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ORIGINAL ARTICLE

Post-COVID 19 and Neuropathic Pain

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Abstract

Objective: In this study, we compared neuropathic pain in post-COVID patients with a healthy control group who did not have COVID-19. We aimed to draw attention to neuropathic pain in the post-COVID period.

Patients and methods: A total of 169 individuals participated in the study. 89 cases constituted the post-COVID group and 80 cases constituted the control group. In our case series, patients were in the post-COVID period and the control groups were assessed with the Douleur Neuropathique 4 (DN4) and Self-Leeds Assessment of Neuropathic Symptoms and Sign (SLANSS) questionnaire for neuropathic pain.

Results: The age, gender, clinical and demographic features of the participants were not statistically different between the groups ($p < 0.01$). A Mann-Whitney test indicated that both S-LANSS and DN4 total scores were greater for the post-COVID group (Mdn = 2) than for the control group (Mdn = 5). The U values for S-LANSS and DN4 were 1941.500 and 1938.0 respectively. Both p values < 0.001.

Conclusion: COVID-19 causes long-term complications, including pain. The etiopathogenesis and treatment of COVID-19 related pain syndromes, which we will see in the coming years, will be revealed by extensive and long-term studies. With this study, which will shed light on the process of COVID and neuropathic pain, it was tried to draw attention to the pain that has an important place in the quality of life in post-COVID-19 patients.

Introduction

Neuropathic pain is a frequent condition caused by a lesion or disease of the central or peripheral somatosensory nervous system. Neuropathy is complex pathophysiology that is not yet fully elucidated, which contributes to underassessment and under treatment.

COVID-19 became a public health crisis that strongly influenced the psychological and physical health of the general population. Muscle pain is one of the most frequent symptoms among COVID-19 patients besides having fever, cough, and dyspnea. A study that involved 59,254 COVID-19 patients from 11 countries revealed that muscle pain occurred to 36% of the patients [1]. To date, the increased or de novo risk of neuropathic pain after COVID-19 has not been clearly established.

In this study, we compared the frequency of neuropathic pain in PCR-negative patients in the third month after COVID infection with a similar control group. The aim of this cohort study will be to determine the presence of neuropathic pain in the post-COVID-19 period. Douleur Neuropathique 4 (DN4) and Self-Leeds Assessment of Neuropathic Symptoms and Sign (S-LANSS) scores will be used to screen for neuropathic pain.

Patients and Methods

The study was a cross-sectional prospective study approved by Hitit University School of Medicine Ethics Committee (349/06.01.2021) and conducted by STROBE guidelines for reporting observational studies (www.strobestatement.org) and the Declaration of Helsinki. All participants gave their informed consent for this study. A total of 169 individuals participated in the study. 89 cases constituted the post-COVID group and 80 cases constituted the control group. The patient group was formed from randomly selected cases who applied to the neurology outpatient clinic in the third month of post-COVID and were PCR negative. There was no difference between the groups in terms of age

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and gender. DN4 and S-LANSS questionnaires were applied to both groups for neuropathic pain. Tests were performed by the same neurologist in both groups. The patients were in the third month of the post-COVID period. In this group of patients who were PCR negative, neuropathic symptoms had started after COVID.

Exclusion criteria from the study

1. Presence of one of the factors that play a role in the etiology of central or peripheral neuropathic pain: Diabetes Mellitus, thyroid disorders, kidney failure, being diagnosed with cancer and/or being under antineoplastic treatment, using drugs that may be involved in the etiopathogenesis of neuropathic pain, a known familial or inflammatory polyneuropathy diagnosis have been diagnosed with stroke and demyelinating disease, spinal cord injury, or myelitis, radiculopathy, mononeuropathy.
2. To be under medical treatment that plays a role in the etiology of neuropathic pain.
3. Alcoholism, exposure to toxins, detection of B vitamin deficiencies.

Inclusion criteria for this study

1. Be in the 18-60 age range.
2. Cases diagnosed as COVID-19 with PCR positivity and PCR negative in the third month of follow-up.
3. No previous neuropathic pain complaints.
4. To be evaluated and excluded in terms of factors that plays a role in the etiology of neuropathic pain.

