ORIGINAL ARTICLE

CONTENTS

COVID-19 aggravates well tolerated spinal cord injury – related neuropathic pain

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ABSTRACT

Aim: To compare the intensity of the pain, medication requirements and the evolution of symptoms of neuropathic pain patients with or without COVID-19 infection and to determine whether the severity of the infection influenced these variables.

Materials and Methods: In all, 400 adults with chronic neuropathic pain (≥3months duration) were included-200 positive and 200 negative for SARS-CoV-2. Baseline demographic and clinical characteristics were comparable between groups (age, sex, BMI, comorbidities, pain duration; all $p>0.22$) to meaningful outcome comparison. Pain severity, analgesic consumption, pain course and symptom deterioration were assessed pre-/post-COVID-19 or similar follow-up for the controls.

Results: In COVID-positive group score values raised from 4.6 ± 1.1 to 7.7 ± 1.4 ($p<0.05$), at a more significant extent in women (4.7-8.2, $p<0.01$) as in diabetic patients (4.6-8.1, $p<0.001$). The COVID-negative group had no significant change (4.2-4.3, $p=0.42$). Post-COVID, 72% of infected patients needed more analgesics and 65% of them other drugs, vs. 15% and 12%, respectively, in the negative group $p<0.001$. Pain curves trajectories evidenced steeper increments in COVID-positive (85% vs. 25% in severe vs. mild COVID-19 worsening, $p<0.001$, revealing a directly related pain severity to the infection.

Conclusions: SARS-CoV-2 infection is an aetiologic factor that independently leads to a substantial worsening of chronic neuropathic pain, an increase in analgesic needs, and a more severe symptom burden. The impact is most pronounced among women, diabetic patients and those with severe COVID-19. These results highlight the significance of proactive pain management approaches and longitudinal tracking in this population.

KEY WORDS: neuropathic pain; COVID-19, pain worsening, Visual Analog Scale, analgesic titration, sex; diabetes, disease severity

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ABBREVIATIONS

COVID-19: Coronavirus Disease 2019
CNS: Central Nervous System
ACE2: Angiotensin-Converting Enzyme 2
TMPRSS2: Transmembrane Protease Serine 2
DN4: Neuropathique 4
CRPS: Complex Regional Pain Syndrome
NRS: Numeric Rating Scale
ASIA: American Spinal Injury Association
AIS: Impairment Scale

INTRODUCTION

The severe acute respiratory coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) has been known to infect and kill an increasing number of people in China starting December 2019. During the pandemic, the medical sector faced significant challenges. Of all the infectious respiratory diseases, COVID-19 emerged as one of the biggest public health threats. The neurological manifestation of COVID-19 is one of these. Three categories of pain exist: nociceptive pain, which is produced by tissue disease or damage (e.g., burns); neuropathic pain, which is caused by disease or injury to the sensorimotor system; and a mix of neuropathic and nociceptive pain [1]. Although neuropathic pain can result from a variety of nerve-damaging stimuli in the central or peripheral nervous systems, the clinical presentation of the pain is consistent across the many neuropathic syndromes and causes [2]. Patients usually have paradoxical sensory impressions, with lesion-induced decreased feelings and discomfort as the predominant pleasant symptom. Patients typically encounter these impressions for the first time [1]. When neurological disorders occur, such as when parkinsonian tremor develops following substantia nigra degeneration [3] or when spasticity develops following spinal cord injury [4], it is not uncommon for indications of hypersensitivity and allodynia to coexist. As a subjective sensory symptom, pain differs from these motor disruptions in that it is not apparent, is challenging to quantify, and contains psycho-

