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COMMENTARY

What lies behind and beyond acute COVID-19 pain?

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1 | WHAT LIES BEHIND AND BEYOND ACUTE COVID-19 PAIN?

In this issue of the *European Journal of Pain* you will find the article by Oguz-Akarsu and collaborators entitled "Insight into Pain Syndromes in Acute Phase of Mild-to-Moderate COVID-19: Frequency, Clinical Characteristics, and Associated Factors" (Oguz-Akarsu et al., 2021). This observational cohort was one of the handful yet to have described in detail the phenomenon of pain during acute COVID-19 and, to the best of our knowledge, the first to have examined the associations between distinct pain syndromes in such context.

The authors conducted phone interviews with 222 subjects (aged 42 ± 14 years old; 47% female), diagnosed with symptomatic but mostly mild-to-moderate COVID-19 (63% were hospitalized, only 1% in intensive care unit) within the past 1.5 to 3 months. They found that pain was reported by 72%, more specifically: myalgia (50%), headache (49%), pain with neuropathic symptoms (25%) and polyarthralgia (14%). It was noticeable that widespread pain occurred in about a third of their sample and that 59% of them reported having suffered from more than one of the aforementioned pain syndromes. These impressive figures generally fall in line with those of previous work in this field, such as the case-control study published by Soares et al, which showed a prevalence of 65% for new-onset pain and 20% for new-onset chronic pain among COVID-19 survivors (Soares et al., 2021).

Most interestingly, Oguz-Akarsu et al demonstrated that these pain syndromes were statistically associated among themselves. They also had many similar features, for example both headache and myalgia occurred very early, in the first few days of the infection; female sex and anosmia were significantly more common among patients who developed myalgia, headache and/or neuropathic symptoms. Larger samples of well-described patients would be of great interest to conduct additional multivariable analysis and further explore these associations. Nonetheless, currently, these results strongly point to the existence of shared underlying mechanisms for such distinct pain syndromes.

There are, however, more than a few candidates for this role. Disease-specific complications, such as prolonged hypoxemia, loss of cardiopulmonary performance, and thrombosis due to hypercoagulable states may be involved. Moreover, treatment-related elements may also be implicated, for example prolonged immobilization, sedation, pain resulting from invasive procedures, prolonged use of corticosteroids and neuromuscular blocking. Nonetheless, Oguz-Akarsu et al study included largely mild-to-moderate, although clearly symptomatic, COVID-19 survivors, which significantly reduces the probability that any of these factors was a major common driver for the studied pain syndromes in this population. Direct viral invasion of some tissues (such as cartilage, smooth muscle and vessels) may play a role, but direct evidence of invasion to neurons and skeletal muscle remains elusive. Furthermore, although it cannot be denied the contribution of psychological factors,

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such as post-traumatic stress disorder and social isolation, it is unlikely that they alone may explain the pain phenomenon as a whole.

A more likely hypothesis for a common mechanism underpinning these distinct pain syndromes possibly is the inflammatory response. Indeed, a cytokine storm has been described to occur during COVID-19. Moreover, a recently published case-control study has indicated that COVID-19 patients who develop headache during the acute phase of this infection may have a specific interleukin and cytokine signature (Trigo et al., 2021). When compared to patients who had not developed headache, these subjects presented with significantly higher levels of interleukin-10 (Trigo et al., 2021). Similar work for other pain syndromes would certainly be welcome in the near future.

The importance of developing a more in-depth understanding of the biological processes that generate the distinct pain syndromes in acute COVID-19 cannot be overemphasized. Besides possibly leading to significant implications for the treatment of pain in this setting, this knowledge may also shed a light on the mechanisms that will eventually result in the persistence of pain for some of these survivors, as well as on how to predict and prevent it. In this sense, work such as this from Oguz-Akarsu et al, aimed at describing the phenotype and clinical correlations of pain in acute COVID-19, are valuable starter points that may show the direction for further basic research in this field, and corroborate its findings. As the world slowly moves towards the lifting of social distancing measures, and clinical research with in-person interviews and physical examination becomes ever more feasible, the opportunity arises for future studies that will improve our knowledge about the clinical features of pain in the acute COVID-19 setting, and their implications.

CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

GTK wrote the first draft of the commentary and both authors validated the final text.

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