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Original Research Article

Study of Pattern of Neuropathy in Chronic Liver Diseases in a Tertiary Care Center of Bhopal, Madhya Pradesh

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Abstract:

Background: Chronic liver disease (CLD) is a leading cause of death worldwide, especially in developing nations. CLD is increasing in prevalence, as has been established recently. The most common causes of CLD include chronic viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, and hemochromatosis.

Aims and Objectives: To study the pattern of neuropathy in patients with CLD.

Materials and Methods: Present cross-sectional study was performed on 100 consenting patients with cirrhosis of any etiology having age >18 years at the Department of Medicine Gandhi Medical College, Hamidia hospital, Bhopal, between January 2021 to September 2022. Detailed clinical examination, liver function tests and serum vitamin B12 were done. Motor and sensory electrophysiological tests were performed in the upper and lower limbs on the right ulnar, median, common peroneal posterior tibial, and sural nerves using Neuroperfect plus-4Ch EMG/ NCV/ EP (Medicaid systems) machine. The results were analyzed and interpreted based on the normal nerve conduction values as detailed in standard references.

Results: Chronic liver disease was more prevalent in the age groups of 31-50 years (65%) with male preponderance (75%), in a rural area (89%), those with primary education (65%) and were daily laborers (73%), 63% were consuming alcohol, consuming tobacco (37%) and were smokers (26%). The incidence of peripheral neuropathy (PN) in patients with CLD was 58%. The majority had mixed (23%) type of PN followed by a motor (22%) and sensory (13%) PN. Of those with alcoholic etiology, 59.7% had PN, half of the patients with cryptogenic etiology had PN, 56.5% of patients PN had hepatitis B as etiology, and 60% of the patients with hepatitis C etiology had PN ($p=0.011$). All 37 patients with alcoholic etiology, had axonal neuropathy; similarly, all the 5 patients with cryptogenic and 3 hepatitis C etiology were axonal. Whereas out of 13 patients with hepatitis B etiology, 12 had axonal and 1 had axonal +demyelinating neuropathy ($p<0.001$). In the Motor nerve conduction test, distal latency was significantly higher in patients with mixed type of neuropathy; however, amplitude and nerve conduction velocity was reduced considerably in mixed type of neuropathy. The sensory nerve conduction test revealed that amplitude and nerve conduction velocity was significantly increased in the mixed type of neuropathy.

Conclusion: Peripheral neuropathy is a common complication of CLD related to the etiology of CLD, like alcoholic cirrhosis, hepatitis B virus, and coexisting risk factors like alcoholism and smoking. The PN in CLD is predominantly sensorimotor, mixed axonal degeneration, and demyelinating type. Routine investigations for assessing PN may still not be indicated since the clinical implications are not studied extensively.

Keywords: peripheral neuropathy, chronic liver disease, alcohol consumption, complication

Introduction

Cirrhosis is a progressive liver condition that can cause many unpleasant symptoms and death. Studies have shown that patients with chronic liver disease (CLD) and concomitant autonomic neuropathy have an impaired or abnormal response to life-threatening events such as septicemia and variceal hemorrhage. [**1**]

Neuropathy is more common in alcoholics with liver impairment than in those without. According to certain studies, autonomic neuropathy has been linked to CLD. However, there have been reports that seem to contradict one another, leading to great uncertainty. [**2**]

Cirrhosis and chronic hepatitis are two forms of CLD that are linked to peripheral neuropathy (PN). However, the prevalence and symptoms of this neuropathy have been reported inconsistently. [**3]** Some have questioned whether or not neuropathy is a direct result of liver illness. [**4]** Others have reported an incidence of 19-100%. [**5]** Sural nerve segmental demyelination has been observed in patients with no clinical symptoms of neuropathy, according to histopathological examinations. Chronic liver illness has also been linked to autonomic neuropathy. Despite the numerous studies published on the topic, there is still disagreement about the nature and severity of hepatic neuropathy. In chronic liver illness, a recent study demonstrated axonal sensory-motor polyneuropathy predominated over the demyelinating neuropathy previously hypothesized. [**6]**

Nerve conduction tests in cirrhotic individuals have shown a wide range in PN prevalence, from 19% to 80%. [**7]** As there is a shortage of local data, the current study would greatly assist in establishing the local perspective. Since liver cirrhosis already places a heavy financial and emotional strain on patients and their families, routine screening of suspected patients would aid in identifying the problem and allow for a prompt intervention to avert adverse consequences. Since there are not many options for therapy, especially in low-resource areas, the best strategy is a quick diagnosis. Therefore, in the present study, the pattern of neuropathy in patients of CLD due to alcohol, hepatitis B, and autoimmunity was studied.

