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Study of Polyneuropathy Pattern in Post COVID-19 Pneumonia

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ABSTRACT

Background: The COVID-19 pandemic resulted from the coronavirus causes severe acute respiratory syndrome (SARS) (SARS-CoV-2). Although, COVID-19 mainly impacts the respiratory tract and lungs, reports of neurological symptoms are on the rise. Post-infectious neurological diseases caused by an inflammatory response against the nervous system have been reported among them. **Subjects and methods:** The study included 62 patients presented with the clinical picture of polyneuropathy after covid-19 infection (38 males and 24 females). In addition to thorough and complete medical and neurological examinations, all patients were subjected to nerve conduction studies using Medelec-Oxford Synergy EMG device with 20 Hz-10 kHz filter setting and 50 millisecond analysis time.

Results: The mean age of patients with post-COVID-19 polyneuropathy was 45.7 ± 12.49, the most common presenting symptoms were mixed sensorimotor neuropathy (41,9%), the duration of illness was 3.27 ± 0.89 months, the duration of hospitalization due to respiratory symptoms was 15.26 ± 4.73 days, and nerve conduction studies revealed 58.1% had axonal polyneuropathy only, and 30.7% had bilateral peroneal nerves neuropathy.

Conclusions: Patients with COVID-19 may experience polyneuropathy of both lower limbs, which is primarily axonal and affected mainly both peroneal nerves.

Keywords: SARS-CoV-2, Polyneuropathy, Axonal, Demyelinating, Peroneal.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was initially discovered in December 2019 in Wuhan, China, and rapidly spread globally. The World Health Organization proclaimed it to be a pandemic on March 11th, 2020. While the respiratory system is the most commonly affected in SARS-CoV-2 infection, neurological complications of the peripheral and central nervous systems have been documented [1, 2]. Although COVID-19 research is rapidly evolving, novel findings necessitate careful scrutiny in order to formulate a new hypothesis and reach sound conclusions [3].

Neurological manifestations affect approximately 36.4% of SARS-Cov-2 sufferers and extend multiple territories of the central and peripheral nervous systems, while subacute peripheral neuropathy is a rare occurrence [4]. Although COVID-19 has been linked to an increasing number of neurological symptoms [4], it is still unclear which factors are linked to the rising risk of neurologic manifestation. It has been proposed that neurological symptoms occur more prevalent in patients with serious illness but not in those over the age of 65 years [5, 6].

COVID-19's neurological symptoms may be due in part to the biochemical disturbances of cytokine release syndrome (CRS), neuro-inflammation, and sepsis [7]. Neuropathy can also result from the patient's immune response to the viral infection [4]. Virus infection has been linked to immune-mediated neuropathies, including chronic inflammatory demyelinating polyneuropathy and Guillain-Barre syndrome [8]. These neuropathies could be caused by an infection in its early phases, a chronic infection, or a delayed reactivation after a long period of dormancy. The bulk of these neuropathies affect tiny nerve fibers, and neuropathic pain is a common, persistent, and protracted side effect [9].

Peripheral neuropathies in patients with COVID-19 primarily arise from immune mechanisms and the neurotoxic side effects of medications used to treat the virus. To a lesser extent, they may also result from peripheral nerve compression due to extended periods of immobilization in the ICU. Viral neuropathy is not induced by SARS-CoV-2 [10].

SUBJECTS AND METHODS

This is a cross-sectional study that was conducted at Al-Azhar University Tertiary Hospital, Al-Azhar University, Egypt, in the period from the first of June 2021 to the end of February 2022. The study included sixty-two patients (38 male and 24 female) who were diagnosed with covid-19 via clinical picture, MSCT chest and nasopharyngeal swap for performing PCR for COVID 19 virus. Recruited patients were hospitalized to the hospital for 2-4 weeks without connection to mechanical ventilator and presented with clinical picture suggestive of polyneuropathy within 3 months of the onset of covid -19 symptoms.

Exclusion criteria: Patients with acute respiratory symptoms and who were on mechanical ventilation, as well as critically ill patients with polyneuropathy. Patients with other co-morbid diseases that cause polyneuropathy including alcoholism, uremia, diabetes mellitus, hepatic failure and drugs that induce neuropathy. Patients who declined to participate.

