Title of the article: Characteristics and Risk Factors of Persistent Neuropathic Pain in Recovered COVID-19 Patients

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Post COVID-19 Neuropathic Pain

Abstract

Objectives: To assess risk factors for persistent neuropathic pain in subjects recovered from COVID-19 and to study the serum level of neurofilament light chain (NFL) in those patients.

Design: Case-control study

Setting: Persistent post COVID-19 pain

Subjects: 45 patients with post COVID-19 pain and another 45 age and sex-matched healthcare workers who recovered from COVID-19 without pain.

Methods: The included participants were subjected to medical history taking, screening for depressive disorders, comprehensive neurological examination, and pain evaluation using the Douleur Neuropathique en 4 questions (DN4). All patients who had a score at least 4/10 on DN4 were included. The serum NFL level was measured for both groups at the time of patients' enrollment.

Results: The frequency of depression, moderate and severe COVID-19 cases, disease duration and serum ferritin were significantly higher in the cases with post COVID-19 pain than controls. Binary logistic regression revealed that depression, azithromycin use, moderate and severe COVID-19 increased the odds of post COVID-19 pain by 4.462, 5.444, 4.901, & 6.276 times, respectively. Cases with post COVID-19 pain had significantly higher NFL (11.34 ± 9.7, 95%CI: 8.42 - 14.25) than control group (7.64 ±5.40, 95%CI: 6.02-9.27), (P-value= 0.029). Patients with allodynia had significantly higher NFL (14.96 ±12.41, 95%CI: 8.58 - 21.35) compared to those without (9.14 ±6.99, 95%CI: 6.43 - 11.85) (P-value= 0.05).

Discussion: Depression, azithromycin, moderate and severe COVID-19 are independent predictors of persistent post COVID-19 pain. Serum NFL may serve as a potential biomarker for persistent neuropathic pain after COVID-19.

Keywords: SARS-CoV-2; Post COVID-19 pain; Allodynia; Neurofilament light chain; Ferritin

Manuscript

Introduction

The world faced an extraordinary health emergency represented by coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. Although many patients infected with COVID-19 may develop a fever, cough, diarrhea or vomiting, there is evidence that COVID-19 can cause damage to organs other than the lungs [2].

While most researches are racing to study the pulmonary and extra-pulmonary complications associated with COVID-19, few are directed towards the post COVID-19 phase. Although some people had overcome the infection and reached the stage of full recovery, some people still suffer from some residuals such as post-viral cognitive and physical fatigue [3].

Neuropathic pain was reported to be one of the noteworthy manifestations of some viral infections such as herpes zoster virus, human immunodeficiency virus (HIV), Epstein–Barr virus, cytomegalovirus, enteroviruses, and some tropical viruses [4]. Neuropathic pain was also reported in patients recovered from SARS virus, which belongs to the family of coronaviruses and caused a global outbreak in 2003 [5]. So far, there are no available data regarding pain in recovered patients from SARS-CoV-2 infection.

Neurofilament light chain (NFL) is one of the structural scaffolding proteins of the neuronal cytoskeleton. It maintains axonal stability and makes axons grow. In both central and peripheral neurodegenerative disorders, NFL is released into the interstitial fluid due to the disruption of the axonal membrane, and is eventually released into blood and cerebrospinal

fluid (CSF). Therefore, NFL can serve as a sensitive biomarker for screening and follow-up of neuro-axonal injury [6].

In this context, the aim of this study was to evaluate characteristics of neuropathic pain in recovered COVID-19 patients and to study various clinical and laboratory factors related to COVID-19 period as potential risk factors for post COVID-19 pain. We also aimed to assess serum level of NFL in patients with post COVID-19 pain in comparison to those without, and to study its relation to pain intensity.

Methods

Study design and Participants

This case-control study included 90 adults recovered from COVID-19 infection. Recovery state of COVID-19 infection was defined according to World Health Organization (WHO) [7], as improvement in all COVID-19 symptoms, no fever for three consecutive days and two consecutive nasopharyngeal swabs (by real-time reverse transcriptase-polymerase chain reaction) were negative for SARS-CoV-2 at a 24-hour interval. Recovery duration was defined as the duration between the time at which the patient fulfilled the criteria of recovery, and the time of enrollment in the present study.

