COVID-19 and pain
Review

Pain during and after COVID-19 in Germany and worldwide: a narrative review of current knowledge
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Abstract

Pain is a common symptom accompanying the coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Nonspecific discomfort such as sore throat and body ache are frequent. Parainfectious pain such as headache, myalgia, or neuropathic pain has also been reported. The latter seems to be associated with an autoimmune response or an affection of the peripheral neuromuscular system or the central nervous system because of the viral infection. Furthermore, chronic pain can be a complication of intensive care unit treatment due to COVID-19 itself (such as intensive care–acquired weakness) or of secondary diseases associated with the SARS-CoV-2 infection, including Guillain–Barré syndrome, polyneuritis, critical illness polyneuropathy, or central pain following cerebrovascular events. Data on long-lasting painful symptoms after clinically manifest COVID-19 and their consequences are lacking. In addition, preexisting chronic pain may be exacerbated by limited and disrupted health care and the psychological burden of the COVID-19 pandemic. Medical providers should be vigilant on pain during and after COVID-19.

Keywords: Coronavirus disease 2019, COVID-19, SARS-CoV-2, Acute pain, Chronic pain, Peripheral neuromuscular system, Central nervous system, Guillain–Barré syndrome, Polyneuritis, Critical illness polyneuropathy, Poststroke pain

1. Introduction

Pain is a common symptom accompanying the coronavirus disease 2019 (COVID-19). Acute pain along with respiratory infection may be classified as localized (eg, sore throat or pharyngalgia), remote pain (eg, headache), or generalized discomfort (eg, body ache, limb, or muscle and joint pain). Furthermore, COVID–19–associated pain may occur as a consequence of either the neurotropic properties of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or an autoimmune response to the virus. Although several potential pathomechanisms have been discussed, the exact mechanisms underlying the various persistent pain syndromes associated with COVID-19 are unknown.

This narrative review aims to update and sensitize the readership to pain as a relevant COVID-19 complication. The MEDLINE database was searched for the free text terms “COVID-19” or “SARS-CoV-2” combined with the terms “acute pain” or “chronic pain” (for synonyms, see Table 1) in adults among publications in only German or English until 10/02/2020. Additional citations were obtained from references of the identified publications and ongoing registered trials on the German Clinical Trials Register (https://www.drks.de/drks_web). There were no restrictions on the publication type. First, incidences of any acute pain during COVID-19 in Germany and worldwide will be summarized; second, disorders accompanying COVID-19 that increase the risk for the development of persistent pain will be reported. Third, implications for patients with chronic pain will be discussed.

2. Acute pain associated with the infection but not specific to COVID-19

Aside from the main clinical signs indicating a respiratory infection, such as cough (46%), fever (39%), and rhinorrhea (21%), different pain conditions have been described as occurring during infection with SARS-CoV-2. In the first days of COVID-19 infection, patients complain about acute pain in proximity to the respiratory tract, such as sore throat or pharyngalgia. Furthermore, remote
pain such as headache, abdominal, or chest pain, or generalized pain such as body ache, limb, or muscle and joint pain have been reported in the literature (Table 1). Of these acute pain manifestations, headache and myalgia are the most common and may occur in up to 71% of patients.49,74,76 Headache seems to be heterogeneous and may have similarities with migraine, tension-type headache, and trigeminal autonomic cephalgia.59 The occurrence of pain symptoms seems to be potentiated if patients are infected with SARS-CoV-2 and influenza virus simultaneously.21 Thus, acute pain seems to represent a clinically relevant manifestation of COVID-19. Generally, symptoms seem to be similar to those accompanying a common cold. However, joint and chest pain in particular, and less often headache and myalgia, seem to persist in up to one-fifth of the patients for up to 2 months.11 Possible mechanisms are discussed further below.