Materials and Methods

The present cross-sectional study was performed on 100 consenting patients with cirrhosis of any etiology having age >18 years at the Department of Medicine Gandhi Medical College, Hamidia hospital, Bhopal, between January 2021 to September 2022.

Patients with age less than 18 years, diagnosed with vitamin deficiency, diabetic neuropathy, suffering from known parasitic infection, hepatitis A, D, and E hepatopathy, and known cases of cardiac diseases and hereditary diseases were excluded.

Definition

Ultrasonographic evidence of a cirrhotic liver (shrunken or nodular), portal vein dilation, splenomegaly, ascites, or endoscopic evidence of esophageal varices and a combination of supportive laboratory tests, were used to confirm the clinical diagnosis of cirrhosis. All patients were given electrophysiological tests except those whose pedal edema made it difficult to do so.

Detailed clinical examination was done, and apart from basic liver function tests, other special tests like serum vitamin B12 were also done.

Motor and sensory electrophysiological tests were performed in the upper and lower limbs on the right ulnar, median, common peroneal posterior tibial, and sural nerves using Neuroperfect plus-4Ch EMG/ NCV/ EP (Medicaid systems) machine and the motor and sensory nerve conduction results were charted. The results were analyzed and interpreted based on the normal nerve conduction values as detailed in standard references.

Statistical Analysis

Data were recorded in the Microsoft Excel program, and statistical analysis was performed by the SPSS program for Windows, version 25 (SPSS, Chicago, Illinois). Continuous variables were presented as mean ± SD, and categorical variables were presented as absolute numbers and percentages. Data were checked for normality before statistical analysis. A descriptive analysis was performed to obtain the general characteristic of the study population.

Categorical variables were analyzed using the chi-square test or Fisher's exact test. Continuous variables were assessed using ANOVA or independent sample t-test. $P<0.05$ was considered statistically significant.

Results

CLD was more prevalent in the age groups of 31-50 years (65%). There, 24% of patients had ages between 51-70 years, whereas 11% were younger than 30.

CLD was more common in males (75%), in rural areas (89%), those with primary education (65%) and were daily laborers (73%), 63% were consuming alcohol, consuming tobacco (37%), and were smokers (26%).

The most common etiology of liver disease was alcohol consumption (62%), followed by hepatitis B (23%). In 10%, it was cryptogenic, and in 5%, it was due to hepatitis C.

The most common signs and symptoms of patients with CLD were pain & temperature sensation (100%), presence of light/touch/pressure (100%) followed by the presence of vibration (95%), proprioception (95%), ascites (85%), pedal edema (64%) and absence of ankle reflex (56%). The majority of the patients with CLD had Child pugh class B (54%), followed by Class C (32%) and Class A (14%).

The incidence of PN in patients with CLD was 58%. The majority of the patients with CLD had mixed (23%) type of PN followed by a motor (22%) and sensory (13%) PN.

Table 1: Association between etiology of liver disease with PN

Etiology of Liver Disease	PN		Total	P value
	Absent	Present		
Alcoholic	25 (40.3)	37 (59.7)	62	0.011
Cryptogenic	5 (50)	5 (50)	10	
Hepatitis B	10 (43.5)	13 (56.5)	23	
Hepatitis C	2 (40)	3 (60)	5	

Data is expressed as number of patients (percentage)

Of those with alcoholic etiology, 59.7% had PN, half of the patients with cryptogenic etiology had PN, 56.5% of patients PN had hepatitis B as etiology, and 60% of the patients with hepatitis C etiology had PN (p=0.011).

