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SPECIAL ARTICLE

PSYCHOLOGICAL AND NEUROPSYCHOLOGICAL COMPLICATIONS OF PATIENTS WITH COVID - 19, AFTER THEIR HOSPITALIZATION IN INTENSIVE CARE UNITS

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Abstract

The globally recognized COVID-19 pandemic has brought about unprecedented and unexpected upheavals in science data. The consequences of SARS-CoV-2 are evident in public health and primarily in almost every human system. Due to the extent of the damage that it sometimes causes to the body, it is possible that patients need to be treated in an Intensive Care Unit.

In particular, during the hospitalization not only organic problems were observed, but also psychological, neuropsychological and neuropsychiatric disorders, which are caused by the nature of the virus. Important findings show that the mental health effects of the virus are not limited to the time frame of hospitalization in the ICU, but remain after discharge.

Post-intensive care syndrome, post-traumatic stress disorder and fatigue are some of the most important persistent effects, so their in-depth understanding is considered necessary.

Key words: COVID - 19, neuropsychological complications, ICU treatment, post intensive care syndrome, post - traumatic stress disorder.

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INTRODUCTION

The disease caused by the novel coronavirus also known as Severe Acute Respiratory Syndrome Coronavirus (SARS - COV – 2) was first recognised on the 31st of December 2019 in the Wuhan region China, and was named Coronavirus Disease 2019 (COVID - 19).[1-4] It was rapidly transmitted globally and was formally characterized as a pandemic by the World Health Organization on March 11th 2020, while by May 18th more than 5 million confirmed cases were reported.[2,6] Until March 2021, more than 126 million people worldwide were infected by the virus, and more than 2 million deaths occurred.[7] Until October 2020, although almost half of the infection cases that were reported affected the age group of 25 - 64 years, the majority of mortality outcomes has been shown in the elderly.[8] As a result of this hyper - contagion, all national healthcare systems across the globe were tested and forced to directly adapt to the new situation, with strategies that aim at the prevention of secondary transmission of the disease, along with the systematic identification of the COVID - 19 carriers, patients, or close contacts of a confirmed case, following their assessment and isolation.[2,3,9] The coronaviruses belong to the Ribonucleic Acid (RNA) virus family and they can cause infection with a wide clinical spectrum, that can range from common cold symptoms to severe acute respiratory syndrome. During genome sequencing it was defined that SARS – COV 2 is identical to SARS at a percentage of 80%. However, according to new data, the disease which was initially characterized as a pure respiratory illness now seems to affect a variety of systems.[10,11] This is supported by reported cases with manifestation of both cardiovascular, haematological and urinary symptomatology, while according to the National Health System (NHS), there is a considerable increase on problems of neuropsychological etiology, that can be persistent even after the hospital discharge of the COVID - 19 patients.[3,5] As it is shown from epidemiological data, approximately 1 out of 5 people is being hospitalized for the SARS - COV - 2 infection, and almost 1 of 10 is being admitted to the ICU, with the higher percentage of patients having severe disease and developing Acute Respiratory Distress Syndrome (ARDS) followed by the need for intubation and mechanical ventilation (MV).[12] Many patients that suffered from COVID - 19, still continue to face psychological issues, including Post Traumatic Stress Disorder (PTSD), anxiety and depression, after being treated and discharged from the hospital, just like it happened before with the survivors of SARS coronavirus in 2003.[13] The fact that new evidence, considering the neuropsychological impact of the SARS - COV 2 disease, comes to light, leads to the conclusion that apprehension of the illness' long - term complications are getting dubious and the need for continuing treatment support, regarding both biological and psychological health issues after hospitalization, is getting more and more important.[3,14]

PATHOGENICITY AND NEUROPATHOPHYSIOLOGY OF COVID - 19

The SARS - COV - 2 infection can evoke illness of the respiratory tract with a clinical spectrum that ranges from asymptomatic infection to severe viral pneumonia, respiratory failure, septic shock, metabolic acidosis, multiple organ impairment and death.[5,10,15] According to Wiertz CMH et al.,[15] three histological patterns are being noticed: alterations in the epithelium and alveolar impairments, the production of small clots in the pulmonary blood vessel network and the expression of interstitial fibrosis. The typical symptoms of the disease include cough, dyspnoea, reduced activity tolerance and fatigue, whereas atypical symptoms contain nausea, diarrhoea and acute abdominal pain.[15] It is now recognised that the disease affects a wide variety of organ systems. Besides the respiratory, issues from other systems emerge, like myocardial impairment, thromboembolic events, acute renal malfunction, neuropathy and weakness.[1,15,16]

