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Short communication

Neurocovid-19: A clinical neuroscience-based approach to reduce SARS-CoV-2 related mental health sequelae

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ABSTRACT

Coronavirus Disease 2019 (COVID-19), caused by SARS-CoV-2, is a disaster due to not only its psychosocial impact but it also to its direct effects on the brain. The latest evidence suggests it has neuroinvasive mechanisms, in addition to neurological manifestations, and as seen in past pandemics, long-term sequelae are expected. Specific and well-structured interventions are necessary, and that's why it's important to ensure a continuity between primary care, emergency medicine, and psychiatry. Evidence shows that 2003 SARS (Severe Acute Respiratory Syndrome) survivors developed persistent psychiatric comorbidities after the infection, in addition to Chronic Fatigue Syndrome. A proper stratification of patients according not only to psychosocial factors but also an inflammatory panel and SARS-Cov-2's direct effects on the central nervous system (CNS) and the immune system, may improve outcomes. The complexity of COVID-19's pathology and the impact on the brain requires appropriate screening that has to go beyond the psychosocial impact, taking into account how stress and neuroinflammation affects the brain. This is a call for a clinical multidisciplinary approach to treat and prevent Sars-Cov-2 mental health sequelae.

COVID-19, a unique disaster - The outbreak of Coronavirus Disease (2019) (COVID-19), caused by Severe Acute Respiratory Syndrome - Coronavirus-2 (SARS-CoV-2), can be considered as a unique disaster (from Latin: *Astrum* + *dis,* "bad star"), where individuals in a large population are randomly exposed to the trauma of a virus that has direct effects on the Central Nervous System (CNS), and subsequently induces an immunological response (Troyer et al., 2020).

SARS-Cov-2 mechanism and multi-organ targeting - SARS-CoV-2's mechanism of infection exploits the virus' strong binding affinity to the angiotensin-converting enzyme-2 (ACE2) to gain entry into cells (Wang et al., 2020a). This receptor is expressed in lungs, heart, kidneys, testicles, venous endothelial cells and small intestinal enterocytes (Zou et al., 2020). ACE2 is also widely expressed in the mouse and human brain although current human evidence is strongest for its expression on endothelial and smooth muscle cells (Xia and Lazartigues, 2008). Moreover, type I interferon IFNs (IFNα), and to a lesser extent Type II IFNs (IFNγ), upregulate ACE2 in airway epithelial cells, and SARS-CoV-2 may be using the IFN response for its benefit (Ziegleret al., 2020). Acute inflammation is part of innate immunity's response to harmful stimuli, and triggers adaptive immunity, whereas excessive or chronic inflammation causes disease.

How the virus enters the CNS - In patients diagnosed with viral encephalitis, gene sequencing showed SARS-CoV-2's presence in the cerebrospinal fluid, confirming its neuroinvasive potential (Zhou et al., 2020). Several hypotheses have been advanced to explain how SARS-CoV-2 enters the CNS: hematogenous dissemination, neuronal retrograde transport and the passage via the nasal cavity across the cribriform plate that supports the olfactory bulb (Zhou et al., 2020). The virus can be disseminated throughout the body via the bloodstream, and across vascular beds of different organs by disrupting ACE2 bearing endothelial cells (Varga et al., 2020). The presence and persistence of human coronaviruses in the brain have been proposed to cause acute

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and long-term sequelae, whereas their activities in prodromal or asymptomatic phase are still unknown.

COVID-19's neurological symptoms - Approximately 40%–88% of severe COVID-19 patients present with neurological symptoms (Mao et al., 2020), along with neurodegeneration, neuroinflammation and demyelination signs (Zanin et al., 2020). However, we cannot assume that all neurological symptoms are a consequence of direct CNS involvement and new sudden onset neurological manifestation should be considered. A Predominant Organ's Involvement Model is necessary to provide specific and timely interventions (Troyer et al., 2020). The complexity of COVID-19's pathology requires appropriate screening for neurological and psychosensorial manifestations in individuals testing positive for SARS-CoV-2, whether they have respiratory symptoms or are asymptomatic. One third of COVID-19 positive patients exhibit anosmia, hyposmia and hypogeusia, occurring even in otherwise asymptomatic patients. Clinicians need to consider SARS-CoV-2's direct effects on the CNS and immune system.

