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Original article

Peripheral Neuropathy Burden in Hemodialysis and Liver Cirrhosis in a Sample of Egyptian Patients

Mohammad Ali Saeed Hassan [1], Mohamed Ghareeb Mohamed [2]

Department of Neurology, Faculty of Medicine, Al-Azhar University, Egypt [1]
Department of Hepatogastroentrology and Infectious Diseases, Faculty of Medicine, Al-Azhar University, Egypt [2]

Corresponding author: Mohammad Ali Saeed Hassan.
Email: m.elomairy@gmail.com
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ABSTRACT

Background: Chronic kidney disease [CKD] and liver cirrhosis [LC] are significant public health challenges in both developed and developing countries, resulting in an impairment in quality of life worldwide. Patients' morbidity and mortality are primarily due to neurological problems that occur as a result of these conditions. Peripheral neuropathy [PN] is a common neurological complication that has been related to the severity of the disability.

The aim of the work: To evaluate the prevalence and patterns of PN in cirrhotic and uremic patients on hemodialysis [HD] at Al-Azhar University Hospitals in Cairo, Egypt.

Patients and Methods: A cross-sectional study was performed on patients recruited from nephrology unit, tropical and internal medicine departments at Al-Azhar University Hospitals in Cairo. Sixty HD patients and sixty cirrhotic patients were investigated. All patients were submitted to clinical evaluation as well as electrophysiological studies and laboratory investigations.

Results: Neuropathy was diagnosed in 76.7% and 73.3% of HD and LC groups respectively. Patients with neuropathy showed significantly higher duration of dialysis and cirrhosis in both groups, higher urea and potassium levels and autonomic presentation [39.1%] in HD group and higher grades “B” & “C” in Child-Pugh classification and motor [18.2%] and asymptomatic [29.5%] presentations in LC group. Sensory symptoms were present in 45.7% and 34.1% in HD and LC groups respectively with no significant difference. Both axonal and mixed types were insignificantly more prevalent than pure demyelinating neuropathy in both groups.

Conclusion: The present study emphasized the high prevalence of PN in patients with CKD on HD and patients with LC with different patterns of presentation denoting wide variety of pathological mechanisms.

Keywords: Chronic Kidney Disease; Liver Cirrhosis; Peripheral Neuropathy; Hemodialysis; Egyptian.

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* Main subject and any subcategories have been classified according to the research topic.
INTRODUCTION

Peripheral neuropathy (PN) is nerve damage or disease that affects sensation, movement, gland or organ function, and other aspects of health, depending on the type of nerve involved [1].

Primary axonopathies [axonal] and primary myelinopathies [demyelinating] are the two main pathological groups of peripheral neuropathies [2].

The diameter of the affected axon may be used to further divide neuropathies. Motor axons and sensory axons responsible for proprioception are among the large myelinated axons. Sensory fibres responsible for light touch, pain, temperature, and preganglionic autonomic functions are among the thinly myelinated axons. Pain, temperature, and postganglionic autonomic functions are all communicated by small unmyelinated fibres [3].

Neuropathy is categorized clinically into three subtypes, mononeuropathy, polyneuropathy, and mononeuropathy multiplex, which is an essential step for proper diagnosis [4,5].

Chronic kidney disease (CKD) and liver cirrhosis (LC) are significant public health challenges in both developed and developing countries, resulting in poorer quality of life worldwide. Because of the various complications associated with these disorders, such as ascites, encephalopathy, esophageal varices, atherosclerosis, myopathy, and both PN and autonomic neuropathy, these patients are at an elevated risk of mortality and morbidity [6–8].

While the majority of the patients were asymptomatic, neurological examination indicated distal superficial or deep sensory loss, as well as distal loss of reflexes, and studies of neuropathy in end-stage renal disease and LC have revealed that 70–100% and 19–80% of these patients, respectively, experience neuropathic symptoms despite meeting current treatment adequacy goals. On nerve conduction findings, sensory neuropathy was more widespread than motor axonal polyneuropathy [8–11]. The precise metabolic abnormality that causes uremic neuropathy is still unclear. Urotoxins such as guanidine derivatives, parathyroid hormone, middle molecules, myoinositol, hyperkalemia, and others have been proposed as potential causes of peripheral neuropathy, although they have yet to be confirmed [12,13].

