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The legacy of neuropsychiatric symptoms associated with past Covid-19 infection: a cause of concern.

Neuropsychiatric symptoms associated with past Covid-19

Abstract

Although primarily affecting the respiratory system, growing attention is being paid to the neuropsychiatric consequences of SARS-CoV-2 infections. Acute and sub-acute neuropsychiatric manifestations of COVID-19 disease and their mechanisms are nowadays, and more than ever, better studied and understood; on the contrary, many months or years will be necessary to fully comprehend how significant the consequences of such complications will be. In this editorial, we discuss the possible long-term sequelae of the COVID-19 pandemic, deriving our considerations on experiences drawn from past coronaviruses' outbreaks, such as the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS), and from the knowledge of the mechanisms of neurotropism and invasiveness of SARS-CoV-2. Acknowledging the global spread of COVID-19 and the vast number of people affected, to date amounting to many millions, the matter of this pandemic's neuropsychiatric legacy appears concerning. Public health monitoring strategies and early interventions seem to be necessary to manage the possible emergence of a severe wave of neuropsychiatric distress among the survivors.

Key Words: Covid-19; neuropsychiatric symptoms; neuropsychiatric sequelae; mental health; Post-Traumatic Stress Disorder; depression

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Core Tip: While acute neuropsychiatric manifestations of COVID-19 are object of study, far less is known about long-term neuropsychiatric sequelae of COVID-19 infection. Much of the knowledge about this topic can be drawn from past coronaviruses outbreaks and from the study of the mechanisms through which SARS-CoV-2 harms the Central Nervous System (CNS). A relevant wave of both psychiatric (anxiety and

depressive disorders, post-traumatic syndromes) and neurological symptoms could be expected. There will be a vital need for monitoring and early intervention towards this burden of potential neuropsychiatric distress.

INTRODUCTION

Starting December 2019, several cases of pneumonia of unknown etiology were reported in Wuhan, China. A novel coronavirus was identified as the cause of such illnesses, and on January 12, China made public the gene sequence of the new SARS-CoV-2 coronavirus[1]. On January 30, 2020, the World Health Organization (WHO) declared the outbreak of COVID-19 (COrona VIrus Disease-19) a Public Health Emergency of International Relevance, and on March 11, 2020, the same organization proclaimed the beginning of the COVID-19 pandemic [1]. It was the start of the global crisis we are still struggling with[2].

Coronaviruses are single-stranded RNA viruses; in the past, they have been responsible for two well-known epidemics: (1) the 2002 Severe Acute Respiratory Syndrome (SARS), caused by SARS-CoV-1, and (2) the 2012 Middle East Respiratory Syndrome (MERS). Like other coronaviruses, the newly identified SARS-CoV-2 affects the respiratory tract, usually causing mild and self-limiting symptomatology like that of the common cold. In susceptible individuals, the virus can reach the lower respiratory tract causing pneumonia and severe acute respiratory syndrome[3]. However, COVID-19 does not only induce a respiratory syndrome, but it can elude the immune response and spread to distant apparatuses, as the renal and cardiovascular[4] ones. In particular, like SARS and MERS, COVID-19 showed to be neuro-invasive[5,6]. A growing body of literature shows that 27 to 41% of COVID-19 patients may present neuropsychiatric complications during the acute stage of the illness[7]. The most reported ones are anosmia, ageusia, headache, confusion, agitation, cerebrovascular events, encephalopathies, anxiety, depressed mood, impaired memory and insomnia[8–10].

On the contrary, far less is known about long-term neuropsychiatric sequelae of

COVID-19 infections[11]. The delayed effect of this pandemic, particularly that on the population's mental health, will require many months, or even years, to be fully acknowledged. Considering that many millions of people have been affected by COVID-19, this becomes a matter of deep concern. Given the aforementioned observations, this editorial aims at discussing the possible long-term effects of the COVID-19 pandemic on neuropsychiatric health.

LONG-TERM NEUROPSYCHIATRIC SEQUELAE: A CAUSE OF CONCERN. Most of the hypotheses about COVID-19 Long-term effects on the nervous system can be drawn from evidence on SARS-CoV-1 and MERS neuropsychiatric sequelae. As to SARS-CoV-1, high rates of depression (39%), pain disorders (36.4%), panic disorder (32.5%) and Obsessive-Compulsive Disorder (OCD) (15.6%) were reported among survivors. The mean time of onset of such complications ranged 31 to 50 mo post-infection[12]. According to another study, one year after the SARS-CoV-1 outbreak, 64% of the survivors showed some sign of psychiatric morbidity[13], while 30 mo after the outbreak, the prevalence of any psychiatric disorder was 33.3%[14]. A meta-analysis reported rates of neuropsychiatric sequelae in SARS-CoV-1 and MERS survivors raging 10 to 20%; the symptomology most often displayed was insomnia, anxiety, depression, fatigue and memory impairment[7].

Moreover, an examination of the literature's data about the relationship between other non-epidemic coronaviruses and neuropsychiatric consequences can be helpful. Human coronavirus HCoV-NL63 infection was associated with mood disorders and suicide attempts[15]. Furthermore, exposure to viral infections, both in utero and during child development, has been linked to an increased risk for schizophrenia[16,17]. In this regard, when compared to controls, an increase in antibodies for four human coronavirus strains was found in patients with a recent psychotic onset [18]. In light of this, such data suggest a possible relation, between coronavirus infection and psychosis, that could emerge, in the long run, also from SARS-CoV-2.