The patients' group included 45 recovered subjects from COVID-19 patients who were diagnosed as having probable neuropathic pain according to the grading system of the International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG) [8]. Cases with post COVID-19 pain were consecutively recruited from the Neurology Clinic, Beni-Suef University Hospital in the period from September 1, 2020 to November 1, 2020. The control group included another 45 age and sex-matched subjects who

had successfully recovered from COVID-19 without pain. This group was represented by the volunteer healthcare workers category.

Screening phase

Recovered COVID-19 patients, who were seeking medical advice for subjective pain with neuroanatomical distribution in relation to COVID-19 infection, were evaluated at the Neurology Clinic, Beni-Suef University Hospital.

They were subjected to a detailed medical history taking including demographic data, smoking and comorbidities. Screening for depressive disorders was performed at the time of patients' recruitment according to the Diagnostic and Statistical Manual of Mental Disorders (DSM–5) of persistent depressive disorder, which requires the presence of symptoms of depression over a period of at least two years [9]. An expert neurologist did a comprehensive neurological examination in order to fulfill the definition of probable neuropathic pain according to the grading system of the International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG) [8].

The Douleur Neuropathique en 4 questions (DN4) was performed to delineate neuropathic from nociceptive pains, with the cut-off score for the diagnosis of neuropathic pain as 4/10 [10]. If the patient scored ≥ 4/10, the diagnosis of neuropathic pain was established. Whereas, the diagnosis of nociceptive pain was applied if the patient scored < 4/10. All participants who had a score at least 4/10 on the DN4 were included, while all participants who had a score < 4/10 were excluded.

Exclusion criteria for both groups included a history of neuropathy, whether painful or non-painful (before the onset of COVID-19 infection), prominent joint or muscle pains, diseases

known to cause neuropathic pain (ex. autoimmune diseases, malignancy or diabetes) or neurodegenerative disorders. Patients receiving neurotoxic drugs were also excluded.

Pain evaluation

The DN4 [9] is a 10-item checklist; seven items are concerned with the pain characteristics (burning, painful cold, and electric shocks) as well as pain-associated symptoms (tingling, pins and needles, numbness, and itching). The rest are three items related to the neurological examination in the pain area (hypoesthesia to touch, hypoesthesia to prick, and brushing). Hypoesthesia was assessed for both touch and prick. Allodynia was defined if the pain in the painful area was caused or increased by brushing. Further analysis of neuropathic pain included frequency and pain intensity by using the visual analogue scale (VAS) [11]. The frequency of pain (days per week) was also reported.

Data regarding the period of COVID-19 infection

We reviewed the participants' clinical files from the Isolation Hospitals in Beni-Suef Governorate to obtain information about the period of COVID-19 illness regarding the clinical and the laboratory data, in addition to the prescribed medications for COVID-19 infection.

1. Clinical characteristics

The clinical data included symptoms (fever, cough, dyspnea, vomiting, and diarrhea), duration of illness (the time from the onset of the first symptom until disappearance of the last one) and severity of COVID-19 infection. Based on such clinical assessment and initial chest imaging findings and according to WHO classification, severity of COVID-19 infection was graded in to mild, moderate or severe. The mild state was defined by typical symptoms without evidence of viral pneumonia or hypoxia, while moderate or severe cases were defined if there was any clinical and radiological evidence of pneumonia. In moderate infection, patients had SpO2 ≥

90% on room air. In severe infection, one of the following was required: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air. [7]

2. Inflammatory Markers

The results of the laboratory data regarding serum ferritin and C-reactive protein (CRP) at the onset of COVID-19 infection, were obtained.

