SARS-Cov-2 neuroinvasion – direct and indirect central nervous effects, behavioral consequences at the population level

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Introduction

The consequences of SARS-Cov-2 neuroinvasion and the interaction with angiotensin-converting enzyme 2 (ACE2), the reduction of the enzyme expression and the development of the inflammatory syndrome against the background of a dysfunctional immune syndrome, the association of panendothelitis, lead to central nervous system (CNS) injury, with complex and variable consequences according to multiple factors, such as neurological and psychiatric comorbidities, hypertension or diabetes mellitus, autoantibodies, and individual vulnerability.

The significant increase in oxidative stress is related to viral aggression, systemic inflammatory processes, and panendothelitis. In the following, we will see aspects of CNS injury that may be generated inclusively by hematoencephalic barrier permeability disturbance, representing a fundamental structure that prevents CNS invasion with exogen substances or inadequate concentrations of endogen substances necessary for metabolism.

It is relevant to mention that the glucose that is strictly necessary for cell life, in general, does not passively enter the CNS but actively.

Next, we will try to synthesize the aspects regarding neuroinvasion mechanisms and the consequences of viral aggression on the function and homeostasis of the CNS. We will also analyze in detail the mechanisms involved in pathogenic processes following SARS-Cov-2 neuroinvasion [1–5].

Mechanisms and consequences of SARS-Cov-2 neuroinvasion

Several symptoms, such as anosmia, ageusia, cognitive and attention disorders, recent-onset anxiety, depression, psychosis, seizures, and suicidal behavior described in Covid-19 disease, are considered uncorrelated with SARS-Cov-2 respiratory failure [6–9].

SARS-Cov-2 penetration takes place due to the interaction with the enzyme (receptor) ACE2, resulting in vascular endothelial damage, consequent inflammation, thrombosis, and brain damage.

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It is believed that the systemic inflammatory process, even in the brain, facilitates the penetration of the virus found in the brain's vascular endothelium, with potential consequences on the morphofunctional integrity of the hematoencephalic barrier.

In this context, a decrease in the synthesis of neurotransmitters in the brain (serotonin, dopamine, norepinephrine) with an increase in kynurenine, glutamate, and N-methyl-D-aspartate (NMDA) with known neurotoxic consequences. All these processes either induce the onset of neuropsychological pathological processes or aggravate pre-existing ones [6, 10].

Depression and suicidal behavior are marked by an increase in plasma kynurenine, IL-1 and IL-6 in both blood and cerebrospinal fluid and increased C-reactive protein, correlated with glutamate [11].

A wide range of neurological and mental symptoms are described in those with moderate to severe Covid-19 disease. These symptoms may be direct, caused by viral invasion in the brain, or indirect, in the context of systemic reactions of the body in severe or critical forms, with coagulopathy, sepsis, activation of autoimmune mechanisms, or multiple organ failure [12].

The neurological changes are mainly severe, but 2–6% of the subjects had an acute stroke and, fewer of them, encephalitis. Patients who died presented meningitis and/or encephalitis and more frequently cerebrovascular, ischemic, and/or hemorrhagic lesions during the autopsy, which were not supported by direct evidence of the presence of SARS-Cov-2 in the CNS.

Data from autopsies and cerebral samples show that the highest viral load is in the olfactory bulb, adjacent to the nasopharyngeal mucosa and closely connected to the amygdala, hippocampus, and entorhinal area, as well as with the vagus and trigeminal nerves that enter in the brain in the pontine tegmental region [12]. The quoted author mentions a series of studies that support the viral invasion of the brain through the olfactory bulb, vagus, and trigeminal nerves. Samples collected from blood and cerebrospinal fluid were negative, highlighting that the diagnosis of viral contamination, in this way, is inadequate, implicitly does not argue in favor of a hematogenous viral invasion pathway of the brain. The comments of the authors that underline the reduced prevalence of SARS-Cov-2 are interesting, as shown by various studies, and suggest that the data would be due to the determination of samples only selected from brain regions and only at one time during Covid-19 disease.