The idea of middle molecules, which are molecules with molecular weights ranging from 500 to 2000 Daltons, larger than urea and creatinine and thus cleared at a much slower pace by dialysis, was placed into focus for a long time with the advent of renal replacement therapy [12].

Hepatic neuropathy is believed to be caused by metabolic inhibition of axonal membrane activity, vitamin B12 deficiency, metabolic damage to Schwann cells, and even a disordered insulin metabolism, similar to diabetic neuropathy [14,15].

HCV neuropathy is more likely caused by virus-induced immune responses than by direct nerve infection and in situ replication, and direct autoantibody reactions can also play a role in affecting neuronal structures [16].

Serum anti-ganglioside antibodies have been detected in many peripheral neurological disorders associated with viral hepatitis as part of humoral autoimmunity against neuronal antigens [17].

Sural nerve biopsy experiments accounted for the bulk of pathological research; metabolic derangement in Schwann cells is thought to be the culprit. Since it is an axonopathy, long nerve fibres are more affected than shorter fibres since the metabolic needs of the peri karyon with longer fibres are not fulfilled as those of the peri karyon of the shorter fibres. Dying back neuropathy occurs as a result of this. Splitting of the myelin lamellae and separation of the lamella from the neighboring axolemma was revealed by electron microscopy, along with smaller mitochondrial anomalies. Neurofilamental or neurotubular defects are rare [12,15].

AIM OF THE WORK

The aim of the present study was to evaluate the prevalence and patterns of PN in patients with CKD on hemodialysis (HD) and patients with LC as an attempt to understand more about pathophysiological mechanisms and hence approaching proper management as well as better orientation for better care and control.

PATIENTS AND METHODS

Study design, setting and population:

A cross-sectional study was performed on 120 patients recruited from nephrology unit, tropical and
internal medicine departments at Al-Azhar University Hospitals in Cairo during the period from 1st May 2019 till 29th February 2020. Sixty HD patients and sixty cirrhotic patients were investigated and divided into 2 groups.

**Inclusion criteria**

Group A: 60 patients with end stage CKD on HD 4 hours /cycle, 3 cycles / week regardless age, sex or the cause of kidney disease.

Group B: 60 patients with LC regardless age, sex or the cause of liver disease. Patients with LC were classified according to modified Child-Pugh classification into class A [31.9%], class B [40.4%] and class C [27.7%]. Classification is based on total points assigned to one of three classes: Child class A = 5 to 6 points; Child class B = 7 to 9 points; Child class C = 10 to 15 points [18] [Table 1]

**Exclusion criteria:**

Patients who had a renal transplant, patients with other known causes of PN [as hypothyroidism, alcohol, diabetes mellitus, etc.], patients on drugs that may cause PN [as vincristine, phenytoin, cisplatin, etc.] and patients with malignancy or vitamin B12 deficiency.

**Procedures**

All Patients were subjected to the following:

- History taking, including socio-demographic factors, cause, onset, and length of kidney or liver disease, duration of HD, detailed neurological history, with specific attention to the existence of polyneuropathy risk factors and the incidence of symptoms suggesting peripheral neurological damage.

- Neurological examination with special emphasis on peripheral nerve examination using Michigan Neuropathy Screening Instrument [12].

- Laboratory investigations for every patient before electrophysiological examination including CBC, renal and liver functions, albumin, INR, serum K, Ca and Na, thyroid profile, HBA1c and Vit B12.


**Ethical approval:**

It was obtained from the local ethical committees at Al-Azhar faculty of medicine for boys in Cairo. Informed written consent was obtained prior to enrollment in the study. Privacy and confidentiality were maintained throughout the study process using a unique code number for each patient.

**Statistical analysis of data:**

It was carried out using the SPSS computer package version 25.0 [IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp., USA]. For descriptive statistics: the mean ± SD was used for quantitative variables while the frequency and percentage were used for qualitative variables. Chi-square test or Fisher’s Exact test were used to assess the differences in frequency of qualitative variables while Mann-Whitney test was used to assess the differences in means of quantitative non-parametric variables.