Questionnaires and Definitions

To screen for neuropathic pain in both groups, DN4 and S-LANNS questionnaires, whose validity and reliability studies were conducted in our country, were used [2,3]. In the study, individuals with a DN4 score of more than four, and S-LANSS score of 12 or more, and those who defined neuropathic pain with both tests were evaluated as having neuropathic pain.

Statistical Analysis and Results

Statistical analyzes in this study were performed using the SPSS (Version 22.0, SPSS Inc. Chicago, IL, USA Hitit University Licensed) package program. A total of 169 individuals participated in the study. 52.7% (n = 89) of the participants were in the patient group and 47.3% (n = 80) were in the control group. The age and gender of the participants were not statistically different between the groups (p = 0.810).

A Mann-Whitney test indicated that both S-LANSS and DN4 total scores were greater for the post-COVID group (Mdn = 2) than for the control group (Mdn = 5). The U values for S-LANSS and DN4 were 1941.500 and 1938.0 respectively. Both p values < 0.001 (Table 1). The median duration of neuropathic pain after COVID in the patient group was an average of 15 days. The most common neuropathic complaint in the post-COVID group; tingling, numbness and burning. We did not detect a prominent localization area in its anatomical distribution.

We also found a significant difference between the mean Visual Analog Scale (VAS) values of the control and post-COVID-19 groups. The mean of VAS was 5.35 (n = 89) in the post-COVID 19 group and 2.86 (n = 80) in the control group (p < 0.001) (Table 2).

Discussion

Reports of neurological sequelae of COVID-19 infection are emerging, indicating both central and peripheral nervous system involvement; symptoms such as confusion, headache and dizziness, and anosmia, ageusia, and nerve pain are now described

Table 1: Mann-Whitney U-test results for the DN4 and S-LANSS total scores per COVID status.

	Group	N	Mean rank	Sum of rank	Mann-Whitney U	Z	Sig
DN4	**Post-COVID**	89	103.22	9187.00	1938.000	-5.221	0.000
	Control	80	64.72	5178.00			
	Total	169					
S-LANSS	**Post-COVID**	89	103.19	9183.50	1941.500	-5.180	0.000
	Control	80	64.77	5181.50			
	Total	169					

A Mann-Whitney test indicated that the both S-LANSS and DN4 total scores was greater for post-COVID group (Mdn = 2) than for control group (Mdn = 5). The U values for S-LANSS and DN4 were 1941.500 and 1938.0 respectively. Both p values < 0.001.

Table 2: The mean Visual Analog Scale (VAS) values of the control and post-Covid-19 groups.

Group Statistics					
	group	N	Mean	Std. Deviation	Std. ErrorMean
Vasskala	Post COVID	89	5,3596	3,00850	3,1890
	Control	80	2,8625	3,05951	3,4206

in retrospective cohorts and case reports [4]. As time progresses long- term neurological complications will be documented following COVID-19 infection. So that it is therefore imperative to keep in mind the possible neurological or other complications that may occur after the acute phase of the disease and to make the clinicians care for such complications. Based on the pain in the acute period in this article, we compared the frequency of neuropathic pain in the healthy control group and the post-COVID-19 case group and then briefly discuss how COVID-19 may interact with the peripheral nervous system to cause pain in the late stages of the disease.

Pain be a primary symptom of many infectious diseases, this COVID-19 is associated with painful symptoms. In patients with COVID-19, even before or without the manifestation of other symptoms related to SARS-CoV-2 infection, suggest a possible sensory dysfunction in the course of this disease. We don't know detailed about the long-term complications after COVID-19. In literature do not have consistent data regarding the prevalence and clinical characteristics of neuropathic pain in patients infected with COVID-19. In this article we found a statistically significantly higher frequency of neuropathic pain with simple questionnaires in PCR-negative patients in the third month of post-COVID-19. Neuropathic pain rare neurologic manifestation of COVID-19, it was found in 2.3% of hospitalized COVID-19 patients in one case series [4]. This study suggested that neuropathic pain will be encountered very frequently as a neurological complication in the post-COVID 19 period, but long-term and comprehensive prospective studies are needed for these complications.