3. Treatment characteristics

Data regarding the medications used for treatment of the included patients from COVID-19 infection were also obtained from the participants' clinical files. The treatment protocol applied at the selected hospital, followed the COVID-19 treatment Guidelines Panel of National Institutes of Health [12]. The panel recommended using azithromycin 500 mg for 1 day followed by 250 mg once daily for 4 days. For patients with a high risk of prolongation of QT interval, doxycycline can be used. In cases with secondary bacterial infection, ceftriaxone or levofloxacin can be added.

Serum neurofilament light chain (NFL)

NFL measurement was done for both groups at the time of patient enrollment. Five milliliters of the blood sample were obtained and then allowed to clot for 2 hours at room temperature or overnight at 2-8 C before centrifugation for 15 min at 100xg at 2-8 C. The supernatant was aspirated to carry out the assay and to measure NFL.

This ELISA kit was applied to the in vitro quantitative determination of Human NFL concentration in serum, following the manufacturer's instruction (Novus Biological a biotechne brand, USA).

The ELISA kit used the Sandwich –ELISA principle. The micro ELISA plate supplied was pre-coated with an antibody specific to Human NFL. First standards or samples were put to the

micro ELISA plate wells and combined with the specific antibody. Then we added a biotinylated detection antibody specific for Human NFL and Avidin-Horseradish Peroxidase (HRP) conjugate successively to each microplate well and incubated. Unbound components were washed away. The substrate solution was added to each well. Only those wells that bind with Human NFL, biotinylated detection antibody, and Avidin –HRP conjugate would become blue in color. Stop solution was added to terminate the enzyme-substrate reaction, and the color changed into yellow color. The optical density (OD) was measured by using spectrophotometer at a wavelength 450nm ±2nm. The OD value was proportional to the concentration of Human NFL. We could calculate the concentration of human NFL in the samples in relation to the OD of the samples to the standard curve.

Sampling

All recovered COVID-19 patients with persistent neuropathic pain who visited the Neurology Clinic, Beni-Suef University Hospital, in the period from September 1, 2020 to November 1, 2020 and fulfilled the eligibility criteria were included in the study.

Ethical approval and patient consents:

Ethical approval was obtained from ethical committee, Faculty of medicine, Beni-Suef University. Approval number is FMBSUREC/04102020/Hussein_2. Written informed consents were taken from the participants. The study was done in accordance with the principles of the Declaration of Helsinki.

Statistical analysis:

Data were analyzed using IBM SPSS (Statistical Package of Social Science) Version 25. Data were tested for normality of distribution by using Kolmogorov–Smirnov test. Demographics, clinical and laboratory characteristics of patients with post COVID-19 pain and controls were

presented as mean and standard deviation for normally distributed quantitative data, median and inter quartile range (IQR) for not normally distributed quantitative data, and frequency & percentage for categorical data. Independent sample t test was used for comparison between patients and controls in quantitative normally distributed variables, Mann-Whitney test was used for quantitative non-normally distributed variables and Chi-square test was used for categorical variables. Correlation between VAS and neurofilament light chain was done using Spearman correlation test. Binary logistic regression model was done to identify predictors of occurrence of post COVID-19 pain after being adjusted for their potential mutual confounding effect. P-value ≤ 0.05 was considered statistically significant.

Results

The present study included 45 patients with persistent pain after COVID-19 (cases with post COVID-19 pain) and 45 subjects who recovered from COVID-19 without pain (control group). The two groups were matched in age (P-value= 0.39) and sex (P-value= 0.824), (Table 1). Characteristics of post COVID-19 pain were demonstrated in Table (2).

Clinical characteristics of COVID-19 patients in relation to post COVID-19 pain

The frequency of depression, moderate and severe COVID-19 cases were significantly higher in cases with post COVID-19 pain in comparison to the control group (P-value= 0.027, 0.003 respectively). Cases with post COVID-19 pain had also significantly higher disease duration compared to the control group (P-value= 0.001). There was no significant effect of smoking, comorbidities, GIT symptoms or fever on the occurrence of post COVID-19 pain (Table 1).

Inflammatory markers during COVID-19 infection in relation to post COVID-19 pain

Cases with post COVID-19 pain had significantly higher serum ferritin than the control group (P-value =0.011); however, there was no statistically significant difference between both groups in CRP.