Currently, there are little published data from Germany on the issue of acute pain during COVID-19. The first 50 patients treated at the Aachen University Hospital initially reported an internationally comparable frequency of pain symptoms such as pharyngalgia (2%) or sore throat (4%), without relevant differences between those who developed acute respiratory distress syndrome later and those who did not.22 Adults suffered less

### Table 1
COVID-19-associated acute and subacute pain.

| Painful symptoms (synonyms) | German incidence in % | International incidence in % | Potential underlying causes/pathologies | References (examples) | Observational trials or retrospective records (n = total included patients) | Systematic reviews† (n = total included trials) |
|-----------------------------|------------------------|------------------------------|----------------------------------------|------------------------|-----------------------------------------------------------------|-----------------------------------------------|
| Sore throat and throat pain | 4–8.5                  | 5.1–44.4                     | Local infection of the upper respiratory tract | Bhatraju 2020 (n = 24) | Dreher 2020 (n = 50),22 Guan 2020 (n = 1099),32 Guibjardsdson 2020 (n = 1321),33 and Mao 2020 (n = 214) | Li 2020 (n = 10),47 Rodriguez-Morales 2020 (n = 19)63 |
| Pharyngalgia                | 2                      | 13.1–17.4                    | Local infection of the upper respiratory tract | n.f. | Dreher 2020 (n = 50),22 Wang 2020 (n = 138) | Zhu 2020 (n = 38)82 |
| Body ache                  | n.f.                   | 7.7–28.8                     | Cytokine release during common cold         | Aksan 2020 (n = 1)1 | Guan 2020 (n = 1099),32 Guibjardsdson 2020 (n = 1321),33 | n.f. |
| Limb or joint pain and arthralgia | n.f.                   | 2–14.9                       | Arthritis                                | Yang 2020 (n = 52),88 | n.f. |
| Chest pain, chest tightness, and angina | n.f.                   | 2–35.7                       | Pneumonia, cough, lower respiratory tract sign, myalgia, and thromboembolism | Greenan-Barrett (n = 4)30 | Yang 2020 (n = 52),88 | Zhu 2020 (n = 38)82 |
| Abdominal pain             | n.f.                   | 2.2–4.7                      | Diarrhea, gastroenteritis and acute abdomen | Saeed (n = 9)65 | Mao 2020 (n = 214),52 Wang 2020 (n = 138) | Zhu 2020 (n = 38)82 |
| Headache                   | 2                      | 2–71.1                       | Meningeal affection accompanying cerebrovascular events, encephalitis, meningitis, intracerebral hemorrhage, encephalopathy, cranial polyneuropathy, inflammatory (activation of nociceptive sensory neurons by cytokines and chemokines), viral neuro-invasion, hypoxemia, and thrombosis secondary to COVID-19-induced hyper-coagulable states | Bhatraju (n = 24),8 Filatov 2020 (n = 1)26 | Chen (n = 99),13 Dreher 2020 (n = 50),22 Guan 2020 (n = 1099),32 Guibjardsdson 2020 (n = 1321),33 and Huang 2020 (n = 41),27 Liu 2020 (n = 36),29 Mao 2020 (n = 214),52 Tian 2020 (n = 262),73 Tostmann (n = 20),76 Wang 2020 (n = 138),52 Xu 2020 (n = 62),46 and Yang 2020 (n = 52),88 | Asadi-Pooya 2020 (n = 2),5 Chen 2020 (n = 92),14 Li 2020 (n = 10),47 Rodriguez-Morales 2020 (n = 19),63 Tsai 2020 (n = 79),79, Tolebeyan 2020 (n = 20),74 and Zhu 2020 (n = 38)82 |
| Myalgia, muscle pain, skeletal muscle injury/pain, muscle ache, and muscle soreness | 12                     | 3.2–76.9                     | Myositis, ICU-acquired weakness, critical illness myopathy; generalized inflammation and cytokine response | n.f. | Dreher 2020 (n = 50),22 Guan 2020 (n = 1099),32 Huang 2020 (n = 41),27 Liu 2020 (n = 36),29 Mao 2020 (n = 214),52 Wang 2020 (n = 138),52 Xu 2020 (n = 62),46 and Yang 2020 (n = 52),88 | Li 2020 (n = 10),47 Rodriguez-Morales 2020 (n = 19),63 Tsai 2020 (n = 79),79 and Zhu 2020 (n = 38)82 |
| Neuralgia, neuropathic pain, and nerve pain | n.f.                   | 2.3                          | Guillain–Barre syndrome, Miller–Fisher syndrome, and critical illness polyneuropathy | Kallergis 2020 (n = 1),1 Erdi 2020 (n = 1),2 Sedaghat 2020 (n = 1),69 Tostcano 2020 (n = 1),75 and Zhao 2020 (n = 1)69 | Aksan 2020 (n = 1)1,2 | Mao 2020 (n = 214)52 | n.f. |