Patient stratification: an important step forward - Patients should be stratified according to neurological, psychosensorial, and inflammatory status irrespective of the psychosocial consequences of quarantine. Inflammatory markers should be assessed, including CBC with differential, hsC-reactive protein, D-dimer, lactate dehydrogenase, transaminase, azotemia (uremia), creatinine, creatine kinase and IL-6. Peripheral cytokines involved in anti-viral responses may elicit neuropsychiatric symptoms and neuroinflammatory responses (Troyer et al., 2020). An increased secretion of pro-inflammatory cytokines and chemokines such as IL-6, IFNγ, MCP1 and IP-10 are found in the blood of COVID-19 patients (Tay et al., 2020). Hyperketonemia has also been reported. Interleukin (IL)-6, Tumor Necrosis Factor (TNF)-*alpha*, IL-8, IL-10, and IL-2R are significantly higher among fatal COVID-19 cases as reported for SARS-CoV-1's infection (Tay et al., 2020; Yang et al., 2020). T-lymphocytes, expressing ACE2 Wang et al., 2020b, play a decisive role in maintaining immune homeostasis: lymphopenia and increased neutrophil–lymphocyte ratio have been seen in approximately 80% of SARS-CoV-2's patients (Tay et al., 2020). Type I IFN deficiency is a hallmark of severe COVID-19 and is present before their decline. These COVID-19 patients might benefit from IFN administration and from the concomitant exacerbated inflammation combined with anti-inflammatory therapies targeting IL-6 or TNF-α. This intervention may serve as an example for why stratification of patients with markers of their immune response is advantageous (Hadjadj et al., 2020).

Given all of the above evidence, it would be useful to search for antibodies in the cerebrospinal fluid of those patients where CNS involvement is strongly suspected.

Basal ganglia dysfunction and related disorders as COVID-19 sequelae - SARS-Cov-2 a beta-Coronavirus, which is in the order of *Nidovirales*, member of the family *Coronaviridae* and subfamily *Coronavirinae* (Park, 2020), is associated with such central and peripheral neurological effects as dizziness and headache as well as hypogeusia and hyposmia respectively (Dickman, 2001). Although different in mechanism of action and clinical manifestations, an interesting parallelism in the neurological domain, could be drawn with other viruses, which are known for being associated with neurological symptomatology as in Spanish Influenza Pandemic of 1918, and Encephalitis Lethargica, first described by Constantine von Economo (Steardo et al., 2020). The long-term sequelae of COVID-19 are still unknown but Basal Ganglia dysfunctions and related disorders seem to be present as outcomes, given that basal ganglia and other structures are likely to be affected by aberrant hemorrhagic (Franceschi et al., 2020) or neuroinflammatory processes in the central nervous system (Dickman, 2001).

Implications of immune-inflammatory signaling - Elevated immune-inflammatory signaling is a relevant mechanism to the pathoetiology of mood disorders (Pfau and MénardScott, 2018). Another threat to the CNS is represented by inflammatory factors that specifically impact neurodevelopment (Khandaker et al., 2014); convergent evidence suggests that exposure to the mother to inflammation during pregnancy is associated with the later development of neuropsychiatric disorders in human offspring (Gumusoglu and Stevens, 2019).

During infection, fetal villous tissues secrete a number of inflammatory and immunoregulatory cytokines and chemokines, contributing to their presence at the fetal-maternal interface. SARS-CoV-2 infection during pregnancy and childhood may lead to the manifestation of neurodevelopmental disorders. Individuals exposed to SARS-CoV-2, as well as offspring of exposed mothers, should be assessed for neuropsychiatric, neuroimmune and inflammatory status in longitudinal studies to better understand the pathophysiology, and to allow for early intervention.