Table 2: Association between the etiology of liver disease with the type of neuropathy

Etiology of Liver Disease	Type of Neuropathy		Total	P value
	Axonal	Axonal +Demyelinating		
Alcoholic	37	0	37	<0.001
Cryptogenic	5	0	5	
Hepatitis B	12	1	13	
Hepatitis C	3	0	3	

Data is expressed as number of patients (percentage)

Out of 37 patients with alcoholic etiology, all 37 had axonal neuropathy; similarly, all the 5 patients with cryptogenic and 3 hepatitis C etiology were axonal. Whereas out of 13 patients with hepatitis B etiology, 12 had axonal and 1 had axonal +demyelinating neuropathy (p<0.001).

The present study obtained a significant association between the etiology of liver disease and a subtype of neuropathy. Out of 62 alcoholic etiology, 24.2% had mixed neuropathy, 19.4% had a motor, and 16.1% had sensory neuropathy. Of 10 cryptogenic etiology, 30.4% had mixed neuropathy, 10% had a motor, and 30% had sensory neuropathy. Out of 23 patients who had hepatitis B etiology, 30.4% had mixed neuropathy, 26.1% had a motor, and none had sensory neuropathy. Out of 5 patients who had hepatitis C etiology, 60% had motor and none had sensory neuropathy.