It is mentioned that viral detection varies widely with the stage and severity of Covid-19 disease, and although the patients died, the duration of the disease is not known for all cases. The study sample represents a very small part of the total brain volume; to that is added the variability of the RT-PCR method in terms of sensitivity and specificity from different diagnostic centers.

There is a consensus on the persistence of neuropsychiatric symptoms in patients recovering from Covid-19 disease. Sleep disorders and fatigue are present in about a quarter of the survivors. In addition, in the first six months, there are other symptoms such as cognitive impairment, anxiety, depression, and symptoms of post-traumatic stress, lasting about six months, without a correlation between these disorders with the severity or the duration of the disease [13]. Understanding the mechanisms that lead to neural injury requires a comprehensive approach, involving continuous research even on murine models [14].

Several explanations regarding ethnic and gender susceptibility to SARS-Cov-2 infection (for instance, the aforementioned enzymes are highly expressed in males) could be detected by corroborating the effects of genetic variants of ACE2 and transmembrane serine protease 2 (TMPRSS2) that are present not only at the level of the CNS. The neural injury that SARS-Cov-2 generates is produced either by direct invasion of the immune cells, which are, in turn, infected or secondary to local and systemic inflammatory phenomena that are determined by the virus.

ACE2 is considerably expressed in various locations of the CNS, such as the spinal cord, cortex, hippocampus, cerebellum, and others, while TMPRSS2 is only mildly expressed at this level. Nonetheless, both ACE2 and TMPRSS2 are significantly co-expressed in the olfactory system [15]. In addition, the affinity of SARS-Cov-2 for ACE2 is 10 to 20 times higher as compared to its predecessor, SARS-Cov.

Moreover, several authors rendered the fact that direct viral invasion might not be the single most crucial pathogenetic pathway that explains the infliction of the CNS in SARS-Cov-2 infection, but also alternative mechanisms, including respiratory distress, hypoxia, thrombosis, and systemic inflammation, might be as equally guilty for this process [5, 14].

It has been shown that the binding of SARS-Cov-2 leads to the downregulation of ACE2, which represents a primary mechanism that contributes to both neural and systemic inflammation. This process might be explained by the role of ACE2 in controlling the renin-angiotensin-aldosterone (RAA) system, which antagonizes the negative, deteriorating consequences of angiotensin II, such as vasoconstriction and pro-inflammatory effects, secondary to decreased synthesis of Ang (1–7), which, on the contrary, has protective, antihypertensive, and anti-inflammatory effects. Indirectly, by activating microglia and macrophages, SARS-Cov-2 is able to stimulate the release of cytokines and chemokines into the bloodstream, which leads to immune hyperactivity [16].

The procoagulant and hyperinflammatory effects of this infection are strongly related to the levels

of ACE2. The expression can decrease with advanced aging and with the presence of cardiovascular risk factors, especially in male subjects and those with arterial hypertension and diabetes mellitus. The previously mentioned factors might also promote the lowering of ACE2 levels, especially after the interaction with SARS-Cov-2, a phenomenon that is closely associated with disease severity and mortality [17].

Understanding the functional disruption of the RAA system is an important stage in elucidating the involvement of CNS in the COVID-19 infection [18]. This system is severely perturbed on account of SARS-Cov-2 and ACE2 interaction which leads to the progressive decrease of its expression that, in turn, results in consistent systemic and local inflammation, indirectly affecting the normal physiology of the SNC, including cognition [19]. Furthermore, the long-term local activation of the RAA system increases the levels of Ang II and the AT1 receptor, generating inflammation, fibrosis, arterial hypertension, excessive vasoconstriction, and sodium reabsorption. Additionally, the protective branch of this system, the conversion of Ang II to Ang (1–7), significantly diminishes, thus favoring the abovementioned negative processes.

