et al. Exacerbation of peripheral neuropathy during alpha-interferon therapy in a patient with mixed cryoglobulinemia and hepatitis B virus infection. J Rheumatol 1996;23(9):1641-1643
 16. Beuthien W et al. Vasculitic complications of interferon- α treatment for chronic hepatitis C virus infection: case report and review of the literature. Clin Rheumatol 2007; 24(5):507-515.