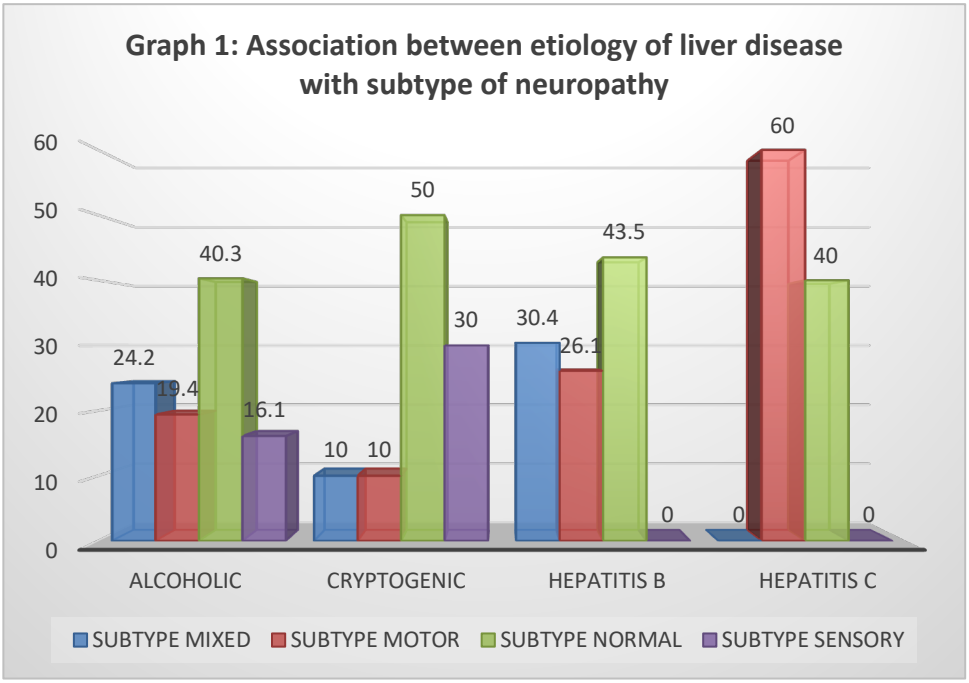

Table 3: Motor nerve conduction test between subtypes of neuropathy

Motor nerve conduction test		Mixed	Motor	Sensory	Normal	P value
Distal Latency (ms)	RMN	3.66±0.51	3.62±1.44	2.10±0.02	3.14±0.56	<0.001
	RUN	3.02±0.58	2.37±1.13	1.61±0.03	2.39±0.39	<0.001
	RCPN	1.39±1.75	2.43±2.05	3.20	3.50±0.39	<0.001
	MRPTN	2.0±3.45	2.61±2.39	3.30	5.14±0.84	<0.001
	LCPN	1.59±2.06	2.11±2.03	2.20	4.80±0.94	<0.001
	LPTN	1.45±2.03	2.40±2.20	4.11±0.03	3.70±0.65	<0.001
	LMN	3.05±1.65	2.93±1.72	3.10	2.91±0.38	0.939
	LUN	2.11±1.18	1.95±1.54	2.40±0.02	2.83±0.58	0.004
Amplitude (ms)	RMN	9.62±2.40	9.31±5.76	13.20	13.87±4.88	<0.001
	RUN	6.30±3.10	6.55±4.96	12.10±0.02	8.99±2.36	<0.001
	RCPN	2.84±3.76	3.22±4.17	8.90	5.95±2.32	<0.001
	RPTN	1.01±1.75	3.79±5.94	16.60	13.5±3.57	<0.001
	LCPN	2.00±2.97	5.92±7.55	8.75±0.11	14.07±4.03	<0.001
	LPTN	2.38±3.25	3.07±4.25	16.26±0.28	4.90±3.48	<0.001
	LMN	8.53±4.88	7.07±4.83	15.73±0.11	11.89±2.37	<0.001
	LUN	4.64±3.04	5.25±4.47	5.70±0.02	8.21±2.80	<0.001
Nerve Conduction Velocity (ms)	RMN	45.94±5.90	43.33±15.93	52.13±0.24	50.73±7.27	0.007
	RUN	47.39±2.51	45.28±22.88	59.3	59.35±10.34	<0.001
	RCPN	19.89±24.0	31.98±25.64	71.35±0.55	52.48±4.54	<0.001
	RPTN	16.2±27.88	23.30±26.46	59.46±0.29	51.73±4.49	<0.001
	LCPN	15.622±20.11	26.18±25.25	51.20±0.36	47.72±5.17	<0.001
	LPTN	18.81±24.29	30.71±29.03	46.500	53.78±6.97	<0.001
	MLMN	42.183±27.88	39.38±25.63	61.500	55.34±7.54	<0.001
	LUN	37.1±20.50	35.04±25.31	51.1	70.13±28.07	<0.001

Data is expressed as mean ± standard deviation

In the Motor nerve conduction test, distal latency was significantly higher in patients with mixed type of neuropathy; however, amplitude and nerve conduction velocity was reduced considerably in mixed type of neuropathy.

Table 4: Sensory nerve conduction test between sub-types of neuropathy

Sensory nerve conduction test		Mixed	Motor	Sensory	Normal	P value
Amplitude (ms)	RMN	7.61±2.86	10.13±4.31	2.9	6.52±2.70	<0.001
	RUN	5.1±1.32	8.28±3.53	6.1	7.95±2.73	<0.001
	RSN	0.61±2.04	10.53±3.74	0	18.44±14.14	<0.001
	LSN	0.76±2.53	15.12±5.11	36.43±0.46	12.87±4.38	<0.001
	LMN	7.17±2.05	10.31±5.03	0	10.61±2.86	<0.001
	LUN	8.92±3.99	7.94±2.05	3.28±0.03	12.06±3.32	<0.001
Nerve Conduction Velocity(ms)	RMN	59.9±14.23	55.83±16.65	40.8±0.59	48.58±10.06	<0.001
	RUN	61.39±16.77	58.46±13.16	41.5±0.98	60.3±10.91	<0.001
	RSN	9.95±32.98	53.73±14.53	0	62.48±12.26	<0.001
	LSN	7.53±24.97	75.32±22.27	0	61.65±11.21	<0.001
	LMN	53.47±12.16	57.2±13.17	0	54.4±8.64	<0.001
	LUN	58.022±11.51	56.29±14.36	57.15±1.24	63.11±12.77	0.115

The sensory nerve conduction test revealed that amplitude and nerve conduction velocity was significantly increased in the mixed type of neuropathy.