Medications used in treatment of COVID-19 in relation to post COVID-19 pain

The medications used among the study population including steroids and antibiotics were demonstrated in Table (1). The frequency of cases treated with Azithromycin was significantly higher among cases with post COVID-19 pain in comparison to control group (P-value <0.001), but there was no effect of steroids on the development of post COVID-19 pain.

Risk factors of post COVID-19 pain by multivariate analysis

Binary logistic regression was done using the following variables: depression, infection duration, azithromycin intake, serum ferritin, severity of COVID-19 infection (moderate versus mild & severe versus mild).

The regression model revealed that depression, azithromycin use, moderate and severe COVID-19 increased the odds of post COVID-19 pain by 4.462 (95%CI: 1.073-18.553), 5.444 (95%CI: 1.631-18.169), 4.901 (95%CI: 1.309 -18.348) & 6.276 (95%CI: 1.134-34.729) times, respectively (Table 3).

Serum neurofilament light chain in relation to post COVID-19 pain

Cases with post COVID-19 pain had significantly higher NLF (11.34 ± 9.7, 95%CI: 8.42-14.25) in comparison to control group (7.64 ±5.40, 95%CI: 6.02-9.27) (P-value= 0.029) (Cohen's d effect size: 0.471) (Figure 1).

Patients with allodynia (37.8% of patients) had significantly higher NLF (14.96 ±12.41, 95%CI: 8.58-21.35) in comparison to those without (9.14 ±6.99, 95%CI: 6.43-11.85) (P-value= 0.05) (Figure 2).

There was a statistically significant positive correlation between neurofilament light chain and VAS (r = 0.484, P-value = 0.001) (Figure 3).

Discussion

The post-COVID-19 phase remains a thorny area, filled with questions that need to be answered. To our knowledge, this is the first study that evaluated the characteristics and risk factors of persistent neuropathic pain in recovered COVID-19 subjects.

The coronaviruses may induce neuropathic pain by direct or indirect mechanism. There is a growing body of evidence indicating that angiotensin-converting enzyme 2 (ACE2) is the gateway for SARS-CoV-2 entry into cells [13]. A high expression of ACE2 has been detected in a variety of cell types including neurons and microglia in the spinal dorsal horn. From this perspective, the neuro-invasive potential of SARS-CoV-2 can be explained [14]. Besides this direct mechanism, SARS-CoV-2 may induce or aggravate neuronal damage by massive release of pro-inflammatory mediators such as interleukin (IL)-6, IL-10, and tumor necrosis factor alpha (TNF-α), called as “cytokine storm” [15].

These proposed mechanisms are consistent with our findings. The higher the chance of exposure to the injurious effect of the virus, either through a longer duration of the COVID-19 infection or the severity of the infection, the greater the likelihood of pain. Therefore, early and appropriate treatment targeting inflammatory mediators triggered by SRAS-COV-2 might reduce the risk of neuropathic pain in recovered subjects.

The present study showed that depression was an independent predictor of neuropathic pain in subjects recovered from COVID-19. Pain and depression are closely related, and one can lead to the other due to shared neuroanatomical and biological mechanisms. It has been shown that the pain pathway shares the same areas of the brain involved in mood management, including

the prefrontal cortex, anterior cingulate, and thalamus [16]. In the context of COVID-19 infection, both depression and neuropathic pain may arise from a common underlying inflammatory process induced by the cytokine storm [17].

Serum ferritin has been documented as an acute phase reactant independent of its main role as an iron transfer protein. In acute or chronic inflammation, serum ferritin leaks out from damaged cells, losing most of the iron on the way. This released iron form can inspire further cell damage mediated by toxic free radicals [18]. This may explain our findings in which serum ferritin was significantly higher in patients with post-COVID-19 pain in comparison to controls. However, the binary logistic regression model in our study revealed that serum ferritin was not a predictor of post COVID-19 pain. The most probable explanation is that elevated serum ferritin may be a product of longer or more severe infection.