Excessive inflammation and enhanced oxidative stress are important factors directly involved in neurodegeneration. It has been suggested that the administration of angiotensin-converting enzyme inhibitors and/or AT1-receptor blockers antagonizes these neurodegenerative effects and even improves cognition [20]. Moreover, Ang (1–7) has been shown to be present in the CNS, especially within the brainstem and the hypothalamus, being considerably involved in the baroreflex modulation of cardiac physiology [5].

It is known that by downregulating the expression of ACE2, the increased activity of the Ang II/AT-1 receptor axis is independently correlated with enhanced inflammatory response and significantly higher sera levels of IL-6, TNFα, IL-1β, and IL-10. When it comes to moderate and severe forms of Covid-19 infection, the increase of pro-inflammatory cytokines and chemokines, especially interleukins, has tremendous roles in triggering the cytokine storm syndrome, leading to acute respiratory distress syndrome. It is considered that this cytokine storm is the culprit mechanism that generates most of the complications in Covid-19.

Moreover, another mechanism involved in the cytokine storm phenomenon is considered the purinergic receptor, which has a critical role in neuroinflammation because it renders the excessive activation of the NLRP3 inflammasome, along with caspase-1, IL-1β, and IL-18. Also, it is acknowledged that SARS-Cov-2 might be able to activate this inflammasome directly [5]. Recent data, which are in conjunction with the abovementioned findings, emphasized the role of purinergic receptor P2X7 as

being widely distributed within the CNS, being also linked to various inflammatory and neurodegenerative processes [5, 21].

In Covid-19 infection, psychiatric complications are conditioned by biological factors such as advanced aging, obesity, pregnancy, and other comorbidities, and psychosocial factors, such as isolation, quarantine, and financial crisis. It has been proved that social isolation disrupts the hypothalamic-pituitary axis, which leads to the enhanced production of corticosteroid hormones. Moreover, a lower socioeconomic status has also been correlated with increased serum levels of inflammatory biomarkers, especially IL-6 and C reactive protein [22].

The hyperactivation of the hypothalamic-pituitary axis is a major flaw found in major depression, while hypercortisolism significantly contributes to the atrophy of the hippocampus, considerably influencing sleep modulation [22]. Inflammation and pro-inflammatory cytokines have a major impact on the subcortical and cortical circuitry, especially at the levels of the basal ganglia and the cingulate gyrus, thus modulating motricity, motivation, anxiety, wakening, and the fight or flight status. Moreover, the chronic activation of these regions can, in time, lead to the development of depression and anxiety in vulnerable individuals.

Withal, as a result of the excessive activation of the systemic inflammatory process that occurs in the SARS-Cov-2 infection, the blood-brain barrier is disrupted, astrocytes are injured, while microglia activate, thus leading to neuroinflammation and neuronal apoptosis. Therefore, the aforementioned phenomena lead to neurodegeneration and the injury of the limbic system of the cortical regions, which are accompanied by anterograde and retrograde amnesia. Moreover, after discharge, it is considered that in up to one-third of patients, their viral load might continuously inflict endothelial cells, leading to vascular injury, cerebral hypoperfusion, neuronal dysfunction, and cognitive decline.

The study by Putri *et al.* has shown that survivors of Covid-19 infection should be further assessed for anxiety, depression, and stress, especially to identify progressive psychiatric disorders. Recent research of great significance among more than 230000 Covid 19 survivors revealed that 34% were diagnosed with a neuropsychiatric disease in the first six months [23]. The incidence rate of neuropsychiatric diseases increased to 38.73% for hospitalized patients, to 46.42% for the patients in the intensive care unit (ICU)o, while the incidence rate reached 63.34% for the patients diagnosed with encephalopathy. The quoted authors mention that potential mechanisms for the described pathology include viral invasion of the CNS, hypercoagulability state, and neurological effects of the immune system triggered by the SARS COV 2 virus [23].