The statistical methods were verified, assuming a significant level of p< 0.05 and a highly significant level of p< 0.001

**RESULTS**

The study included 60 patients with CKD on HD and another 60 patients with chronic liver diseases associated with LC. The mean age of HD group was 51.6 ± 9.6 ranged from 25 – 62 years and 55% were females while the mean age of LC group was 54.6 ± 9.4 ranged from 29 – 73 years and the majority [60%] were males. No significant differences were detected between both groups regarding age [P=0.086] and sex [P=0.143]. Neuropathy was diagnosed in 76.7% and 73.3% of HD and LC groups respectively with no significant difference between them. [Figure 1]
Liver cirrhosis group
ropathy, motor and
Neuropathy
73.3
26.7

Values present as number & % were analyzed by Fisher’s Exact.
and albumin didn’t show significant differences
mean levels of creatinine, GFR
were significantly higher among patients with
mean duration of dialysis and cirrhosis was significantly
higher among patients with neuropathy [Table 2].
In HD group, the mean urea and potassium levels
were significantly higher among patients with neuropathy while the mean levels of creatinine, GFR
and albumin didn’t show significant differences
between patients with or without neuropathy [Table 3]

In LC group, the grades “B” & “C” in Child-Pugh
classification were significantly higher among patients
with neuropathy [P=0.002] [Figure 2]
In patients suffered from neuropathy, the main
causes of HD were CGN [32.6%] followed by CIN
[21.7%] and the least was HTN [6.5%] while the main
causes of LC were viral [59.1%] followed by non-viral
causes in 22.7% and mixed causes accounted for
18.2% with no significant differences between patients
with or without neuropathy [Table 4]
In patients suffered from neuropathy, motor and
asymptomatic presentations were significantly higher
among patients with LC whereas autonomic
presentation was significantly higher among patients
on HD. The type of neuropathy didn’t differ significantly
between both groups [Table 5]

Table [2]: Relation of demographic data and duration of illness with neuropathy among the studied groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>With neuropathy</th>
<th>Without neuropathy</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Min – Max</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age [years]</td>
<td>50.1 ± 9.8</td>
<td>50.5 ± 9.4</td>
<td>0.893</td>
</tr>
<tr>
<td></td>
<td>25 – 60</td>
<td>25 – 62</td>
<td></td>
</tr>
<tr>
<td>Duration of dialysis [years]</td>
<td>5.1 ± 1.7</td>
<td>3.4 ± 1.0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>3 – 12</td>
<td>2.5 – 10</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>20 [43.5]</td>
<td>0.763</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>26 [56.5]</td>
<td></td>
</tr>
<tr>
<td>Liver cirrhosis group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age [years]</td>
<td>58.2 ± 7.6</td>
<td>54.8 ± 8.1</td>
<td>0.138</td>
</tr>
<tr>
<td></td>
<td>41 – 73</td>
<td>29 – 63</td>
<td></td>
</tr>
<tr>
<td>Duration of cirrhosis [years]</td>
<td>11.3 ± 3.4</td>
<td>6.5 ± 3.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>8.5 – 17</td>
<td>2.5 – 14</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>26 [59.1]</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>18 [40.9]</td>
<td></td>
</tr>
</tbody>
</table>

Values present as number & % were analyzed by Fisher’s Exact. Values present as mean ± SD were analyzed by Mann-Whitney U test. *: Significant.

Table [3]: Relation between laboratory data and neuropathy among hemodialysis group.

<table>
<thead>
<tr>
<th>Variables</th>
<th>With neuropathy</th>
<th>Without neuropathy</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Min – Max</td>
<td></td>
</tr>
<tr>
<td>Creatinine [mg/dl]</td>
<td>8.09 ± 2.75</td>
<td>8.01 ± 2.65</td>
<td>0.924</td>
</tr>
<tr>
<td></td>
<td>3.4 – 12.5</td>
<td>3.5 – 12.7</td>
<td></td>
</tr>
<tr>
<td>Urea [mg/dl]</td>
<td>158.3 ± 36.2</td>
<td>135.1 ± 34.1</td>
<td>0.037*</td>
</tr>
<tr>
<td></td>
<td>90 – 220</td>
<td>85 – 210</td>
<td></td>
</tr>
<tr>
<td>GFR [ml/min/1.73m²]</td>
<td>92.9 ± 14.7</td>
<td>93.4 ± 13.7</td>
<td>0.910</td>
</tr>
<tr>
<td></td>
<td>39 – 119.9</td>
<td>38 – 120.1</td>
<td></td>
</tr>
<tr>
<td>Albumin [g/dl]</td>
<td>4.07 ± 0.24</td>
<td>4.08 ± 0.29</td>
<td>0.897</td>
</tr>
<tr>
<td></td>
<td>3.71 – 4.39</td>
<td>3.74 – 4.42</td>
<td></td>
</tr>
<tr>
<td>Potassium [meq/L]</td>
<td>5.4 ± 0.56</td>
<td>4.8 ± 0.53</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>4.76 – 6.12</td>
<td>4.22 – 5.68</td>
<td></td>
</tr>
</tbody>
</table>