SARS - COV - 2 seems to critically evoke outcomes to the nervous system due to its ability to contribute to coagulation disorders, clotting and inflammation. According to Tucker and Czapla[17] a Spanish study that included 841 hospitalized patients showed that more than half of them were characterized by at least one neurological symptom, whereas the 19,9% showed symptoms of neuropsychiatric nature like insomnia, depression and psychosis. In the acute phase of the disease, 36.4%[1] of the patients develop neurological symptoms, including headaches, distorted mental state, seizures, loss of taste

and smell and paraesthesia.[14,16,17] Conditions like encephalopathies, chronic inflammatory demyelinating polyneuropathy, Guillain - Barré, Miller - Fisher syndrome and epileptic seizures can be connected with the acute phase, without known previous medical history.[14,18] The coronaviruses are neuro-invasives and can cause neuropsychological fallouts, either with the direct infection of the central nervous system or via indirect expression of immunological response related symptoms.[11] In COVID - 19 patients there are noticed elevated levels of interleukin - β, interferon, CCL2 cytokines and CXCL10 chemokines, which indicate the T - helper lymphocyte activation.[11,19,20] The cytokine storm effect that participates in the immunological response to the coronavirus, can cause psychiatric symptoms due to neuroinflammation, whereas the disruption that is caused by the infection of the immune system additionally contributes even further to the psychological stress and the stress induced by the general inflammation.[11,19,20] According to a systematic review, higher levels of interleukin – 6 (IL6), IL8 and tumor necrosis factor – a (TNFa) along with reduced levels of CD4 and CD8 T - lymphocytes were associated with the clinical condition.[20] Critical neurological complication constitutes the Critical Illness Polyneuropathy, a situation that can affect both the motor and the sensational neurological function, that finally leads to axis degeneration.[1,6,11] Beyond the symptoms of the illness itself, the patients may experience a variety of stress factors and trauma - induced events, such as difficulty accessing hospital wards, mental isolation, deaths of other patients or loved ones and other unwanted effects towards mental health, due to treatment factors.[6,14] The experience of ICU treatment by itself can effectively increase the possibility of developing post traumatic stress disorder syndrome (PTSD), depression and anxiety.[16,18] Furthermore, patients that received ICU treatment for ARDS reported neurocognitive deficits as high as 47%, even two years after being discharged.[16,18] Also, individual factors that occur include the fear of the disease, uncertainty of the future, traumatic memories and stigma, and further aggravate the possibility of psychopathological results being developed.[11] Aside from the fact that the biological problems appear mainly at the acute phase of the disease and its treatment, the cognitive impairments and mental health disorders are occurring later in the future, when the patients have returned to their everyday routine and can be connected directly to the disease itself or its treatment.[8,14,15] Therefore, the long term complications that seem to be caused by the nature itself of the disease, along with the increased possibility for ICU admission, from which the consequences have already been described, can lead to persistent symptoms or even syndromes after ICU hospitalization and treatment.[21]

POST INTENSIVE CARE SYNDROME

The situation that can be presented after the admission of a patient in ICU and can include every physical harm but also, any damage to the cognitive and mental field, arising as a consequence of a critical illness, is characterized as Post-ICU Syndrome or Post Intensive Care Syndrome (PICS).[3,15,21] Individuals with severe COVID-19 symptoms are treated in ICUs, usually with MV to support breathing.[12,16] In particular, patients with COVID - 19 who are led to severe respiratory failure are commonly treated with sedation, steroids and synaptic inhibitors, approaches that have been associated with PICS challenge, either in the immediate period after discharge from the hospital, or later, when patients return to their daily life.[15,21,23] It has been reported that a significant proportion, accounting for 56% of patients, develops one or more PICS-related problems, even one year after ICU discharge. Crucial part of patient management is recognizing the syndrome and providing urgent care for their rehabilitation. In many cases, however, immediate intervention is not possible, due to the risk of spreading hospital-acquired infections. Therefore, the majority of patients with severe respiratory failure do not receive the necessary care for their rehabilitation, resulting in an increased chance of developing PICS symptoms after hospital discharge.[15,23]

POST-TRAUMATIC STRESS DISORDER

Widely recognizable factors of PICS are the post-Traumatic Stress Symptoms (PTSS) and the onset of PTSD, in patients admitted to ICU.[5] PTSD is defined as a stress-related disorder, with consequent autoimmune disease that may occur after exposure to a serious traumatic event or injury.[9] In addition, it is referred to as the development of symptoms related to in-