Discussion

India is coming to recognize the urgency of addressing liver diseases as a public health issue. The burden of liver disease in India is enormous because the country was responsible for 18.3% of the two million deaths caused by liver disease worldwide in 2015. [8] In the present study, CLD was more prevalent in ages 31-50 (65%). There, 24% of patients were between 51-70 years, whereas 11% were younger than 30. According to a Rotterdam study of 2811 older adults aged more than 65 years, the overall prevalence rate of non-alcoholic fatty liver disease was 35.1%. [9] The study by Periyasamy et al. reported that the age group between 41-50 years showed the highest prevalence of 38 cases (35.5%). [10]

Our study reported that CLD was more common in males (75%) than females (25%). A study by Guy et al. reported that men are 2-fold more likely to die from CLD and cirrhosis than women, according to an analysis by the National Center for Health Statistics reported in 2005. [11]

CLD was more common in patients from rural areas (89%) than in urban areas (11%). There were notable discrepancies between the subjects of the current investigation and the other studies done on patients with liver cirrhosis. The primary causes of this magnitude difference are the various methods for diagnosing neuropathy, the multiple definitions, and the different study contexts. These variations are probably caused by the fact that the demographic profile in the current study is primarily rural, which carries various risk factors, or by the varying degree of liver disease among study subjects included in the study. According to Asadullah et al., the prevalence of ultrasound-diagnosed NAFLD was 65.7% in urban regions and 61.1% in rural areas, respectively, when age and sex were standardized. [12]

Epidemiological studies in several nations have revealed that liver-related mortality is negatively influenced by low socioeconomic level (SES). 13 In our study, most patients with CLD had only received their primary school (65%), while 29% had received their middle education and were daily laborers (73%). Low educational attainment (i.e., little more than primary education) is a factor and a reliable substitute marker of SES. In industrialized and developing nations, it has been discovered to be linked to a higher HBV or HCV infection prevalence. [13]

On analyzing the habits of the patients with CLD, it was found that 63% were consuming alcohol, 37% were consuming tobacco, and 26% were smokers. Lucey et al. reported that about 90% to 100% of heavy drinkers have steatosis, 10% to 35% have AH, and 8% to 20% have alcoholic cirrhosis. [14] The point prevalence of cirrhosis is 1% in persons drinking 30 to 60 g of alcohol daily and up to 5.7% in those consuming 120 g daily. [14] Smoking has a detrimental effect on the development of hepatocellular carcinoma, the advancement of fibrosis, the incidence and severity of fatty liver disease, and the prognosis of patients with liver disease, according to Marti-Aguado et al. [15]

In our study, hepatitis B (23%), followed by alcohol usage (62%), accounted for the majority of causes of liver disease. 10% of cases were cryptogenic, while 5% were brought on by hepatitis C. Chronic hepatitis B and C virus infections, alcohol-related liver disease, and non-alcoholic steatohepatitis are the leading causes of liver cirrhosis. [16] According to the study by Sepanlou et al., NAFLD (59%) is the leading cause of prevalent disease, followed by HBV (29%), HCV (9%), and ALD (2%). [17]

In our study, important clinical signs of patients with CLD were pain & temperature sensation (100%), presence of light/touch/pressure (100%) followed by the presence of vibration (95%), proprioception (95%), ascites (85%), pedal edema (64%) and absence of ankle reflex (56%). According to Kharbanda PS et al study of North Indian patients with liver cirrhosis, five (15%) of the patients had moderate neuropathy symptoms, whereas seven (21%) had clinical indicators. Four (12%) of the patients had a sensory impairment, two (6.1%) had a motor weakness, and five (15.1%) had impaired or nonexistent tendon jerks (mainly ankle jerks). [18] Sensory symptoms were found in 44% of participants, motor weakness in 24.71% of patients, impaired or absent ankle jerks in 21.3% of patients, and sensory impairment in all of these groups: the temperature was absent in 28% of participants, the vibration was absent in 18.70% of participants, touch perception was absent in 15.30% of participants, position sense was lacking in 13.30% of participants, and pinprick was absent in 6.70% of participants. [19] Inconsistencies in clinical characteristics may have resulted from the study's limited sample size or the advanced stages of cirrhosis experienced by the individuals included in the study.