Neuro-behavioral sequelae and psychosocial support **-** Functional disability after Acute Respiratory Distress Syndrome represents a well-known hazard (Margaret et al., 2011) but the neuro-behavioral sequalae of SARS-CoV-2 may not be detected by the common psychological assessment and the concomitant support may be not enough. To counter the direct and indirect CNS harm inflicted by this virus including stress and inflammation, a continuity between primary care, emergency medicine, inpatient treatment, and psychiatry is needed using clinical assessment at specific phases and stages (Fava et al., 2012). Studies suggest that psychotherapy leads to measurable neuroimaging changes associated with functional improvement (Barsaglini et al., 2014) and psychosocial interventions may be associated with an improvement of beneficial immune system function and a decrease in harmful immune system function, with changes persisting for at least 6 months following treatment (Shields et al., 2020)As seen in SARS (Severe acute respiratory syndrome) survivors, Ho-Bun Lam and colleagues (Lam et al., 2009) showed that many SARS survivors developed psychiatric morbidity that persisted at 4 year follow up, and many psychosocial factors (such as being a health care worker at the time of infection, being unemployed after recovery and having perception of social stigmatization) increased the risk of developing psychiatric morbidity. More specifically, only 3.3% of the SARS survivors who participated to the study had a history of psychiatric disorders before contracting SARS; otherwise many patients experienced at least one psychiatric illness after SARS infection (42.5%) and the main diagnoses included posttraumatic stress disorders (54.5%), depression (39%), somatoform pain disorder (36.4%), panic disorder (32.5%) and obsessive-compulsive disorder (15.6%). The study suggests the use of specific instruments and trained personnel to improve diagnostic evaluation and stratification. Even if the long-term outcome of Covid-19 is unknown at this time, patient stratification will allow for assessment of anti-inflammatory interventions (such as the use of fluoxetine, fluvoxamine, SSRI and trazodone) and a reduction of stigma associated with mental health sequela of the disorder. Such stratification utilizing an inflammatory panel, may help to tailor appropriate therapeutic and rehabilitative programs. While this was not done for SARS survivors, it is now time to do so for COVID-19 patients. Also, psychosocial support should be an essential part of the patient's overall multidisciplinary medical treatment, and this would also reduce the stigma of mental health treatment. Many individuals subject to lockdowns and social distancing may succumb to loneliness-associated elevated levels of markers for inflammation and an increased sensitivity to negative social experiences (Eisenberger and Moieni, 2020). Although SARS-CoV-2 may stress several systems of the body in the process of overcoming the infection including the brain, an individual's response need not be pathological (Tedeschi and Calhoun, 2004). The net stress experienced by a given individual is not deterministic, but their response defines "subjective vulnerability" and "resilience characteristics" or what is called "post traumatic growth".

Where do we go from here? – As of May 21st, there have been more than 5.2 million cases (and 330 thousand deaths) worldwide resulting from the SARS-CoV-2 pandemic, and an effective vaccine is badly needed. In developed nations with resources that are not available in most of Africa, some parts of Asia, and Latin America, it is time to utilize all of the tools of modern medicine to assess the effects of this devastating virus on the human brain and it's neurological, psychiatric, and

psychosocial consequences (such as suicide prevention of COVID 19-infected healthcare workers, economic impact, and grief response in family members). The direct effects of the virus (viremia), immune-mediated response, and sequelae from ACE2 positive cell destruction (blood clots, stroke) need to be considered. Beyond testing for viral RNA sequences or antibodies, we should collect samples and carry out complete molecular (and syndromic) testing and there needs to be a coordinated response by the different branches of medicine. "After 40 years, psychiatry is becoming more mindless than brainless, perhaps digital phenotyping will help the pendulum swing back toward a fresh look at behavior, cognition, and mood" (Insel, 2017). There is no better time than now to head Insel's advice.

Author contribution

SP developed the idea, and all authors made a substantial contribution to the development and writing of this article. SP, acting as corresponding author, had the final responsibility for the decision to submit for publication.

Declaration of competing interest

As authors, we declare no competing interests.

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