Cross-reactive autoantibodies generated in Covid 19 [24] trigger an autoimmune activation [2],

causing long-term health problems. Cross-reactive autoantibodies as a response to SARS COV 2 infection could contribute to a clinical phenotype that may explain some symptoms' persistence after the typical convalescence period. Sepsis generated by SARS-COV 2 along with the systemic inflammatory response can determine acute and chronic lesions of the CNS, including the hematoencephalic barrier. These processes determine encephalopathy with specific neurocognitive disorders. The definition of sepsis indicates this condition is generated by infection, likewise by the organism's dysfunctional response to the infection.

The hematoencephalic barrier representing the functional and anatomic interface between the nervous parenchyma and cerebral circulation, explains the mechanism of disruption in the central nervous homeostasis, which increases permeability and inflammation of the barrier. Damaging different cellular components of the hematoencephalic barrier such as astrocytes, endothelial cells, microglia, pericytes and neurons (with excitotoxicity and neuronal dysfunction) results in increased permeability of the barrier, microthrombi formation, ischemia, increased production of cytokines, neuroinflammation, cognitive dysfunction [25].

As a consequence of sepsis, the CNS has two types of reactions: a complex response induced by infection and immune trauma, mediated by the production and release of cytokines, as well as sepsis-associated encephalopathy, known as "sickness behavior", representing a suite of behavior changes developed among patients during the disease. This reaction consists of fever, behavior, and neuroimmune changes.

While being activated by the inflammatory mediators, the solitary nucleus and locus coeruleus subsequently stimulate autonomic nuclei, behavior, and neuroendocrine centers. To summarize, the observed consequences consist of depression, social withdrawal, tachycardia, variable arterial pressure, and decreased alertness. Additionally, the behavioral disorders in acute sepsis involve delirium, seizures, mental disorders, and increased mortality. It can be assumed that the manifestation of impaired brain function is delirium.

Encephalopathy is associated with sepsis and other mentioned disorders; also, patients exhibit long-term disorders with neurological decline, memory loss, attention deficit disorder, and impaired speech. A clinical research about psychopathological consequences and possible psychological issues among COVID 19 survivors, one month after being discharged from the hospital (402 adults), reported the presence of post-traumatic stress disorder among 28%, depression in 31%, anxiety in 42%, obsessive-compulsive disorder in 20% and insomnia in 40% [26]. Following the incidence rate of psychiatric and neurocognitive disorders three months after being discharged from the hospital by

dosing inflammatory biomarkers (immunoinflammatory systemic index), the authors ascertain that post-COVID 19 psychiatric disorders, the related sequelae, and the severity of depression are correlated with the intensity of the inflammatory process. Thereby the authors conclude that the extension of the inflammatory process makes the patients susceptible to persistent depression and neurocognitive dysfunction.

Neuropsychiatric manifestations in post-COVID 19 syndrome

The impact of psychosocial stress factors, as well as the impact of direct and indirect biological damage to the CNS among the COVID 19 survivors, makes the perfect environment for the occurrence of the post-COVID 19 syndrome, also called "long-term COVID 19". Among the psychosocial stress factors that were reported, the most important triggers for psychiatric diseases were: quarantine regimen or hospitalization, especially prolonged hospitalization or in the ICU, prolonged or minimal effort fatigue with related lifestyle changes, fear of contaminating others, fear of reinfection and fear of long-term complications.

The Covid 19 pandemic established some new social rules, hard to bear for the general population that required the activation of some coping mechanism in addition to the ones usually used. Those new coping mechanisms were both functional (finding new relaxation methods or new ways of spending free time, developing new professional skills) and dysfunctional, some of them having long-term consequences (*e.g.*, substance abuse, harmful use of the internet, and limited social interactions, even in safe epidemiological conditions).