The current study showed a result that may seem a bit strange, as taking azithromycin might contribute to an increased likelihood of pain, even though patients only took it for five days. Waetzig et al. examined the effect of azithromycin on differentiated PC12 cells, a well-established model system for neurons. The investigators found that azithromycin caused 47% of neurite in differentiated PC12 cells to be lost after 96 hours, by altering tropomyosin-related kinase A (TrkA) signaling and impeding the function of lysosomes. Thereby, azithromycin may induce autophagy in neuronal cells [19]. It has to be mentioned that increased occurrence of post COVID-19 pain in patients using Azithromycin in our study can be attributed not only to the azithromycin induced autophagy in neuronal cells but also to the significantly longer disease duration and higher severity of COVID-19 infection among the group of patients who used Azithromycin.

Neurofilament light chain aroused considerate attention as a biomarker for neuronal cell damage and eventual neuronal cell death. It is released in the blood and cerebrospinal fluid, depending on the extent of neuroaxonal damage and independent of causal pathways, therefore offering a key advantage not only as a severity biomarker of neuronal degeneration, but also in early detection of subclinical axonal injury [6].

Interestingly, elevation of NFL level was reported by a recent research work to occur as a consequence of COVID-19 infection itself. In such work, NFL was found to be subtly elevated in the serum of patients with mild-moderate COVID-19 infection. This elevation may be due to direct neuronal invasion by the virus, or due to cerebral hypoxia induced by the COVID-19 infection [20]. In the present study, NFL was significantly higher in recovered COVID-19 cases who had post COVID-19 pain than those who didn't have. There was also a statistically significant positive correlation between neurofilament light chain and pain intensity. This may indicate that the elevated NFL is linked to the neuropathic pain and the underlying neuronal degeneration rather than to COVID-19 infection itself.

In accordance with our findings, NFL was found to be a biomarker for the severity of neuropathic pain in pre-diabetic patients with peripheral neuropathy [21].

Axonal injury in painful neuropathy in association with Wallerian degeneration might trigger expression of some voltage-directed sodium channels in damaged neurons leading to sensitization in C nociceptor fibers and consequently the occurrence of allodynia [22]. This perspective supported our finding, as serum neurofilament light chain serving as a candidate marker for axonal injury was significantly higher in patients with allodynia than those without.

The strength of our study was that it is the first study to assess the characteristics and risk factors of persistent neuropathic pain in patients recovered from COVID-19 in addition to the

assessment serum level of neurofilament light chain in those patients in relation to pain intensity.

Our work has some limitations. Firstly, the small sample size. Secondly, we didn't do nerve conduction studies (NCS) to assess neuropathy in patients with persistent post COVID-19 neuropathic pain. However, the severity of clinical neuropathy does not always correlate to NCS findings. NCS can mainly detect large fiber damage but may be insensitive to subtle changes in small nerve fibers. Another limitation was the divergent sampling strategies (cases from a neurology clinic and a control group of health care workers). The age and sex matching of the two groups was performed to minimize bias from the sampling strategy.

We hope this initial work will inspire a future larger study addressing the pathophysiological mechanism of neuropathic pain.

Conclusion

Depression, azithromycin, moderate and severe COVID-19 are independent predictors of persistent post COVID-19 pain. There was a significant increase in the serum level of NFL in patients with persistent post COVID-19 neuropathic pain. The level of NFL in those patients is positively correlated with pain intensity.

Declarations:

Authors report that the content has not been published or submitted for publication elsewhere.

Competing interests

Authors have no competing interest, and the work was not supported by any organization.