trusive memories, emotions and thoughts, memory avoidance attempts, negative changes in cognitive function and mood, as well as hyperarousal after exposure to a traumatic event.[2,9,14] In fact, it seems that 1 out of 5 COVID-19 survivors develop symptoms of PTSD from the very first year, and this has been associated with reduced quality of life.[24] Experiences during the trauma may lead to limitations and disorders of daily life, or even mental disorders such as depression, schizophrenia and medicine abuse. In previous domestic outbreaks, the incidence of PTSD after a serious infection ranged from 4% to 41% in the general population, while, in the case of COVID-19, 29-33% of patients were reported and a smaller percentage in the healthy population.[2] It is scientifically suggested that PTSD complies with a biphasic stress response model. Acute stress enhances the immune response, while chronic stress can lead to suppression of the immune response, with increased susceptibility to infections.[9] The release and changes in the expression of cytokines, the production of inflammatory factors and the process of conversion of T2-helper cells by T1-helper cells seem to play a role in both acute and chronic stress.[9] There is a wide diversity of risk factors that are connected with the appearance of PTSD, and they can be both predictors and ICU - treatment related factors. Predisposing factors include patients' characteristics such as age, gender and various pre-existing medical conditions, and informal factors such as interpersonal conflicts, low socioeconomic status and reduced social support.[2,14] Women appear to be more associated with PTSD symptoms than men.[11,23] A study by Stephen J Halpin et al.[5] found that in patients with COVID-19 who were admitted to ICU, 76.9% of women reported PTSD-related symptoms compared with 38.5% of men who reported similar symptoms, rates that did not appear to differ from those who were admitted to other nursing departments. Other factors include pre-existing depression, anxiety, alcohol abuse and low educational level,[23] while in 80% of people, who developed PTSD in ICU, obesity was observed.[5]

Beyond the factors that predispose to PTSD, there are other variables related to treatment in the clinical field and especially in the ICU, with an incidence of 30 - 40%[14] considering post traumatic symptoms in patients who survived from ARDS. Invasive therapies such as sedation and antipsychotic treatment, variables related to ICU environment such as immobility, endotracheal intubation, tracheostomy, sleep deprivation and conditions such as sensory problems and acute delirium, are strong risk factors for the development of PTSS and PTSD.[14,22] Stephen J Halpin et al.,[5] reported in their study that patients' PTSD levels of those admitted to ICU were twice as high as those in the nursing departments. The incidence of PTSD was also significantly high in both previous coronaviruses, SARS and MERS, as 26% of SARS survivors met the diagnostic criteria for PTSD 30 months after treatment, while in the case of MERS 42% of survivors noted a high score for PTSD, with 27% remaining above the clinical cut-off, even 18 months after treatment.[14]

The association of PTSD with hospitalization for COVID-19 is complex and is indicated by the large difference of percentages in the studies, by reviewing international literature. Based on information from previous coronaviruses, an increased incidence of PTSD and PTSS is expected in COVID-19 survivors [14]. Lisa Mary Sheehy's[1] study reported that in patients admitted to ICU due to ARDS, PTSD was reported in 22-24%, two years after discharge. Another study in Wuhan[6] found high levels of PTSD in patients with COVID-19 as all patients experienced at least one symptom of avoiding memories, feelings or thoughts, two negative mood swings and two symptoms of arousal. Statistical analysis found that 12.4% of these patients were diagnosed with PTSD. Symptoms of COVID-19 such as cough, exhaustion, and chest discomfort were statistically significantly correlated with the onset of post-hospital PTSD. The incidence of COVID-19 in PTSD was higher in young adults, at 31.8% in the United States, and there was a proportional increase in the incidence of PTSD, as the severity of the disease increased. In contrast, PTSD symptoms in ICU patients in France, were confirmed in only 7.4% of the participants.[25] One of the most common factors associated with COVID-19 and ICU hospitalization, leading to PTSS, it is likely to be the onset of ARDS, as post-traumatic symptoms are present in 30 - 40% of these patients even months after treatment, while in patients who were supported with MV the rates for PTSD range between 14% to 51%.[1,3,12,14] Therefore, the identification and treatment

of PTSD in patients with COVID-19 is an important pillar of therapeutic assessment and intervention. Continuous follow-up and evaluation of the condition is needed after hospitalization, with frequent feedback aimed at detecting mental disorders, in order to improve the long-term prognosis of patients with SARS-COV-2 who underwent therapeutic interventions in ICU. [15,23]