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All patients underwent a comprehensive medical and neurological evaluation, which included a detailed history of their age, BMI, height, weight, gender, COVID-19 symptoms (onset, course, duration, severity, oxygen saturation, and treatment regimen), and neuropathic symptoms (onset, course, duration, and severity). The vital signs, skin, respiratory system, extremities, renal system, hepatic system, and cardiovascular system of the patients are all were checked. Neurological investigation included bone, spine, back, gait, cerebellum, sensory systems, motor, cranial nerves, and mental state. Using the Medelec- Oxford Synergy EMG device with a 20 Hz–10 kHz filter setting and a 50-millisecond analysis time, nerve conduction studies were carried out for each patient. All measurements were taken with superficial electrodes, and the temperature of the extremities was maintained greater than 31 degrees Celsius. Under the polyneuropathy protocol, sensory and motor investigations of the ulnar and median nerves (wrist-elbow & finger-wrist) were conducted in one upper extremity, and a motor conduction study of the peroneal nerves and posterior tibial was performed in one lower extremity. Polyneuropathy was defined as a slowing or inability to record an action potential or a low-amplitude action potential in at least two nerves.

Statistical analysis: Suitable statistical procedures were employed, and the findings were tabulated and graphed as needed. $P \leq 0.05$ was regarded as significant. IBM SPSS (Statistical Package for the Social Sciences) v 23 for Windows (Chicago, USA) was used to code, calculate, and analyze the data. Numbers and percentages were used to display the qualitative data. Quantitative variables were shown as mean ± standard deviation (SD).

Ethical approval: The study is in accordance with the Declaration of Helsinki and approved by the ethical committee of Al-Azhar University IRB number: MSR/AZ.AST./NAP020/89/205/3/ 2022. Informed consents to participate in the study were obtained from participants.

RESULTS

The study included 62 patients with clinical signs of polyneuropathy, with a mean age of 45.7 ± 12.49 years, a mean duration of respiratory symptoms of of 3.27 ± 0.89 months, and a mean duration of hospitalization for covid-19 treatment of 15.26 ± 4.73 days (Table 1).

Table (1): Demographic data of the studied patients

Variable	Number	Percent
Sex		
Male	38	61.3%
Female	24	38.7%
Age (years) (Mean ± SD)	45.7 ± 12.49	
Duration of illness (months) (Mean ± SD)	3.27 ± 0.89	
Duration of admission at the hospital for covid-19 treatment (days) (Mean ± SD)	15.26 ± 4.73	

The clinical properties of the patients are described in table (2), as 35.5% of patients had a pure motor presentation, while, 22.6% had a pure sensory presentation, and 41.9% had a mixed sensory-motor presentation.

Table (2): Clinical presentation of the patients in the present study

Variable	N	%
Pure motor	22	35.5
Bilateral foot drop	4	6.5
Distal weakness of both LL	6	9.7
Proximal weakness of both LL	12	19.3
Pure sensory	14	22.6
Stoke hypoesthesia	8	12.9
Allodynia	6	9.7
Mixed sensori-motor	26	41.9

According to nerve conduction study findings, 41.9% of patients had mixed axonal and demyelinating neuropathy, while 58.1% had axonal neuropathy. 30.7% of patients had bilateral peroneal nerves neuropathy, while 27.4% of them had both tibial and peroneal nerves affection (Table 3).

Table (3): Types of polyneuropathies according to the result of nerve conduction study

Types of polyneuropathies	Number	Percent
Axonal polyneuropathy only	36	58.1%
Both peroneal nerves only	19	30.7%
Both tibial nerves only	0	0%
Both tibial and peroneal nerves	17	27.4%
Demyelinating polyneuropathy only	0	0%
Mixed axonal and demyelinating of both tibial and peroneal nerves	26	41.9%

Analysis of F-wave latency across four nerves revealed varying distributions of absent, prolonged, and normal responses, although no statistically significant differences were observed ($p > 0.05$ for all nerves). The left peroneal nerve demonstrated the noteworthy pattern, with 54.8% normal responses, 32.3% absent, and 12.9% prolonged, yielding a p-value of 0.0843 approaching significance. Both tibial nerves showed a predominance of normal responses (51.6% right, 41.9% left) with considerable prolonged latencies (35.5% right, 41.9% left). The right peroneal nerve exhibited the most balanced distribution (45.2% normal, 29% absent, 25.8% prolonged), while not reaching statistical significance. These patterns suggest potential underlying differences in F-wave latency across nerves, particularly in the left peroneal and both tibial nerves. These findings warrant further investigation with larger sample sizes to elucidate the clinical significance of these F-wave latency patterns in neurological assessments of those patients (Table 4).