Availability of data and materials

Authors report that the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' Contribution

RM participated in study design, interpretation of data and helped to draft manuscript. RE participated in collection and interpretation of data and helped to draft manuscript. WF participated in collection and interpretation of data and helped to draft manuscript. MA participated in laboratory work up and helped to draft manuscript. RI participated in laboratory work up and helped to draft manuscript. AY participated in collection and interpretation of data and helped to draft manuscript. MS participated in laboratory work up and helped to draft manuscript. MH participated in study design, collection, analysis and interpretation of data and helped to draft manuscript. All authors read and approved the final manuscript

Consent for publication

Not applicable

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Not applicable

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Table Legends

Table (1): Demographics, clinical and laboratory characteristics of **cases with post COVID-19 pain** and controls

Table (2): Characteristics of post COVID-19 pain

Table (3): Logistic regression to detect predictors of occurrence of post COVID-19 pain

Figure captions

Figure (1): Serum neurofilament light chain in **cases with post COVID-19 pain** and controls

Figure (2): Serum neurofilament light chain in patients with and without allodynia

Figure (3): Correlation between serum neurofilament light chain and VAS

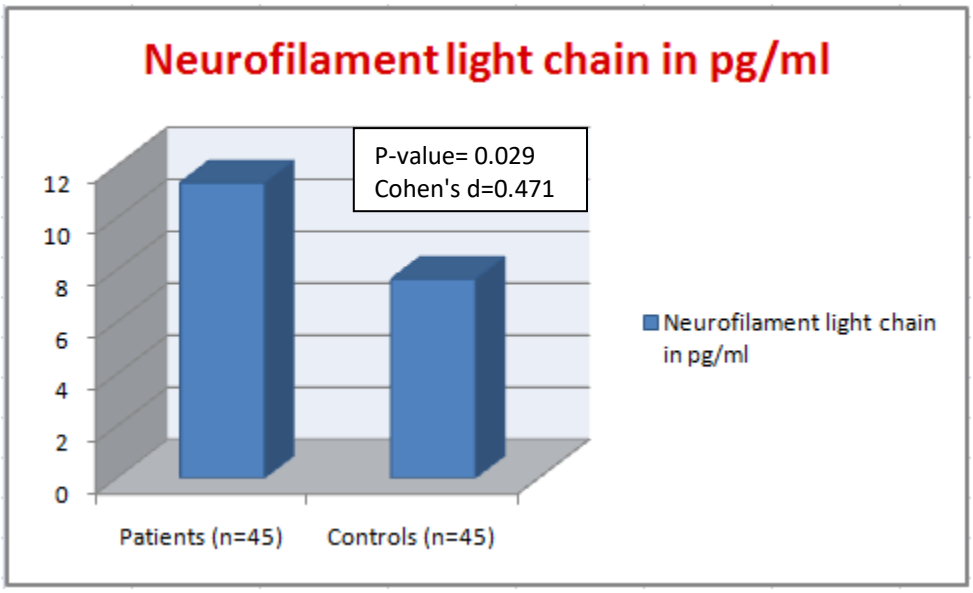

Figure (1): Serum neurofilament light chain in patients and controls

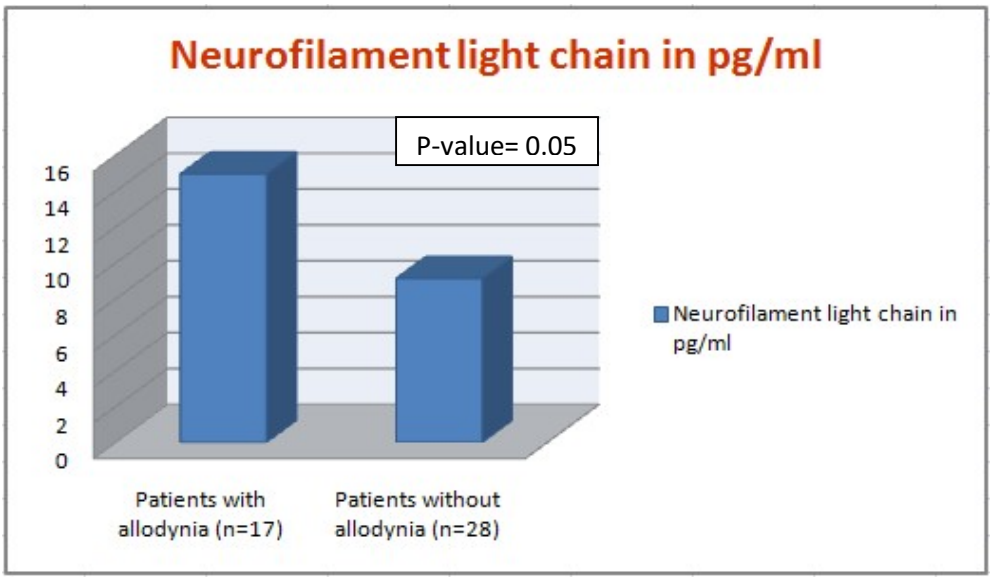

Figure (2): Serum neurofilament light chain in patients with and without allodynia

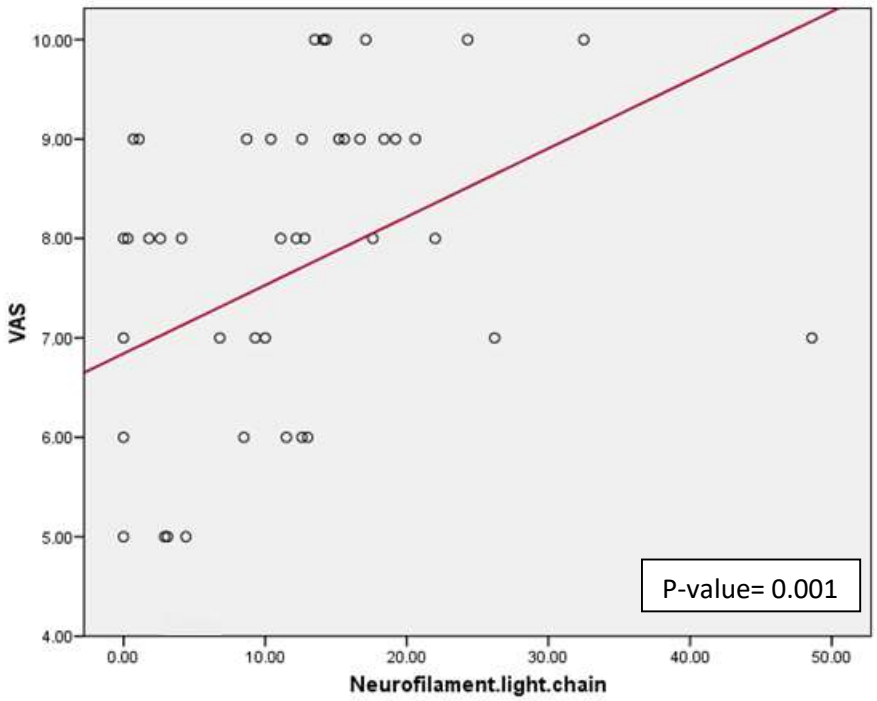

Figure (3): Correlation between serum neurofilament light chain and VAS

VAS: Visual analogue scale

Table (1): Demographics, clinical and laboratory characteristics, and prescribed medications for cases with post COVID-19 pain and controls

			Cases with post COVID-19 pain (*n*=45)	Controls (*n*=45)	*P*-value
Age in years [Mean (SD)]			43 (15.85)	45.71 (13.89)	0.39
Sex [n (%)]		Males	15 (33.3%)	16 (35.6%)	0.824
		Females	30 (66.7%)	29 (64.4%)	
Smoking [n (%)]		Yes	8 (17.8%)	6 (13.3%)	0.561
		No	37 (82.2%)	39 (86.7%)	
Drug abuse [n (%)]		Yes	1 (2.2%)	0	0.315
		No	44 (97.8%)	45 (100.0%)	
Co-morbidities [n (%)]		No	34 (75.6%)	32 (71.1%)	0.118
		HTN	5 (11.1%)	9 (20.0%)	
		Cardiac	4 (8.9%)	0	
		Chronic lung disease	2 (4.4%)	4 (8.9%)	
Depression [n (%)]		Yes	12 (26.7%)	4 (8.9%)	0.027*
		No	33 (73.3%)	41 (91.1%)	
Clinical data related to the period of COVID-19 infection	COVID-19 severity [n (%)]	Mild	11 (24.4%)	27 (60.0%)	0.003*
		Moderate	21 (46.7%)	12 (26.7%)	
		Severe	13 (28.9%)	6 (13.3%)	
	Disease duration in days [Median (IQR)]		18 (14-30)	14 (7-20)	0.001*
	Recovery duration in days [Median (IQR)]		60 (45-65)	60 (30-90)	0.313
	GIT symptoms [n (%)]	Yes	29 (64.4%)	29 (64.4%)	1
		No	16 (35.6%)	16 (35.6%)	