The harmful effect of biological factors is added to these psychosocial components, already mentioned in the previous section (Figures 1 and 2). Inflammatory, hypoxic, and hemorrhagic lesions in the CNS, persistent systemic inflammation, metabolic imbalances, strokes, hypoxia caused by lung damage, and fibrotic changes are major causes of prolonged Covid-19 syndrome [27]. The pathogenesis of neuropsychiatric symptoms in post-Covid-19 syndrome, neuroinflammatory mechanisms, and oxidative stress processes are the most frequently cited causal factors [28].

The main directions for long-term assessment of mental health in Covid-19 survivors are (1) identification of the most common types of symptoms and neuropsychiatric disorders associated with prolonged Covid-19 syndrome (mainly depression, anxiety, insomnia, global cognitive impairment, but also psychosis, difficulty concentrating or chronic fatigue) [27]; (2) identification of risk factors for
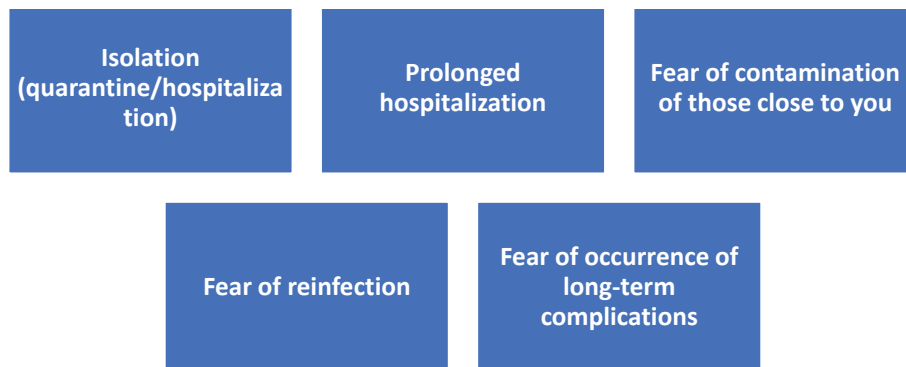
Figure 1. Psychosocial stressors in patients diagnosed with Covid-19.

the onset of neuropsychiatric disorders in Covid-19 survivors (demographics, disease severity, psychological vulnerability, and others); (3) identification of treatment response factors in case of persistent symptoms and the most effective interventions for this population (rehabilitation interventions, psychotherapy or pharmacological therapies).

Clinical analysis of post-Covid-19 syndrome from a neuropsychiatric perspective

According to a meta-analysis (n=19 studies, N=11324 patients who had symptoms installed after at least three months or persistent beyond this limit), the most commonly reported neuropsychiatric symptoms in prolonged Covid-19 syndrome were fatigue (37%), brain fog (32%), memory impairment (27%), attention deficit (22%), myalgias (18%), anosmia (12%), dysgeusia (11%) and headache (10%) [29]. From the category of neuropsychiatric disorders diagnosed in these patients, the most commonly detected were sleep disorders (31%), anxiety (23%), and depression (12%) [29].

Patients who were hospitalized during the acute period of Covid-19 had a lower incidence of anos-