logical and emotional elements in addition to physical ones [1-2]. COVID-19 has been associated with a growing evidence of central nervous system (CNS) invasion [5-10]. Moreover, peripheral neurological signs have been linked with COVID-19 [11–13]. The spike (S) glycoprotein Naked,2,3 belongs to the refined structural organization of SARS-CoV-2. Virion tropism and endocytosis are enabled by the surface binding of SARS-CoV-2 to angiotensin converting enzyme 2 (ACE2) receptors, which are upregulated in some host cells [14–18]. The pathophysiology of COVID-19 neurological complications is associated with several pathways [7]. In the endosome, the SARS-CoV-2 spike (S) glycoprotein is cleaved by transmembrane protease serine 2 (TMPRSS2), furin, and cathe-sins B and L (Cat B and L), which enable SARS-CoV-2 to bind to ACE2 and mediate SARS-CoV-2 cell entry [10]. The nasal olfactory epithelium, a likely alternative site with increased receptor binding by SARS-CoV-2, and the olfactory nerve terminals and their peripheral nervous system are the entry points of the virus into the nervous system. Bilinska and co-workers showed ACE2 and TMPRSS2 expression in sustentacular cells of the olfactory epithelium, demonstrating that this sort of cells can resemble SARS-CoV-2 entry and anosmia [19]). Moreover, a new theory that reports an alternative potential transsynaptic route from nose through respiratory epithelium to the brain through the branch of the trigeminal nerve, but remains poorly proven was introduced [20]. Finally, retrograde dissemination through transsynatic passage was suggested as an alternative mechanism. This is achieved by internalisation or externalisation and a speedy axonal transport mechanism of vesicular transportation to transfer virus retroaxonally back to the cell bodies of neurons through microtubules [21]. There is also a lot of controversy on the concept of cytokine storm disorders, and whether some conditions, including COVID-19, shall be considered part of this spectrum [22]; nonetheless, the cytokine storm due to COVID-19 leads to thrombosis and coagulopathy [23]. In addition, SARS-CoV-2 may interact with toll-like receptors, and hence, interleukin (IL)-1 could be synthesized and released [24-25]. When activated, a cascade of biochemical reactions is initiated, involving caspase-1 to cleave pro-IL-1 and inflammasome activation. The aim is to ascertain whether the novel corona virus increased the risk of recurrent (old) episodes or deterioration of well-tolerated preexisting neuropathic pain in persons with spinal cord injuries.

AIM

The aim of this study is to compare the intensity of the pain, medication requirements and the evolution of symptoms of neuropathic pain patients with or without COVID-19 infection and to determine whether the severity of the infection influenced these variables.

MATERIALS AND METHODS

STUDY DESIGN

Type of study: Observational retrospective cohort study

Duration: 10 months (from November 2020 to September 2021)

Setting: Outpatient clinics and community health centers

Number of participants: 400

INCLUSION CRITERIA (GENERAL)

Adults aged 18-65 years [26-27].

Suffering from chronic neuropathic pain (duration ≥3–6 months) or fulfilling formal criteria (e.g., Douleur Neuropathique 4 (DN4) ≥4, Budapest criteria for Complex Regional Pain Syndrome (CRPS))

Pain intensity at baseline: mean Numeric Rating Scale (NRS) ≥4 [28].

DEMANDS SPECIFIC TO CONDITION

Spinal cord injury severity was based on American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade with complete (AIS A or B)

Diagnosis of neuropathic pain (confirmed via clinical evaluation and validated scales)

Well-tolerated pain prior to COVID-19 infection

History of confirmed COVID-19 infection (PCR or antigen positive)

EXCLUSION CRITERIA

Severe psychiatric or neurological disorders

History of substance abuse

Recent surgery or hospitalization unrelated to COVID-19

Patients currently undergoing pain management interventions

Patients with untreated or severe pre-existing neuropathic pain.

Concurrent severe medical conditions that could confound results (e.g., advanced cancer).

Inability to provide informed consent.

DATA COLLECTION

Timeline: Baseline (pre-COVID), post-COVID (3, 6, and 10 months).

ETHICAL APPROVAL

This study was reviewed and approval by ethical committee within College of Pharmacy, University of Alkafeel.

METHODS

SURVEYS AND QUESTIONNAIRES

Brief Pain Inventory (BPI) for pain severity

Neuropathic Pain Symptoms Inventory (NPSI)

SF-36 Quality of Life Questionnaire

Clinical Assessments: In-person assessments conducted at baseline and follow-up visits.

DATA ANALYSIS

Data is presented as Means ± SEM. GraphPad Prism 9.3.1 was used for data analysis and visualization. The number of observations (n) is given in each figure legend. Control and infected individuals were compared using Student's t-test. Simple frequency for demographic information. Pre- versus post-COVID comparisons were tested for mean differences or significant differences with the paired t-test and Chi-square, respectively. Statistical significance was considered at $P < 0.05$.