* Incidences were only included if publications included at least 5 cases.
† Partially including duplicates to mentioned observational trials.
* n.f., none found.
frequently from sore throat compared with a cohort of German children, who were examined between May and August 2020; in this cohort, sore throat had an overall incidence of 8.5% among children <14 years but was more frequent in older children.62

3. Acute pain associated with neurological complications of COVID-19

The above-mentioned nonspecific complaints due to acute infection of the respiratory pathways should be differentiated from more specific symptoms that arise as a consequence of neurological manifestations in patients with SARS-CoV-2 infection.3,7,24,42,80,82 Pain has been described because of involvement of the peripheral (PNS) and central nervous system (CNS) (Table 1). A recent review identified myalgia as the fifth most common symptom during COVID-19.32 In one of the first publications on neurological manifestations in hospitalized patients due to COVID-19, CNS disorders were reported in 25% and PNS symptoms in 9%, with 5% of the latter described as being cases of neuropathic pain (but without a specified definition in this study), and 23% had muscle affection.52

Some coronaviridae members, such as SARS-CoV, Middle East respiratory syndrome (MERS-CoV), and the human coronaviruses HCoV-229E and HCoV-OC43, have been attributed a neuroinvasive character.16,48,85 Hence, because of the probability of a similar pathogenesis, the neurotropism of SARS-CoV-2 has been discussed as one potential mechanism for the direct affection of the CNS and PNS.18,87,91 Although the exact mechanisms are not known thus far, routes of entry to the CNS might include breaching of the blood–brain barrier, the olfactory bulb, or the vagus nerve, whereas direct nerve or muscle injury might be one reason for the observed neuropathy or myopathy.31

It is also possible that immunologic processes, including molecular mimicry between viral proteins and the proteins of the peripheral nerves (gangliosides), might underlie neuromuscular symptoms during acute COVID-19. To date, several reports on Guillain–Barré syndrome (GBS) from different countries, including Germany,44,67 or GBS variants such as cranial polyneuritis and Miller–Fisher syndrome, have been reported to be associated with COVID-19.34 Pain in GBS is often overlooked; although in a previous prospective study on 156 patients with GBS or GBS variants before the current pandemic, 66% of patients reported pain in the acute phase of disease; in 36% of patients, pain was already present in the 2 weeks preceding the onset of other symptoms such as weakness.64

SARS-CoV-2-induced myopathy (or myositis) might explain the relatively high proportion of patients with myalgia and fatigue (44%–70%) and the increased serum concentration of creatine kinase (CK) > 200 U/L (33%) in the group of patients hospitalized due to COVID-19.3,7,24,42,53,83 Myalgia and increased serum CK concentrations25,83 or rhabdomyolysis15,78 were reported in about one-third of patients infected by other coronaviruses as an indication of a potential viral myositis. Unfortunately, there are no data available yet on further diagnostics in patient populations assessed during the current pandemic, such as electromyography, imaging of skeletal muscle, or histological findings. However, the relatively low cut-off value of >200 U/L, which was used to define the CK increase,62 does not allow the differentiation between myogenic or neurogenic origin, because a slight increase in CK might also be related to neuropathies of a different origin, whereas in the course of myositis, significantly higher serum CK concentrations are usually expected.93 From a pathomechanistic point of view, both direct nerve and muscle affection as well as an autoimmune reaction might potentially play a role. A SARS–CoV-induced cytokine storm could be hypothesized as one possible underlying mechanism for the symptom complex of persistent myalgia and fatigue while also explaining other symptoms such as parainfectious headache and joint pain.51

Reports from Germany on this topic are rare. The only available source refers to the first 50 patients treated at the Aachen University Hospital, for whom headache was reported in 2% and myalgia in 12%,22 in the lower range of incidence compared with the international data.