GFR: Glomerular filtration rate. Values presented as mean ± SD were analyzed by Mann-Whitney U test. *: Significant.
Table [4]: Relation between etiology and neuropathy among the studied groups.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>With neuropathy</th>
<th>Without neuropathy</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In hemodialysis group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGN</td>
<td>15 [32.6]</td>
<td>7 [50.0]</td>
<td>22 [36.7]</td>
<td>0.308</td>
</tr>
<tr>
<td>HTN</td>
<td>3 [6.5]</td>
<td>2 [14.3]</td>
<td>5 [8.3]</td>
<td></td>
</tr>
<tr>
<td>Obstructive CKD</td>
<td>5 [10.9]</td>
<td>1 [7.1]</td>
<td>6 [10.0]</td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td>6 [13.0]</td>
<td>0 [0.0]</td>
<td>6 [10.0]</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>7 [15.2]</td>
<td>0 [0.0]</td>
<td>7 [11.7]</td>
<td></td>
</tr>
<tr>
<td>In liver cirrhosis group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td>26 [59.1]</td>
<td>9 [56.3]</td>
<td>35 [58.3]</td>
<td>0.747</td>
</tr>
<tr>
<td>Non-viral</td>
<td>10 [22.7]</td>
<td>5 [31.3]</td>
<td>15 [25.0]</td>
<td></td>
</tr>
</tbody>
</table>

CGN: Chronic glomerulonephritis, CIN: Contrast-induced nephropathy, HTN: Hypertension, CKD: Chronic kidney disease. Categorical data were analyzed by Chi-square.

Table [5]: Presentation and types of neuropathy among the studied groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hemodialysis group with neuropathy n= 46 [%]</th>
<th>Liver cirrhosis group with neuropathy n= 44 [%]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td>2 [4.3]</td>
<td>8 [18.2]</td>
<td>0.047*</td>
</tr>
<tr>
<td>Sensory</td>
<td>21 [45.7]</td>
<td>15 [34.1]</td>
<td>0.289</td>
</tr>
<tr>
<td>Autonomic</td>
<td>18 [39.1]</td>
<td>2 [4.5]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2 [4.3]</td>
<td>13 [29.5]</td>
<td>0.002*</td>
</tr>
<tr>
<td>Mixed sensory &amp; motor</td>
<td>3 [6.5]</td>
<td>6 [13.6]</td>
<td>0.310</td>
</tr>
<tr>
<td>Type of neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axonal</td>
<td>18 [39.1]</td>
<td>19 [43.2]</td>
<td>0.696</td>
</tr>
<tr>
<td>Demyelinating</td>
<td>10 [21.8]</td>
<td>9 [20.5]</td>
<td>0.881</td>
</tr>
<tr>
<td>Mixed</td>
<td>18 [39.1]</td>
<td>16 [36.3]</td>
<td>0.787</td>
</tr>
</tbody>
</table>

Values present as number & % were analyzed by Fisher’s Exact.

**DISCUSSION**

In our study, the prevalence of PN in the two patients’ groups was high with non-significant statistical difference between the two groups. It was 76.7% in renal patients in agreement with Chandra et al who stated that 78% of HD patients in their study had electrophysiological evidence of polyneuropathy \[21\].

Prevalence was 73.3% in hepatic patients, in agreement with Chaudhry et al who report that the prevalence of PN among liver cirrhotic patient were more than 70% \[22\].

As regards renal functions, only urea showed a statistically significant difference in renal patients with PN. This coincides to some extent with some studies in
which the severity of PN increased as uremia worsens [23]. In agreement with some studies, hyperkalemia also showed a high significant difference in renal patients with PN than in those without PN [24].

In hepatic patients, the prevalence of PN was increasing significantly with worsening according to Child-Pugh criteria which was also noticed by other researchers [14], but this disagrees with few other studies that have shown that there was no relation of severity of cirrhosis to PN [15].