mia, anxiety, depression, dysgeusia, fatigue, headache, myalgia and sleep disturbances at ≥3 months after infection, but also a higher incidence of mnemonic disorders [29]. In conclusion, cognitive dysfunctions ("brain fog", memory and attention disorders) occur with high frequency in the post-Covid-19 phase, and the prevalence of psychiatric manifestations, such as sleep disorders, anxiety and depression, increases over time [29]. Another study evaluated 236 patients initially evaluated in the acute period of Covid-19 infection and later 5–8 months after the diagnosis of this condition [30]. Myalgia, hyposmia, and dysgeusia were identified in 50%, 48.3%, and 45.8% of patients, respectively, in the acute phase of infection. At the same time, fatigue, headache, myalgia, memory problems, anxiety, depression, and insomnia were found in 21.6%, 19.1%, 16.1%, 39.8%, 37%, 45% and 45.8% of patients with prolonged Covid-19 syndrome [30]. A longitudinal study looked at the evolution of neuropsychiatric status among survivors of Covid-19 infection after one year (N=171 participants) and reported that 73.7% of survivors had at least one persistent symptom, according to a standardized fatigue test (48.5%), mnemonic difficulties (32.2%), arthromyalgia (27%), dyspnea (25.7%), headache (15.8%), chest pain (7.6%), paresthesias (7%), cough (5.3%), anosmia (5.3%), agitation/dysgeusia (2.3%), fever
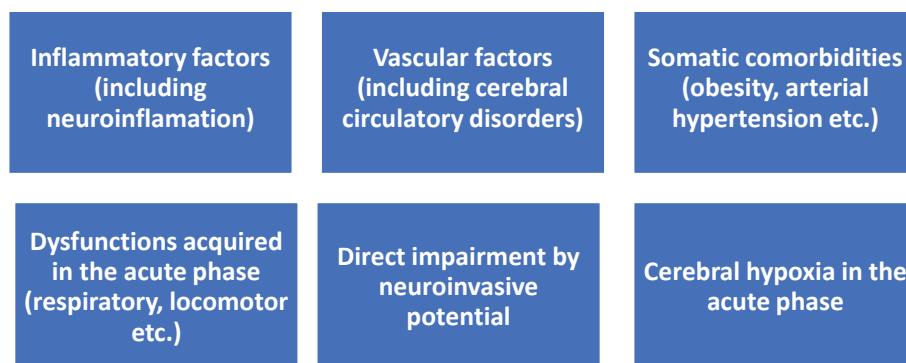

Figure 2. Biological factors that contribute to the maintenance of prolonged Covid-19 syndrome symptoms.

(1.2%) or tremor (1.2%) [31]. It is noteworthy that 24% of these patients reported a degree of cognitive impairment: 11.7% had decreased memory performance, and 12.3% had moderate and severe memory reductions [31]. The most affected neurocognitive sub-domains were semantic verbal fluency (32.7%), verbal memory/verbal learning (20.5%), executive function/working memory (12.3%) and long-term verbal memory (7.6%) [31].

Anxiety, depression, and post-traumatic stress disorder were reported in 35.1%, 32.2%, and 24.6% of patients, respectively. In comparison, a decrease in quality of life was observed in 39.8% and 33.3% of patients for the physical and mental components, respectively [31].

Another longitudinal study found that in Covid-19 survivors (N=900 people at 6 months and 241 people at 12 months, mean age 37 years), only 4.6% were asymptomatic, while 80.5% had mild symptoms, 12.4% moderate symptoms, and 2.5% severe symptoms [32]. Of the total evaluated group, 52.7% still had persistent symptoms related to Covid-19, and 5% were on outpatient treatment for such symptoms [32]. The most commonly reported symptoms were difficulty concentrating, cognitive dysfunction, amnesia, depression, fatigue, and anxiety [32].

A narrative review of the literature found that involvement of the central and peripheral nervous system is reported in more than one-third of cases of patients with SARS-CoV-2 infection with severe respiratory manifestations, and observational studies that include data reported by patients support an incidence of neurological symptoms about 3 times higher [28].

Vulnerability factors for the post-Covid-19 neuropsychiatric syndrome

Individual vulnerability factors for the onset of neuropsychiatric symptoms in Covid-19 survivors have been investigated in several epidemiological studies. One such study, which included 93 patients diagnosed with post-Covid syndrome and people in the control group with similar demographic characteristics, found lower scores on "emotional stability", "emotional balance", "Positive mood" and "self-control", suggesting a high level of neuroticism towards the control group [33]. The same study found a negative correlation between "extraversion", "emotional stability" and "openness", on the one hand, and the level of anxiety and depression, on the other hand [33]. No statistically significant relationships were established between personality traits and cognitive functioning, sleep quality, olfactory function, and fatigue [33]. Personality issues accounted for between 36.3% and 41% of the variation in anxiety and depression severity scores, respectively, and two per-

sonality profiles with low levels of emotional stability were associated with depression and anxiety [33].