Table (4): F-wave results of both peroneal and tibial nerves

F wave latency	Absent	Prolonged	Normal	p-value
Right peroneal	18 (29%)	16 (25.8%)	28 (45.2%)	0.4299
Left peroneal	20 (32.3%)	8 (12.9%)	34 (54.8%)	0.0843
Right tibial	8 (12.9%)	22 (35.5%)	32 (51.6%)	0.1817
Left tibial	10 (16.2%)	26 (41.9%)	26 (41.9%)	0.1882

Table (5) compared the electrophysiological characteristics of the right and left peroneal and tibial nerves. For the peroneal nerve, the distal latency and amplitude showed no significant differences between sides ($P = 0.077$ and $P = 0.075$ respectively), whereas the conduction velocity also did not differ significantly ($P = 0.298$). However, a significant difference was observed in the F-wave latency ($P = 0.005$), indicating potential lateral variability in nerve function. Similarly, for the tibial nerve, no significant differences were found in distal latency ($P = 0.076$) and conduction velocity ($P = 0.701$), but a significant difference was noted in amplitude ($P = 0.018$), suggesting side-specific differences in nerve amplitude. The F-wave latency for the tibial nerve did not show a significant difference ($P = 0.775$). These findings highlight the importance of considering side-specific variations in nerve conduction studies, which may have implications for clinical assessments and interventions.

Table (5): Results of nerve conduction studies of both peroneal and tibial nerves

Nerve	Measurement	Right (Mean ± SD)	Left (Mean ± SD)	P-value
Peroneal	Distal latency	3.74 ± 1.15	4.15 ± 1.36	0.077
	Amplitude	1.05 ± 0.34	1.16 ± 0.33	0.075
	Conduction velocity	44.92 ± 6.41	46.25 ± 7.55	0.298
	F-wave	52.52 ± 7.56	48.56 ± 7.44	0.005*
Tibial	Distal latency	4.45 ± 1.26	4.06 ± 1.12	0.076
	Amplitude	8.4 ± 2.55	7.4 ± 1.93	0.018*
	Conduction velocity	44.17 ± 8.03	44.75 ± 8.54	0.701
	F-wave	58.37 ± 10.8	57.8 ± 11.08	0.775

Table (6) presented the statistical relationship between the amplitudes of peroneal and tibial nerves and various patient characteristics, including patients age, duration of illness, duration of hospital admission, O_2 saturation, and O_2 therapy. Significant correlations were found between the duration of admission and the amplitudes of both right and left peroneal and tibial nerves (p-values of 0.001, 0.034, 0.011, and 0.012 respectively) indicating that longer hospital stays are associated with changes in nerve amplitude. No significant relationships were observed between nerve amplitudes and age, duration of illness, O_2 saturation and O_2 therapy as all p-values exceeded 0.05. This suggests that, within the parameters of this study, duration of admission was a critical factor influencing nerve amplitude, whereas other factors such as age, duration of illness, O_2 saturation, and O_2 therapy did not show a significant impact.

Table (6): Comparison between the amplitude of peroneal and tibial nerves and patient characteristics

Variable	Amplitude of Right Peroneal	Amplitude of Left Peroneal	Amplitude of Right Tibial	Amplitude of Left Tibial
Age (Years) P-value	0.307	0.147	0.88	0.986
Duration of Illness (months) P-value	0.986	0.788	0.409	0.453
Duration of hospital admission (days) P-value	**0.001**	**0.034**	**0.011**	**0.012**
O2 Saturation P-value	0.247	0.833	0.904	0.85
O2 Therapy P-value	0.232	0.295	0.078	0.105

DISCUSSION

COVID 19 disease most commonly presented with symptoms of ARDS, but CNS involvement is significant. According to **Mao *et al.*** [12] over one-third of SARS-CoV-2 patients experience neurological symptoms. COVID-19-related neuromuscular diseases are the second most frequently observed neurological complications [13]. In patients with COVID-19, peripheral neuropathies are common and mainly arise from immune mechanisms. Viral neuropathy is not caused by SARS-CoV-2 and also SARS-CoV-2-associated GBS is not caused by a direct viral attack but rather by an immune response to the virus [10]. COVID-19 might not infect nerves directly, their roots, or the anterior horn cells, unlike viruses such as West Nile virus or poliovirus. It is likely to be a post-infectious or a para-infectious complication [14].