Although the exact mechanism for how SARS-CoV-2 affects the peripheral nervous system is not yet known, Shiers, et al. found that a subset of human dorsal root ganglion neurons were nociceptors that expressed the mRNA of the SARS-CoV-2 receptor, ACE2. They suggested that the nociceptors could form free nerve endings on the skin and luminal organs, serving as a route for SARS-CoV-2 infection [5]. The SARS-CoV-2 genome has 14 open reading frames encoding 27 proteins, including the spike protein that is known to bind ACE2. The spike protein can also be cleaved by furin, priming the protein to bind for NRP1 and NRP2 [6-8]. The ACE2 gene is known to be expressed in human skeletal muscle, thus direct damage to muscle tissue is also a possible cause of myalgia and widespread musculoskeletal pain in the acute phase of COVID-19 infection. The role of systemic inflammation in augmenting musculoskeletal pain, however, is also a likely contributing factor, particularly given the elevated levels of known nociceptive mediators, such as interleukin-6 (IL-6) in the sera of patients with COVID-19 [9].

Barragan-Iglesias, et al. found that type I interferons promote virus-induced pain [10]. It is increasingly clear that deficits in type I interferon responses of several kinds are key players in severe COVID-19 [11]. INF-1 is critical in the immune response to SARS-CoV-2, triggering the expressions of INF-1 inducible genes. Elderly patients mount an inadequate or postponed IFN-1 response, developing hypercytokinemia and increasing morbidity and mortality due to the typical damage pattern in COVID-19 patients with high interleukin levels in the second phase of the disease [12]. In our study, cytokine values were not measured. We believe that these inflammatory changes detected in the acute period may also play a role in the etiology of neuropathic pain associated with post-COVID-19.

Comprehensive studies with the measurement of cytokine values in patients with neuropathic pain will shed light on the etiology of neuropathic pain in the post-COVID period.

In patients with COVID-19, one study found significant increases in kynurenine, kynurenic acid, picolinic acid, and nicotinic acid concentrations in patients' sera, indicative of kynurenine pathway activation. It is notable a study in mice found that kynurenine signaling was associated with nerve injury-induced depression but not pain behaviors, thus whether altered kynurenine metabolism influences pain in COVID-19 remains unclear [11,13,14].

A study of 14 critically ill patients in Italy found that all patients had a loss of intraepidermal nerve fibers (IENFs) and close to half had clinical symptoms of small fiber neuropathy or dysautonomia [15]. Based on this study, interventional studies including histopathological examinations are needed in patients with neuropathy in the post-COVID-19 process. With the clarification of the etiopathogenesis, advances will be made in the treatment of neuropathic pain in patients in the post-COVID period.

It is very important to treat neuropathic pain, which significantly reduces the quality of life and can be treated. Patients with pain, particularly neuropathic pain normally do not respond well to various therapies. Gabapentinoids, antidepressants, tramadol, and topical agents or botulinum toxin can be used among the treatment options according to the comorbid condition in these patients. Non-pharmacological approaches to treatment should also be kept in mind. We believe that neuropathic pain will be observed frequently among the many neurological complications triggered after COVID 19. In neuropathic pain, studies related to etiopathogenesis are needed. In this way, it can be used for neuropathic pain observed in the post-COVID period in treatments aimed at etiopathogenesis rather than symptomatic.

In accordance with the literature when we compared the VAS between the groups, the mean VAS in the post-COVID group was considerably higher than the

group without COVID-19. One study suggests that 45% of COVID-19 patients experience depression, 47% of patients experience anxiety [16]. We believe that concomitant depression and anxiety may be one of the reasons for the increase in the pain scale in the post-COVID 19 groups. One of the limitations of our study was that we did not apply depression and anxiety scales to the groups. The standard neurological examination of patients with post-COVID neuropathy should be supplemented with special diagnostic methods for neuropathic pain. Although we have found that the frequency of neuropathic pain has increased with simple surveys, we think that these data should be supported by wide-ranging and long-term studies.

Conclusion

The future neurological complications for COVID-19 survivors remain uncertain, and if this virus circulates among us for years to come, long-term effects may accumulate exponentially.

A Comprehensive understanding of how COVID-19 affects the nervous system can provide a better framework for managing pain in this disease. We found that neuropathic pain increased in the post-COVID period. This article has highlighted the need for more long-term clinical follow-up data on patients who have had COVID-19 and neuropathic pain, and for attention to the management of neuropathic pain. More extensive studies investigating neuropathic etiology the pain associated with COVID-19 will be useful.

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