Risk factors associated with persistent neuropsychiatric symptoms in Covid-19 infection survivors in a longitudinal study (N=900 Korean patients) were advanced age, female gender, and disease severity [32].

Regarding the risk of developing Covid-19 mild cognitive impairment, it has been suggested that clinical features may be grouped into certain risk groups [34]. In a study involving adult patients with mild forms of infection who did not require hospitalization and who either reported new and persistent cognitive symptoms (main group, N=22) or had no cognitive symptoms (control group, N=10), with a mean age of 41 years, was found to correlate with late-onset of cognitive impairment in Covid-19 survivors [34]. Nearly 43% of patients developed post-acute cognitive sequelae, and these patients had a significantly higher number of pre-existing cognitive risk factors and a higher proportion of abnormalities in cerebrospinal fluid samples compared to the batch control [34]. Pre-existing cognitive risk factors were diabetes, sleep apnea, HIV infection, depression, anxiety, diagnosis of attention-deficit hyperkinetic disorder, learning difficulties, daily psychoactive medication, history of craniocerebral trauma/hypothyroidism/vitamin B12 deficiency/recurrent use of psychostimulants/alcohol abuse [34]. CSF abnormalities (mainly abnormal oligoclonal bands) were detected in 77% of patients with post-Covid-19 vs. cognitive impairment – 0% in the control group, which is a significant difference [34].

Treatment of the post-Covid-19 neuropsychiatric syndrome

From a therapeutic perspective, given the lack of evidence from longitudinal, randomized studies focusing on post-Covid-19 neuropsychiatric symptoms, there is no evidence-based strategy that can be recommended in these cases. Most of the interventions found in the literature for these patients are supportive [28]. Neurological rehabilitation can be initiated early in patients with moderate-severe neurological symptoms to increase the likelihood of adequate functional recovery [28, 35].

According to the consensus of Stanford Hall, created by a group of experts in rehabilitation, sports and recovery medicine, rheumatology, psychiatry, family medicine, psychology, and pain therapy, the following important measures are recommended for patients with Covid-19 infection from a psychological and psychiatric perspective: in the acute phase the emphasis is on effective communication and informing patients; a re-evaluation will be performed in the recovery phase, to identify those patients who may have an unfavorable psychological

prognosis, as a result of the experiences from the acute period; patients with subsyndromal psychiatric symptoms will be actively monitored; one can initiate trauma-focused cognitive-behavioral therapy, cognitive processing therapy, or eye movement reprocessing and desensitization therapy where there are moderate and severe symptoms of acute stress disorder [35].

Pharmacological interventions have not been systematically evaluated for this population. However, drugs with a higher profile of safety and tolerability, such as new-generation antidepressants, anxiolytics, and hypnoinducers without risk of dependence (buspirone, gabapentinoids, suvorexant), or atypical antipsychotics are preferable, especially in the presence of somatic comorbidities, or of a complex medication administered concomitantly [36–38].

Conclusions

The mild, moderate, or severe clinical forms of Covid-19 disease affects the lungs, but the viral invasion also affects other organs and systems, including the central nervous system. The wide distribution of the receptor, the conversion enzyme 2 (ACE2), even in the vascular endothelium, largely explains the pathogenic consequences of the SARS-Cov-2 invasion in the human body. It is relevant that the first symptoms of the disease (anosmia and ageusia) often remain singular (correlated with the severity of the disease).

In moderate and severe clinical forms, symptoms illustrating CNS impairment, such as cognitive impairment, attention deficit disorder, anxiety, depression, psychosis, seizures, and suicidal behavior, are common and unrelated to respiratory failure.

The persistence of this type of symptoms aimed at affecting the CNS in survivors is over 30% at about 6 months after the Covid-19 disease. The paper analyzes potentially involved pathogenic mechanisms, often synergistic, which largely explain persistent post-Covid central nervous disorders, including those with behavioral connotations.

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