The study found that some patients with COVID-19 infection developed polyneuropathy mainly of both lower limbs, with the type of neuropathy being mainly axonal degeneration (58.1% was axonal type while remaining 41.9% mixed axonal and demyelinating). Axonal neuropathy mainly affected both peroneal nerves (30.7% affected both peroneal nerves only while remaining 27.4% affected both tibial and peroneal nerves). No patient involved in our study was diagnosed as Guillian Barre syndrome. **Elshebawy *et al.*** [14] reported that, instead of axonopathy, demyelinating neuropathy was the most common presentation in patients with COVID-19 infection. Also, **Yaranagula and Koduri** [15] discovered that the rate of patients with demyelinating neuropathy was greater than the previously reported incidence of COVID-19-related neuropathies, at 84.62%, because patients presented with Guillian Barre syndrome were included in their studies. The mechanism behind these manifestations has not yet been fully clarified. Evidence from similar viruses indicates that the mechanisms may involve direct viral effects of the virus on the nervous system or post-infection immune-mediated disease as well as neurological complications of the systemic effects of COVID-19 and critical care admission [16].

Our study found that, there were no correlation between the severity of polyneuropathy (amplitude of peroneal and tibial nerves) and age of patients, duration of disease, O_2 saturation, and O_2 therapy. These results indicated that, the pathogenesis of polyneuropathy could be due to immune mechanism or vasculitis and hypercoagulable state while hypoxia and direct invasion by virus had no role in pathogenesis of polyneuropathy because most patients included in the studies developed polyneuropathy after subside of infection and also condition progressive after that. Vasculitis [17] and the hypercoagulable state associated with COVID-19 [18] have been described to cause thrombosis in the vasa nervorum, which leads to peripheral neuropathy. Proposed mechanisms include clotting pathway activation, complement activation, immune dysregulation, and direct systemic endothelial infection caused by viral dissemination [17]. Moreover, hypoxia results in arterial disease, endothelial dysfunction, systemic inflammation, metabolic dysfunction, sympathetic activation, and oxidative stress, as well as pathological and morphological alterations [19]. Oxidative stress is a major contributor to hypoxia-induced neuropathy [20].

Prolonged hospitalization can cause peripheral nerve pathology as a result of critical illness polyneuropathy (CIP) or as a result of prolonged patient positioning [2]. The primary causes of SARS-CoV-2-linked non-GBS-related peripheral neuropathy seem to be the placement of patients, side impacts of drugs employed to therapy manifestations of COVID-19, and pre-existing damage of peripheral nerves [10].

In terms of the patients' clinical presentation, 35.5% of patients presented with pure motor symptoms (6.5% bilateral foot drop, 9.7% bilateral distal weakness, 19.3% bilateral proximal weakness), 22.6% presented with pure sensory symptoms (12.9% stoke hypoesthesia, 9.7% allodynia), and 41.9% presented with mixed sensorimotor neuropathy.

Yoon *et al.* [21] reported that the most frequently reported symptom was paresthesia (39%), of which (6.5%). According to the neuropathy deficit score, the most frequently observed neurological deficits included an increased vibration perception threshold (19.6%), loss of the Achilles reflex (15.2%), reduced pin-prick sensation (10.9%), distal paresis (8.7%), and impaired temperature perception (4.3%). Furthermore, this clinical presentation is consistent with the findings of **Bureau *et al.*** [4] who report cases of mixed sensorimotor neuropathy associated with SARS-CoV-2 infection, noting nearly

complete resolution following immune modulation, symptomatic treatment, and intensive rehabilitation. Both **Abdelnour *et al.* [22]** and **Bureau *et al.* [4]** experienced maximal symptoms at the onset, subsequently marked by gradual enhancement, indicating that GBS is unlikely. Our current study was unique in that it occurred after typical SARS-Cov-2 respiratory symptoms, indicating that it was most likely a post-infectious immune-mediated neuropathy.

CONCLUSION

Patients with COVID-19 infection may present with a clinical picture of polyneuropathy of both lower limbs, with axonal degeneration affecting primarily both peroneal nerves. Neuropathy is caused by a combination of factors, including inflammatory and immune-mediated reactions, vasculitis and the hypercoagulable state as well as prolonged hospitalization.

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Authors contribution:

Dr. Yasser Hamed: conception and supervision of the work.

Dr. AbdElaziz Shokry: Data collection, analysis, and interpretation of data

Dr. Khaled Mohamed Ali Shehata: Drafting the manuscript & supervision of the work.

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