RESULTS

DEMOGRAPHIC AND CLINICAL FEATURES

Four hundred chronic neuropathic pain patients, 200 with positive-SARS-CoV-2 and 200 with negative-SARS-CoV-2. There was no significant between-group difference in demographic parameters, including age p=0.84, sex ratio p=0.42, BMI (p=0.22), diabetes rate (p=0.77), hypertension rate (p=0.40), previous use of pain medicine p=0.62, and disease duration of neuropathic pain p=0.53, Table 1. These results indicate that the demographic data between the two groups were similar, thus the comparisons of pain-related outcomes were meaningful.

PAIN INTENSITY BEFORE AND AFTER COVID-19 INFECTION

As can be seen in Table 2, between pre- and post-COVID-19 positive patients, pain severity was significantly higher. The average Visual Analog Scale (VAS) score was 4.6 ± 1.1 before vs. 7.7 ± 1.4 (p<0.045) after infection. This decline was most marked for vulnerable subgroups like women (increase from 4.7 to 8.2, p<0.01) and patients with diabetes (increase from 4.6 to 8.1, p<0.001). By contrast, subjects in the COVID-19 negative group showed no significant change in pain intensity over the follow-up period (p=0.42 overall) and small and non-significant increases in pain were apparent in female subjects and those with diabetes. These findings suggest that there may be a formal relationship between COVID-19 and the worsening of neuropathic pain.

PAIN KILLER POST-COVID-19

A significant proportion of patients recruited in the COVID-19 + cohort required escalation in their pain management after the infection, as shown in Table 3. More specifically, 72% of them needed higher doses of medication and 65% had new medications added to their treatment. In comparison, only 15% and 12% of those negative for COVID-19 reported these changes, respectively (both p<0.001), highlighting an enhanced clinical burden among the post-COVID group.

PAIN COURSE AND SYMPTOM WORSENING

Figure 1 demonstrates that pain trajectory over time which is clearly separated between the two group and COVID-19 positive case experienced a sharp rise on pain severity. A higher percentage of patients in the COVID-19 positive group reported worsening of symptoms related to neuropathic pain when compared to the control group as depicted in Figure 2.

ASSOCIATION OF COVID-19 SEVERITY WITH PAIN WORSENING

Analysis depicted in Table 4 revealed that COVID-19 severity was positively associated with worsened pain. Among patients with mild COVID-19, VAS score increased by only a small amount (1.2 ± 0.6) and 25% of patients reported worsening of symptoms p=0.01. The increase in pain was significantly higher in moderate and severe ill patients (2.8 ± 1.2 and 4.3 ± 1.5, respectively), which was reported %65 and %85 as a symptom worsening p<0.001. This gradient implies a direct association between the degree of COVID-19 severity and worsening of neuropathic pain.

DISCUSSION

The current investigation's results are strong evidence for the fact that neuropathic pain perceptions highly escalate among COVID-19 positive patients, dealing with chronic pain. Of interest, the COVID-19 positive and negative group were comparable in demographic and clinical

Table 1. Demographic and clinical characteristics of the study population

Characteristic	COVID-19 positive	COVID-19 negative	p-value
Age (years) (mean ± SEM)	47.3 ± 3.4	45.98 2.3	0.84
Gender (% female)	48%	49%	0.42
BMI (mean ± SD) (kg/m^2)	26.7 ± 2.3	25.8 ± 2.5	0.22
Diabetes (% with diabetes)	41%	39%	0.77
Hypertension (% with hypertension)	52%	47%	0.40
Pre-COVID-19 pain medications (%)	86%	88%	0.62
Duration of pain (months)	17.9 ± 7.3	18.87± 2.9	0.53

Source: compiled by the authors of this study

Table 2. Pain severity before and after COVID-19 diagnosis (mean ± SEM)

Subgroup	Baseline VAS	Follow-up VAS	p-value
COVID-19 positive patients			
Overall	4.6 ± 1.1	7.7± 1.4	<0.045
Female patients	4.7 ± 1.2	8.2 ± 1.3	<0.01
Patients with diabetes	4.6 ± 1.4	8.1 ± 1.5	<0.001
COVID-19 negative patients			
Overall	4.2 ± 0.98	4.3 ± 1.1	0.42
Female patients	4.3 ± 1.1	4.8 ± 1.7	0.51
Diabetic patients	4.5 ± 1.3	4.6 ± 1.05	0.38

