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Review Article

CIENT PERIODIQUE

Neuropsychiatric Manifestations in Relation to SARS-CoV-2 Infection

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Abstract

Since Hippocrates, the role of the brain in mental illness has been accepted and Neuropsychiatry has been introduced as the integrating specialty of psychiatry, neurology, neuropsychology, and neuroscience in general. In light of the patients described with the Acute respiratory syndrome in Wuhan, China, which has spread and considered a pandemic, an analytical summary of the scientific evidence available regarding the involvement of the nervous system by the coronavirus 2019 and its impact in the genesis of neuropsychiatric disorders was made. To elaborate it, the Google Academic search engine and the descriptors COVID-19, SARS.CoV-2 and neuropsychiatric manifestations were used. The Medline, Scielo, Scopus and Medscape databases were used. The general clinical

manifestations of COVID-19, acute neuropsychiatric symptoms including encephalopathies, epileptic seizures, cerebrovascular disease, myelitis, muscular and peripheral nervous system, taste and smell disorders, and Guillain's syndrome are described. In addition, subacute or chronic neuropsychiatric sequelae in relation to SARS-CoV-2 infection are highlighted, which include depression, anxiety and stress related to the pandemic, indicating the care to be taken with health personnel, patients with previous mental illness and chronic neurological diseases, in which symptoms can worsen and even lead to suicide.

Introduction

Neuropsychiatry is an integrative medical specialty, combining knowledge and experience in psychiatry with knowledge or experience in neurology / neuroscience and neuropsychology [1].

Since Hippocrates, the role of the brain in mental illness has been accepted. At the dawn of modern scientific medicine in the late 18th and early 19th centuries, physicians identified themselves as neurologists or psychiatrists for reasons that had more to do with the nature and location of the practice than the mind-problem approach. brain. Modern neurology and psychiatry started from a common neuropsychiatric matrix in the late 19th century, which continued to prevail in European training and practice, until, in the last century with the development of neurobiology and other related sciences, they converge again and [2] a new intellectual framework is developed for understanding the brain, healthy and sick, which is a challenge that must be assumed by those who want to lead the field intellectually, and those who must educate others in it [3].

For this reason, it is necessary to analyze the involvement of the nervous system, which includes the neuropsychiatric aspects, from the perspective of the current situation, in which the world is experiencing an extremely stressful scenario since, in the month of December last year, Several patients were reported in Wuhan (Hubei Province, China), with respiratory symptoms and pneumonia, but who, in turn, involved other organs and systems, including the brain. The causal agent was able to specify that it was a new coronavirus (2019-nCoV), which was named in February 2020, coronavirus causing severe acute respiratory syndrome by coronavirus (SARS-CoV-2), constituting the seventh known coronavirus that infects humans [4,5].

Shortly after the disease was named by the World Health Organization (WHO), coronavirus disease 2019 (COVID-19), given its similarity from the virological point of view and also in its clinical expression with SARS-Cov1 (229E (HCoV-229E), responsible for a syndrome with similar characteristics that also originated in the animal markets of China in 2003 [6-8].

In general, coronaviruses that affect humans, and whose origin and possible reservoir are wild animals, including bats, can be classified into those with low pathogenic capacity, which include HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU (Coronavirus α) and those other highly pathogenic, named under the CoV category, such as SARS-CoV (responsible for the 2003 SARS outbreak), along with the one that produced the Middle East Respiratory Syndrome (MERS-CoV) in 2012 and the current year (SARS-CoV-2). These are called Coronavirus β and have become a real public health problem due to their high pathogenicity and infectivity [9].

The outbreak of pneumonia associated with the new coronavirus that was initially reported in Wuhan, [10,11] it caused a rapid increase in the number of cases throughout the region and progressively expanded to various neighboring countries [12,13] and then to Europe and America, declaring a pandemic by the World Health Organization later [14,15].

It has become clear in recent weeks, by multiple authors, that patients infected with the SARS-CoV-2 virus can present in various ways, including neuropsychiatric manifestations, which may precede lung symptoms and fever or present later [16].

This document aims to make an analytical summary of the scientific evidence available regarding the involvement of the nervous system by SARS-CoV-2. To elaborate it, the Google Academic search engine and the descriptors COVID-19, SARS-CoV-2 and neuropsychiatric manifestations / complications were used. The Medline, Scielo, Scopus and Medscape databases were used.

Clinical Manifestations

The main clinical manifestations of COVID-19 are fever, dry cough, dyspnea, and acute respiratory distress. However, many infected subjects may be asymptomatic or present with mild symptoms, such as headache, non-productive cough, fatigue, myalgia, and anosmia. Some patients can experience SARS a week after symptoms start and can be fatal. Overall mortality is estimated at 8% and is due to respiratory failure with hypoxia or multiple organ failure [17].