Given the insight drawn from other coronaviruses, and considering the mechanisms through which COVID-19 invades and damages the CNS, we can speculate on the long-

term neuropsychiatric symptoms this virus may cause. Coronaviruses can spread to the CNS *via* retrograde axonal transport, from the olfactory nerve, or *via* the hematogenous route[19]. Once in the CNS, the latent virus can be hosted by both neural and immune cells, contributing to the onset of delayed neuropsychiatric complications. There are different pathways through which coronaviruses can affect the CNS, including damages through direct infections, immune or hypoxic damage, and direct binding to the angiotensin-converting 2 (ACE2) enzyme, highly expressed by neurons and glia[20]. These pathways were detected both in patients and in experimental animals affected by SARS-CoV-1[21]. Several reports on SARS-CoV-1 and MERS discussing sub-acute demyelinating complications and neuromuscular and neurodegenerative diseases have been published[19,22,23]. Considering the neurotropism of all coronaviruses, we can imagine similar mechanisms and consequences also in COVID-19 patients. However, SARS-CoV-2 has also shown different mechanisms of neuroinvasiveness. Besides from ACE-2, the neuropilin-1 (NP-1) protein was identified as an additional mediator, facilitating the virus entering the cells[24,25]. This protein is highly expressed in the brain, representing an element of concern, particularly for long-term cognitive sequelae of COVID-19 infections[26]. Early studies showed that cognitive impairment, frequently reported during acute infection, could also persist after recovery. A paper examining patients at a median of 85 days after acute illness showed that 78% of the group reported sustained cognitive difficulties. These deficits did not correlate with depressed mood, fatigue, hospitalization, type of treatment received, acute inflammation, or viremia. If these effects were to extend over time, the impact of SARS-CoV-2 on cognitive functioning might be of great concern[27]. Studies to shed light on SARS-CoV-2 specific neurotropism and its possible neurological consequences are still active[28].

The emergence of Post-Traumatic Stress Disorder (PTSD) associated with a prior COVID-19 infection should also be considered. This is because the experience of a potentially severe disease, such as COVID-19, is considered a traumatic event[29]. On the one hand, the infection can lead to brain vulnerabilities that could increase the risk of

developing clinically relevant psychological distress. On the other, profound stressors linked to the infection, such as medical interventions or isolation, could play a critical role in the development of PTSD, as seen for other diseases[30]. This was also demonstrated after the SARS-CoV-1 epidemic, with a 55% rate of PTSD detected among survivors[12]. There are many reports about the emergence of PTSD consequently to a COVID-19 acute infection, and many more are probably yet to come[31,32].

CONCLUSION

DISCUSSION AND CONCLUSION.

As said, long-term neuropsychiatric complications of COVID-19 infection will remain covert for several months or, possibly, several years. Given the global spread of the COVID-19 infection, even if only a small part of the affected people will develop delayed neuropsychiatric sequelae the public health burden generated by these complications will be significant. Thus, we could expect a "crashing wave" [33] of COVID-19 neuropsychiatric consequences, with a plausible relevant impact on countries healthcare resources and on healthcare workers[34] as well. These consequences might be even more severe for those who were already suffering from a psychiatric or neurological disorder[35,36]. These consequences, hence, might be both psychiatric and neurological. Psychiatric long-term consequences could be observed in the form of an escalation in PTSD, depression and depressive symptoms, anxiety disorders, and, maybe, severe mental illnesses such as psychosis. A variety of neurological sequelae have also been hypothesized.

This editorial may encourage many future considerations. Firstly, clinicians should be aware of the distant burden of neuropsychiatric distress that is potentially linked to COVID-19 infections. Careful attention should be given to survivors, in order to prevent or anticipate possible complications. It might be essential to mention an eventual wave of suicidality as the endpoint of unrecognized depressive syndromes or other severe mental distress. A patient's cognitive examination should also be included in long-term monitoring, exploring executive functions, memory, attention and information

processing.

As possible strategies of intervention against this wave, implementation of telehealth and digital medicine should be cited. Although these are promising and effective ways to deliver health assistance, mainly if applied for mental health purposes, they are still underused in many countries [37]. Research carried out during the pandemic's acute outbreak shows promising results in this field[38–40].

In the event of the likely impact of neuropsychiatric sequelae on the health system, it would be crucial to focus our efforts on strong-effectiveness interventions. Depression, anxiety, PTSD and other emerging issues should be addressed with evidence-based and easy-delivered treatments. Besides from telehealth platforms, group interventions should also be implemented in response to the expected increase in psychological needs.

As treatment approaches for COVID-19 neuropsychiatric consequences, we would imagine an important role for physical therapies and neuromodulation techniques such as Transcranial Magnetic Stimulation (TMS) or Transcranial Direct Current Stimulation (tDCS). Even if there is still no clear evidence, possible applications of neuromodulation techniques have been underlined[41]. Proposed pathways include regulating anti-inflammatory responses through Dorsolateral Prefrontal Cortex (DLPFC) stimulation, improving cognitive outcomes and fatigue. Moreover, the body of literature on the effectiveness of those techniques in many neuropsychiatric disorders has been growing, projecting a promising role for the management of long-term COVID-19 psychiatric sequelae[42,43].

In conclusion, all these considerations underline the need for a watchful follow-up on neuropsychiatric symptoms related to COVID-19, in order to understand the trajectories of possible neuropsychiatric outcomes in the future. Careful research, based mainly on longitudinal and prospective studies, will be vital in this field, both for clinical and scientific purposes.

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