Source: compiled by the authors of this study

Table 3: Changes in pain medication usage post-COVID-19

Intervention	COVID-19 positive	COVID-19 negative	p-value
Increase in dosage (%)	72%	15%	<0.001
Addition of new medication (%)	65%	12%	<0.001

Source: compiled by the authors of this study

Table 4. Correlation between COVID-19 Severity and Pain Worsening

COVID-19 severity	Mean increase in VAS score	Reporting worsening symptoms [%]	p-value
Mild	1.2 ± 0.6	25%	0.01
Moderate	2.8 ± 1.2	65%	<0.001
Severe	4.3 ± 1.5	85%	<0.001

Source: compiled by the authors of this study

characteristics (i.e. age, sex, BMI, and co-morbidities), thus these variables are unlikely to confound the effects of pain outcomes on pain. This tends to support the speculation that COVID-19 infection per se may be involves in the modulation of neuropathic pain intensity. The most striking finding is the increase in the severity of pain in the post-infection phase in the COVID-19 positive group. The mean VAS score changed from 4.6 to 7.7 ($p<0.045$) and females and diabetic patients were especially affected. These subgroup discrepancies are consistent with prior literature arguing that females and participants suffering from metabolic comorbidities, such as diabetes, are more susceptible to processes that amplify pain [1, 29-30]. The lack of correlation between pain variation and COVID-19 negative implies a direct relationship between COVID-19 and the severity of neuropathic pain. The higher demand of escalating doses of pain medication in COVID-19 positive patients highlights more severe clinical status. Since 72% of such patients required increased medication dosages and 65% required additional medications, this also indicates that COVID-19 may impact the intensity and refractory characteristics of neuropathic pain. These findings are in line with the evidence of post-viremic pain syndromes and of neuroinflammatory pathways in response to systemic infections [31-32]. Crucially, the time profile for pain trajectory and percentage of patients reporting worsening symptoms show that COVID-19 patients are also at risk of new or progressive symptoms in

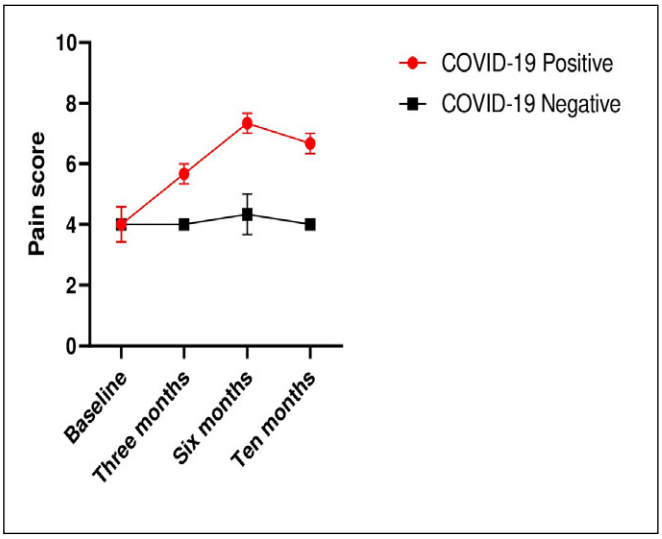

Fig. 1. Pain severity over time (COVID-19 positive vs. negative groups)
Source: Own materials

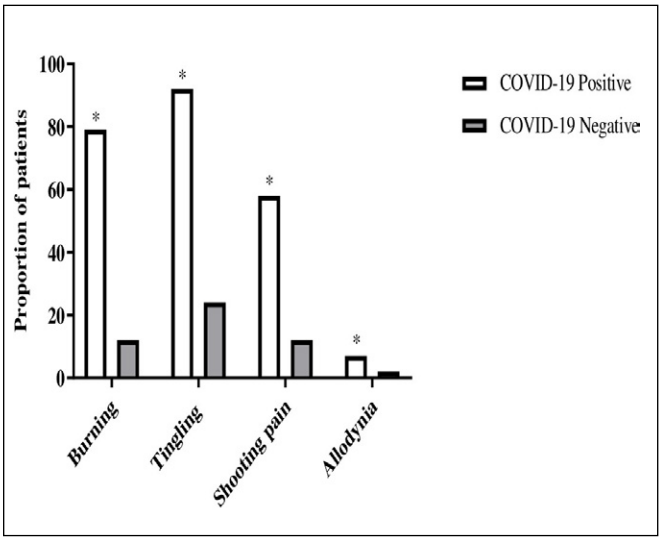

Fig. 2. Proportion of patients reporting exacerbation of neuropathic pain symptoms (n=200, *= significantly different compared to control, t-test)
Source: Own materials