4. Postinfectious pain associated with expected long-term complications

Currently, there are very little data on the long-term complications of COVID-19. In one study, an Italian cohort of 143 patients was assessed 60.3 ± 13.6 days after onset of the first COVID-19 symptoms; a high proportion of individuals still reported pain, with the most frequent types being joint pain (27.3%) and chest pain (21.7%), followed by headache and myalgia.11 In a cohort of 120 French patients, the only reported pain symptom from a list of postdischarge persistent symptoms after a mean of 110.9 days was chest pain, which was reported in 10.8% of patients.29 In a UK cohort of 100 patients, pain was the sixth most frequently reported persistent symptom on average 48 days after discharge, especially in patients who had been treated at an intensive care unit (ICU; 30%) but also in about 15% of the ward patients.35 Furthermore, regarding the recommended prone position during moderate to severe acute respiratory distress syndrome due to SARS-CoV2, complications such as peripheral nerve injury have recently been reported,50 which may lead to chronic neuropathic pain.

Along with pain, critical illness neuropathy (CIN) and myopathy (CIM; both CINM) have been found to be very common in patients who are seriously ill due to coronavirus infection.4,46,78 According to the current clinical experience, patients who receive ICU treatment due to COVID-19 very often develop motor deficits at an early stage, which could be due to CINM. Until now, it has remained unclear whether CINM after COVID-19 develops faster and is more pronounced than CINM after ICU treatment due to other primary diseases. However, because CINM is known to be associated with factors such as disease severity, the presence of an acute respiratory distress syndrome, the use of the prone position,56 and neuromuscular blocking17 high incidences should be expected because of their association with the course of COVID-19 treatment. It is well known that patients with CINM report pain, dysesthesia, and motor weakness that negatively affect their quality of life.53,58,66 In Germany, outside of the mention of 2 cases of CIN of 38 critically ill COVID-19 patients,17 medium-term56 and long-term data are lacking. International data on the medium-term and long-term outcome of ICU-acquired weakness after treatment for COVID-19 are also rare and restricted to single case reports. In Italy, the case of a 62-year-old female COVID-19 patient who developed diffuse and symmetrical muscle weakness after a long stay in the ICU was followed 60 days after initiating rehabilitation; functional impairment improved except for mild weakness in her lower limb proximal muscles.6

In GBS, most attention is given to the progression of weakness and its recovery. However, in a previous prospective study before the current pandemic, 38% of the patients reported pain even after 1 year,64 and residual sensory impairment, including pain symptoms, persisted in 33% even 2 years after onset.27 Therefore, pain as a symptom in patients with GBS associated with COVID-19 requires attention.
Furthermore, it has been recognized that cerebrovascular events are an important neurological manifestation of COVID-19, including both ischaemic stroke and intracerebral haemorrhage. A German multicentre study on 165 patients hospitalized for COVID-19 reported an increased risk of acute stroke among patients with severe COVID-19. Although long-term data from cohorts with COVID-19-associated cerebrovascular diseases are lacking, it is generally known that poststroke pain, including central neuropsychic pain, spasticity-induced pain, musculoskeletal pain, and headache, has an overall prevalence of up to 65%, with differences depending on the pain type and follow-up period (overview in Refs. 36, 77), and remains undiagnosed and undertreated. Nevertheless, poststroke pain is associated with the presence of depression, cognitive dysfunction, and impaired quality of life. These aspects should also be considered in the rehabilitation of patients with COVID-19-associated cerebrovascular diseases.

Other factors may also induce pain symptoms among COVID-19 patients. Single case reports have described encephalitis as complications of COVID-19. Although these conditions can be theoretically associated with persistent chronic pain, the available data are rare.

Importantly, limited access to rehabilitation services due to ongoing lockdowns and reduced health care services may potentially impact the resolution or chronification of pain symptoms.