Taking into consideration this observation with the previous result of the non-significant effect of albumin on neuropathy in renal patients, so neurotoxins in hepatic patients remain firstly accused in this complication in hepatic patients.

As regard etiology of CKD, the present study showed that the CKD was more due to CGN followed by CIN then other causes, congenital, obstructive CKD and lastly hypertension. In contrast to our results, study of Macário et al reported that in Portugal the main etiologies for CKD in the patients under HD treatment were DM followed by undetermined and finally arterial hypertension [25].

Also, regarding the causes of LC, we found that the commonest causes were viral hepatitis specially HCV, then due to non-viral causes [Non-alcoholic steatohepatitis [NASH], alcoholic, biliary, etc.] and lastly due to mixed viral and non-viral causes e.g. [mixed HCV & NASH, HCV & HBV and HBV & NASH], so the most common cause of LC in Egyptian patients was viral hepatitis specially HCV and this agrees with other studies which confirmed viral hepatitis as the commonest cause of LC in Egypt [26].

Most of the Indian studies have showed a predominant alcohol related cirrhosis but studies in Western population showed a predominance of hepatitis C and B related cirrhosis [11, 27].

In the present study we found that there was no significant difference in the occurrence of PN and the causes of CKD or LC. This observation suggests that metabolic dysfunction caused by the illness rather than the etiology is the primary determinant of PN.

As regards to the mean duration of dialysis, it was significantly higher among patients with neuropathy [p<0.001]. This disagrees with Santos as well as Anbarasu & Prathiba who reported that there is non-significant correlation between duration of dialysis and neuropathy. This may be explained by the difference in the mean duration of dialysis between our study and their studies [12, 28].

In agreement with some studies, there was a significant relation between duration of LC and neuropathy where the mean duration of illness was significantly higher among patients with neuropathy [p<0.001] [22].

As regards to symptoms and signs of neuropathy, in uremic patients, sensory symptoms were the most common followed by autonomic symptoms then mixed sensory and motor symptoms and the least were asymptomatic.

Our results were also comparable with the study of Jasti et al as they reported that sensory symptoms were the most common then asymptomatic patients were more than patients presenting with autonomic symptoms and the least presented with motor weakness [23]. This disagrees with Anbarasu & Prathiba who reported that the most were asymptomatic [12].

Among patients with LC, we found that the most common presentation was sensory followed by asymptomatic then motor, mixed sensory and motor and lastly autonomic. These findings were consistent with other studies [11].

Patients presented by motor symptoms and asymptomatic patients were more in hepatic group than in renal group with statistically significant difference, while patients presented by autonomic symptoms were more in renal patients with highly significant statistical difference. There were non-significant differences between the two groups as regard patients presenting with sensory or mixed sensory and motor symptoms.

This result denotes different pathological mechanisms in the two groups and also difference in the preferred affected fibers. It may also imply that while neuropathy in hepatic patients may be hidden and should be searched for, it also should be taken seriously and cautiously in renal patients because of the more prevalent and more dangerous autonomic neuropathy.

While some studies showed predominantly demyelinating neuropathy in hepatic patients [29], predominantly axonal [15], mixed axonal and
demyelinating in renal patients \(^{23}\), our study showed that both axonal and mixed axonal and demyelinating neuropathy were more prevalent than pure demyelinating neuropathy in the two groups but without statistically significant difference. This also may denote the wide variety of pathological mechanisms and different stages of affection in patients.

**Study limitations:** First: short period of the study and critical illness led to small samples with no power analysis and further larger scales cohort studies are necessary for more information as well as the study of each possible neurotoxin in each group and the benefits of its proper management. Second: this is a hospital-based study, it cannot reliably represent the prevalence of neuropathy in CKD and LC patients in the community. Third: due to the presence of edema in CKD and LC patients, electrophysiological parameters can be slightly changed. In addition, we know nothing about electrophysiological characteristics of neuropathy before HD and we could not establish if HD improved or worsened PN. Fourth: different definitions of PN. Lastly: different stages of CKD should be included in further studies and not only patients on HD.

**Conclusion:** PN is a common complication of both uremia and LC which may be hidden and presented differently in either illness, so should be carefully searched for and properly studied for better management.

**Acknowledgment:** We are extremely indebted to all members of neurology, tropical, internal medicine and nephrology units in Al-Azhar University hospitals in Cairo for great help and cooperation.

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