addition to acute pain. The increasing severity of COVID-19 and the stronger pain exacerbation according to the dose-dependent relationship strengthen the pathophysiological relevance, as the more severe the infection the more severe the increase in the pain scores, that is, the worsening of the symptoms. This gradient indicates that mechanisms involving systemic inflammation, cytokine release, and neuroimmune activation might be the basis of the observed effects [32]. It has been reported by a comprehensive systematic review that COVID patients begin to experience neuropathic pain within weeks, and in some cases, months of an infection and that patients with neuropathic pain and COVID often have a worsening of neurologic complications and pain. Joshi and colleagues aimed in their systematic review to study neuropathic pain in both during and post-COVID-19 infection [33]. They presented data about patients who developed neuropathy or neuropathic pain in and around the disease after COVID. Data was extracted and synthesized qualitatively from 939 articles. They made the conclusion that there are neurologic associations with COVID-19 and other coronaviruses, however, new onset of neuropathic pain may be a consequence of subclinical inflammation. Levels of serum IL-6 and intercellular adhesion molecule-1 (ICAM-1) were significantly correlated with painful DSPN (after controlling for age and sex), while not with CRP, Radloff8, TNF-α, adiponectin and IL-1 receptor antagonist [34]. Furthermore, the associations remained significant, even after adjustment for height, waist circumference, blood pressure, cholesterol, smoking, alcohol intake, physical activity, history of previous MI and/or CVA (which was derived by combining the question with similar questions concerning cerebrovascular accident and CVA), history of other neurological diseases, and nonsteroidal anti-inflammatory drug use. Alternative pathogenetic mechanism of the postinfection peripheral neuropathic pain also was suggested. Oaklander and colleagues who studied people with long-term COVID reported that following moderate SARS-CoV-2 infection, the most common, the longest lasting, and disabling small-fiber neuropathy started within 30 days of COVID-19 onset. Many lines of evidence suggest that immune dysregulation is a common sequel to infections [35]. Among 17 tested persons, 59% had at least one test result that favored neuropathy. It consisted of 50% 4/ 8 of autonomic function tests, 17 % 2/ 12 of electrodiagnostic testing, and 63 % 10/ 16 of skin biopsies. Twenty-one days after moderate COVID, one patient was diagnosed with critical illness axonal neuropathy, another with multifocal demyelinating neuropathy, and ten or more with small-fiber neuropathy. No patients had complete recovery of their disease, and the mean follow-up improvement was 52%. Of treated patients, 65% (11/17) had been treated with immunotherapy (corticosteroids, intravenous immunoglobulin (IVIG) or both). In another review article by Attal and co-workers, the most typical viral infections that have been connected to neurological sequelae were reported [36]. These included enteroviruses, poliovirus, HIV, herpes zosters, and a few tropical viruses. the neurological symptoms of COVID-19, specifically myelitis, stroke, and Guillain-Barré syndrome. To precisely quantify the probability of neuropathic pain after COVID-19, longitudinal patient cohorts are necessary. Given the significance of COVID-19's neurological side effects, it is advised that patients who experience neuropathic pain for the first time within a few weeks or months or who do not report worsening neurological symptoms or discomfort do so. When combined, these findings add to the body of information indicating that COVID-19 may be a contributing or precipitating factor for neuropathic

pain, particularly in groups that are already at risk. There are also relevant clinical implications to be made in light of these findings, stressing the relevance of tight pain management in post-COVID subjects and further investigations of the implicated underlying neuroinflammatory pathways. Future research must integrate mechanistic understanding (immunologic, neurovirology, epigenetic) with the best in therapeutics (pharmacologic, neuromodulator, cellular) and trial design.

CONCLUSIONS

SARS-CoV-2 infection is an aetiologic factor that independently leads to a substantial worsening of chronic neuropathic pain, an increase in analgesic needs, and a more severe symptom burden. The impact is most pronounced among women, diabetic patients and those with severe COVID-19. These results emphasize the importance of proactive pain management approaches and longitudinal tracking in this population.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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