5. Impact of the COVID-19 pandemic on chronic pain patients

Because of compromised health care services and their limited accessibility during the pandemic, socioeconomic disadvantages, and exposure to enhanced psychological stressors (eg, because of social disconnection or the risks of increased social proximity), patients with chronic pain may experience an exacerbation of symptoms. Therefore, special recommendations for the care of chronic pain and palliative care patients have recently been published.

Interestingly, in a study investigating 43 chronic German pain patients within the first 2 weeks after the initial lockdown (ie, including, among other restrictions, prohibitions of private gatherings of any kind, closures of recreational and day-care facilities, and access to schools), closures of shops not urgently needed for daily life, cancellations of all planned admissions to hospitals that were not emergency-related, strict regulations for the visitation of patients in hospitals or nursing homes, cancellations of public events, and travel restrictions), pain intensity remained stable or even improved. In this time period, only 11.6% of the entire cohort reported a pandemic-associated worsening of pain, whereas 48.8% reported a worsening of mood. Rumination scores of the pain catastrophizing scale also decreased during that time. Further analysis revealed that patients who had experienced a change in social life as a consequence of pandemic restrictions had higher pain ratings than those without, and feelings of helplessness increased in those patients with higher pain ratings. The results therefore suggest a shift of attention from the chronic pain condition towards the imminent threat of a global pandemic at the beginning of the lockdown. In view of the often postulated stages that are passed through in the course of pandemics, it seems plausible that patients were still in the so-called “heroic” or “honeymoon” phase at the time of the survey. These findings are somewhat supported by the results of another German preliminary study, in which 56.3% of 197 patients reported a stable condition, 37.1% an increase, and 6.6% a decrease of pain intensity within the early phase of the lockdown.

To investigate the development of the assessed parameters in the course of the pandemic will therefore be of great interest, especially because 82 participants (73.2%) in another German study reported a worsening of their pain disorder in the later pandemic phase. However, these self-reported subjective worsening of the pain disorder could not be confirmed when comparing the data on current pain intensity to results of previous data assessment before the pandemic. The authors therefore hypothesized that although the subjective impact is considered high, chronic pain is a relatively stable disease that does not undergo relevant changes due to external factors such as the COVID-19 pandemic. To the best of our knowledge, similar studies from other countries with different pandemic courses have not yet been published. Follow-up examinations regarding differences in pandemic restrictions in various countries are therefore needed to more closely investigate the impact of the COVID-19 pandemic on chronic pain.

6. Limitations

Since the beginning of the pandemic, a multitude of COVID-19-related case reports and other articles have been published on a daily basis. Hence, reviews are almost immediately outdated. Most available data are from countries in Asia, likely because of it being the location at which the pandemic launched. Most data are also from hospitalized patients with moderate and more often severe courses of illness. For the benefit of clinical care, knowledge is mostly obtained from retrospectively assessed data, not registered trials, preprints, single case reports, or hosts of reviews focusing on repetitive issues using heterogenous definitions, which is an approach that has recently been criticized for partly compromising data quality. Furthermore, during the literature search, it is difficult to differentiate between reports on newly obtained data and repeatedly analysed data. Thus, we have chosen a subjective selection of the most significant citations without claiming to be comprehensive. Reliable data of long-term outcomes should not be expected before 2021.

7. Resumé and outlook

Prospectively and systematically assessed data on the incidence and prevalence of acute and persistent pain symptoms due to coronavirus infections, especially COVID-19, and the exact pathomechanisms are missing. Current knowledge suggests that pain accompanying COVID-19 might result from viral neurotropic properties, activation of nociceptive sensory neurons by cytokines and chemokines, direct affection of peripheral nerve and muscles, and autoimmune reactions having the potential to increase the incidence of chronic pain syndromes and worsen preexisting chronic pain states. In addition, the social and economic consequences of the pandemic may impact pain. Therefore, health care providers should be vigilant to pain during and after COVID-19.

Investigations into increase of incidences of persistent pain related to the current pandemic and complications for patients with chronic pain related to the current pandemic are planned or have already started. As preventive therapeutic procedures within acute treatment and rehabilitation protocols are known to be promising, special programmes should be established for post-COVID-19 patients to prevent persistent neuromuscular symptoms, including pain.
Disclosures
The authors have no conflict of interest to declare.

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