The majority of the patients with CLD had Child pugh class B (54%), followed by Class C (32%) and Class A (14%). In a study by Jain et al., the severity of liver cirrhosis in the study subjects was evaluated using the CP score, which revealed that the majority of the subjects (53.4%) belonged to Child class B,

30.4% to Child class C, and just 31 (16.2%) to Child class A. [19]

In our study, the incidence of PN in patients with CLD was 58%. The majority of the patients with CLD had mixed (23%) type of PN followed by a motor (22%) and sensory (13%) PN. In nerve conduction studies, many found that PN prevalence in cirrhotic patients ranged from 19 to 80%. [18, 20] Mittal et al. electrophysiological studies revealed that 67.39 percent of people with cirrhosis of any etiology also suffer from PN, with 43.45 percent experiencing sensorimotor type and the most common type of PN being mixed axonal degeneration and demyelination. Class C children showed significantly higher PN than other child classes (p=0.04). [21] Seven (21% of the total) patients exhibited clinical signs of PN, as reported by Kharbanda et al. Seventy-three percent, or 24 individuals, reported abnormal results on nerve conduction testing. [21] Regarding patterns, axonal sensory-motor polyneuropathy was the most common one. Neuropathy was present in both patients with and without alcoholic cirrhosis. Neuropathy was not more common or severe when encephalopathy was present. In addition, the severity of the liver disease was unrelated to the neuropathy. From our research, we learned that the prevalence of sensory-motor neuropathy is higher than what was reported by Kharbanda et al. in 2003. [21] Jain et al. found a similar rate of sensorimotor impairment, but most studies found a sensory form of PN. [19]

On comparing the etiology of liver disease with the incidence of PN, it was revealed that of those who had alcoholic etiology, 59.7% had PN, half of the patients with cryptogenic etiology had PN, 56.5% of patients PN had hepatitis B as etiology, and 60% of the patients with hepatitis C etiology had PN. In persistent alcohol drinkers, Vittadini et al. (n = 296) discovered a statistically significant association between liver disease and the severity of polyneuropathy. [22] PN is primarily brought on by prolonged and heavy alcohol usage. [23]

In our study, all the patients with alcoholic etiology had axonal neuropathy; similarly, all 5 patients with cryptogenic and 3 hepatitis C etiology were axonal. Whereas out of 13 patients with hepatitis B etiology, 12 had axonal and 1 had axonal +demyelinating neuropathy. Sensory nerve damage was the majority (34.8%) of the electrophysiological pattern of PNS injury in the study by Jain et al. [19], while motor nerve damage was the primary finding in 26.6% of cases, as indicated by MNCS [21]. Our results are consistent with those of Kharbanda et al. [18] and Chaudhry et al. [24] who also showed reduced evoked potential amplitude in the predominantly axonal degeneration type of PN and reduced conduction velocity in the demyelinating type of the sensory and motor nerves neuropathy in cirrhosis.

The present study obtained a significant association between the etiology of liver disease with subtypes of neuropathy. Hepatitis B and C are increasingly being shown to cause neuropathy in the literature, mainly when Hepatitis C is linked to cryoglobulinemia. According to research by Santoro L. et al. from Italy, 15.3% of people with untreated hepatitis C virus (HCV) infection had PN. The fact that their study included patients who had not yet developed liver cirrhosis could be the cause of the lower incidence of PN. But none of the trial participants tested positive for HCV infection. [25]

In the motor nerve conduction test, distal latency was significantly higher in patients with mixed type of neuropathy; however, amplitude and nerve conduction velocity was reduced considerably in mixed type of neuropathy. The sensory nerve conduction test revealed that amplitude and nerve conduction velocity was significantly increased in the mixed type of neuropathy. SNAP and NCV amplitude was found in 32.8%, 48.5%, 35.8%, and 51.5%, respectively, of the right and left ulnar nerves. It was shown that the right and left sural nerves' amplitude of SNAP and NCV were lowered by 46% and 42%, respectively. [19]

The present study is not devoid of limitations: small sample sizes and cross-sectional natures are a few of them. Non-randomization and the absence of a control group for comparison are other limitations of the present study. There is a need for a large randomized clinical trial to provide strength to present study findings. The lack of previous research on the Indian population is another limitation.

Conclusion

PN is a common complication of CLD related to the etiology of CLD, like alcoholic cirrhosis, hepatitis B virus, and coexisting risk factors like alcoholism and smoking. The PN in CLD is predominantly sensorimotor, mixed axonal degeneration, and demyelinating type. Routine investigations for assessing PN may still not be indicated since the clinical implications are not studied extensively.

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