OTHER PSYCHOLOGICAL AND NEUROPSYCHOLOGICAL EFFECTS

The knowledge gained from coronaviruses has shown that they can cause a variety of psychopathological effects,[11,14] directly or indirectly, with the mechanisms described in neuropathophysiology, in combination of course with the complications of the disease and the experience of harrowing stress of a potentially fatal disease, into the inhospitable environment of the ICU.[11] Specifically, in a systematic review concerning the long-term psychological distress of survivors from previous coronaviruses, it was shown that one third of them still had symptoms for more than three months after leaving the hospital or ICU, and even the prevalence of depression and anxiety were estimated collectively at percentages of 33.2% and 30.04% respectively.[26] The critically ill patients with COVID-19 often develop severe respiratory failure and therefore it is likely to need ICU treatment even with long-term support from MV, in deep sedation.[12,14,16,24] Regardless of the intubation frequency however, one third of ARDS survivors from the ICU worsen or begin to show symptoms of cognitive impairment up to one year after treatment, which include deficits in memory, concentration and functionality, such as reduced verbal fluency and processing speed,[12,14] but also signs of impaired mental health up to two years later. This could be linked to acquired brain damages due to hypoxia, but also to the consequences of MV, which could possibly induce intrusive memories of panic and asphyxiation. Several intubated patients under sedative drugs, that overcame ARDS in ICU, showed that they experienced hallucinations when therapeutic interventions were performed, or sleep disorders, which are sometimes still recalled and affect them respectively.[14,22] Along with the nature of the action of the coronaviruses, triggering factor for the occurrence of neuropsychological consequences may be the treatment in the ICU, since only the prevalence of symptoms of depression, anxiety and PTSD in survivors of serious diseases who have already been treated in units is already elevated, ranging from 17% to 44%.[27]

From the aforementioned it is understood that the negative effects on mental health, due to SARS-CoV-2, are not over with the discharge, as many patients continue to experience moderate to severe problems one month after they received their hospital release form.[6] In a French, uncontrolled study, 4 months after discharge from the ICU, the incidence of anxiety was confirmed in 23.4% and depression in 18.1%, while the ICU-related neuromyopathy was observed in 14 of 51 intubated patients (27.5%).[25] High rates of psychological distress were recorded in the study of Garrigues et al.,[28] with the most commonly reported symptoms persisting for more than 100 days after discharge, being exhaustion, which reached 55%, memory loss in 34%, and also sleep and concentration disorders in 30.8% and 28% respectively, although in the same study no statistically significant difference was found between ICU patients and patients in other nursing departments. However, it is obviously difficult to distinguish the effect of patients' poor psychological condition due to fear and the impact of stigma from the neurobiological effects.[18,26] Current data characterize the fatigue, which is associated with the new disease, as one of the most frequently reported symptoms, as it occurred in 72% of patients in the ICU and in 60.3% of patients in other nursing departments.[5] Persistent fatigue as well as other neuropsychological symptoms are reported in rates of 35% in outpatients with COVID-19, and 87% in those who were hospitalized. At this stage, it is generally accepted to speak only of a post-infectious fatigue.[21] Nevertheless, to conclude that symptoms of Chronic Fatigue Syndrome may occur after COVID-19, as shown in a four-year follow-up of SARS survivors,[29] these symptoms should last at least 6 months, and a complete medical record with additional laboratory tests should be taken, for the examination of previous health state and the degree of possible pre-existing fatigue, in order to determine to what extent is the new coronavirus responsible.[21] There is still ambiguity about the exact causes of exhaustion, although it is known that ICU care, after acute lung injury, is likely to lead to

muscle weakness, which is associated with reduced physical activity and quality of life.[26] Also, according to the available data, the cells of the infected, after the end of the infection duration, face difficulties in receiving energy from sources, compared to the cells of the healthy ones. It is presumed that the role of inflammatory processes in the body is very important. The "cytokine storm" caused by SARS-COV-2, in case it afflicts the body for a long time, has been considered to contribute to aging and thus to inhibition of cell proliferation.[19,20] Alongside, in the case of the causes that contribute to the occurrence of fatigue, there are even assumptions about the post-infectious permeability of the blood-brain barrier from pro-inflammatory cytokines and the persistence of elevated levels of anti-inflammatory cytokines after healing from the infection, which implies a persistent inflammation in the body.[19,21] All this information emphasizes the need for vigilance and preparation against these potential long-term neuropsychiatric complications, which lead to a reduction in patients' quality of life after the disease.[27]

CONCLUSIONS

Pandemics constitute a challenge to the functional normality of public health and coerce into the development of goals and coordinated movements by each system. The pandemic of COVID-19 disease as well as its challenges made the presence of organizational issues and deficiencies in the clinical areas noticeable. As mentioned, the effects of the disease are not limited to specific time frames after patients' discharge from the ICU, nor do they always affect the same organ systems. The attention of health professionals should also be focused on the persistent neurological and psychiatric consequences, as groups of symptoms that contribute to the development of PICS, PTSD, anxiety and depression after ICU treatment have already been identified. There are also reports of a group of new symptoms, including post-hospital fatigue, referred to as Post Covid-19 Neurological Syndrome.[8] Therefore, it is reasonable to expect new symptoms and syndromes after COVID-19 treatment, especially when symptoms in this population begin to be studied in detail. Due to the increased frequency of problems, the consequences of the pandemic ring the alarm bell for improved organization and redefinition of our priorities, in order to have adequate preparation and appropriate approach to potential or existing patient health problems, in every aspect and all - time phases of the disease. Health systems must focus on the prevention of COVID-19 and neuropsychiatric consequences, their proper treatment inside and outside hospital structures, but also on post-hospital monitoring and rehabilitation.

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