	Fever [n (%)]	Yes	42 (93.3%)	44 (97.8%)	0.306
		No	3 (6.7%)	1 (2.2%)	
Laboratory data related to the period of COVID-19 infection	CRP in mg/ml[Median (IQR)]		24 (13-48)	13(6-50.5)	0.066
	Ferritin in ng/ml [Median (IQR)]		302 (111- 408.5)	190 (71-273.5)	0.011*
Prescribed medications during COVID-19 infection	Steroids intake [n (%)]	Yes	30 (66.7%)	36 (80%)	0.153
		No	15 (33.3%)	9 (20%)	
	Antibiotics [n (%)]	Azithromycin	37 (82.2%)	21 (46.7%)	<0.001*
		Other antibiotics †	8 (17.8%)	24 (53.3%)	

†In patient group, 6 patients received Ceftriaxone, and 2 patient received Doxycycline. In control group, 16 patients received Ceftriaxone, 3 patients received Doxycycline, and 5 patients received Levofloxacin.

CRP: C-reactive protein, GIT: Gastrointestinal tract, IQR: Interquartile range

**P*-value≤0.05 significant

Table (2): Characteristics of post COVID-19 pain

		Cases with post COVID-19 pain (*n*=45)
VAS [Median (IQR)]		8 (6-9)
Frequency (days per week) [Median (IQR)]		7 (3-7)
Site of pain	Hands and feet	9 (20%)
	Arms and legs	30 (66.7%)
	Radicular	6 (13.3%)
Pain character[n (%)]	Burning	15 (33.3%)
	Painful cold	6 (13.3%)
	Electric shock	17 (37.8%)
	Burning& electric shock	5 (11.1%)
	Burning &painful cold	2 (4.4%)
Associated symptoms [n (%)]	Tingling	7 (15.6%)
	Numbness	19 (42.2%)
	Itching	4 (8.9%)
	Pins and needles	6 (13.3%)
	Numbness & itching	2 (4.4%)
	Numbness &Pins and needles	4 (8.9%)
	Pins and needles &tingling	1 (2.2%)
	Pins and needles, numbness & tingling	2 (4.4%)
Hypothesia[n (%)]	Hypothesia to touch	31 (68.9%)
	Hypothesia to prick	14 (31.1%)
Allodynia[n (%)]	Yes	17 (37.8%)
	No	28 (62.2%)
DN4 total score [Median (IQR)]		4 (4 - 4)

DN4: Douleur Neuropathique en 4, VAS: Visual analogue scale, IQR: Interquartile range

Table (3): Logistic regression to detect predictors of occurrence of post COVID-19 pain

		B	Wald Chi square	*P*-value	Odds ratio	95.0% C.I	
						Lower	Upper
Depression		1.496	4.231	0.04*	4.462	1.073	18.553
Severity of COVID-19	Moderate	1.589	5.569	0.018*	4.901	1.309	18.348
	Severe	1.837	4.428	0.035*	6.276	1.134	34.729
Disease duration		0.004	0.043	0.836	1.004	0.969	1.040
Azithromycin		1.695	7.595	0.006*	5.444	1.631	18.169
Ferritin		0.002	1.480	0.224	1.002	0.999	1.005
Constant		-2.943	15.053	0.000	0.053		

R square 0.396, Dependent variable: occurrence of post COVID-19 pain

OR: odds ratio, CI: confidence interval, **P*-values ≤0.05 are considered significant