The infection can also produce interstitial pneumonia and, in many cases, irreversible damage to the lung tissue that generates serious sequelae or leads to death [18].

Elderly or seriously ill patients are the most vulnerable population group. High blood pressure (24%), diabetes mellitus (16%), ischemic heart disease (6%), cerebrovascular diseases (2.3%) and chronic obstructive pulmonary disease (3.5%) are the most frequent comorbidities in severe forms of COVID-19 [17].

Respiratory viruses are also known to penetrate the central nervous system (CNS) (neuroinvasion), affect both neurons and glial cells (a property known as neurotropism), and induce various neurological pathologies (neurovirulence) [19].

Coronavirus infection has been reported in the brains of experimental animals and infected patients [7]. Considering the affinity for the nervous system, SARS-CoV-2 can infect both neurons and neuroglia.

The study of the neurotropic potential of SARS-CoV-2 using pathological samples and its isolation of the endothelium from the cerebral microcirculation, cerebrospinal fluid and brain tissue can further clarify its role in brain damage and its influence on the cardiorespiratory center in the trunk. encephalic [7].

This topic has elicited diverse opinions in the international arena in search of a better definition and to make an alert call to the scientific and practical medical community to be alert to any neuropsychiatric manifestation related to SARS-CoV-2 infection [20].

Acute Neuropsychiatric Symptoms Associated With SARS-CoV-2 Infection

In accordance with the neurotropic properties of SARS-CoV-2, clinical cases are reported from the first studies carried out, where the nervous system affectations of said affection are exposed, which are more frequent in cases of severe infection, worsening the prognosis of patients. [6,15,21,22].

Necropsy studies have shown the presence of hyperemic and edematous brain cell tissue, as well as neuronal degeneration [47,48] and some researchers have detected SARSCoV nucleic acid in the cerebrospinal fluid (CSF) of the patients and in the brain tissue studied [23,24].

In the study of the first affected cases, in the epicenter of Wuhan, China, 214 patients with SARS-CoV-2 were retrospectively evaluated. The most frequent symptoms at the beginning of the disease were fever, dry cough and anorexia. 36.4% of the patients presented neurological manifestations (78 patients), where involvement of the central nervous system (24.8%) predominated, followed by damage to the skeletal muscle (10.7 %) and the peripheral nervous system (8,9 %) [6,12,25].

Among the CNS manifestations, dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and epilepsy were required. The greatest differences between cases of severe and non-severe infection were observed in the deterioration of consciousness and acute cerebrovascular disease ($P < 0.001$ and $P < 0.05$ respectively) [6].

In another series, neurological symptoms or signs were observed in 84%, with the following distribution: confusion (26/40, 65%), agitation (40/58, 69%), signs of the corticospinal tract (39/58, 67%) and dysexecutive syndrome (14/39, 36%) [26].

The severe hypoxia that patients with COVID-19 suffer is a risk factor for encephalopathy [17].

These have been reported as an initial symptom of COVID-19, which can occur in patients with previous neurological damage and acute respiratory symptoms. The risk of suffering an associated altered mental state is higher in people of advanced age or with previous cognitive deterioration, as well as in those who present vascular risk factors (hypertension) and previous comorbidities.

Acute necrotizing hemorrhagic encephalopathy [25], encephalitis [27], and meningoencephalitis have been described, the latter associated with generalized epileptic seizures and decreased level of consciousness [28].

Epileptic seizures were also described in patients with acute stress reaction and hypocalcemia, and in an Iranian study for the first time, their association in the course of coronavirus infection (COVID-19) [29,30].

Ataxia was only reported in the Wuhan study, in a single patient [6] and more recently in one case who presented with acute cerebellar ataxia followed by encephalopathy, who also had SARS-CoV-2-related pneumonia [5].

Cerebrovascular disease was initially reported in the retrospective study of 221 patients with Wuhan COVID-19, presenting 11 (5%) ischemic strokes; one (0.5%), cerebral thrombosis of the venous sinuses; and one (0.5%), a cerebral hemorrhage [31] and has been evidenced in other subsequent studies [12,31-34].

The first case of post-infectious myelitis was reported in a 66-year-old patient diagnosed with COVID-19 [21,25].

Considering the potential of neuromuscular involvement by COVID-19, SARS-CoV-2 infection could cause Guillain-Barré Syndrome, myositis or polyneuropathy / myopathy of the critically ill patient [33].

The infection could also exacerbate a known neuromuscular disease or lead to the diagnosis of one whose symptoms and signs were masked. Among the autoimmune diseases we find: chronic demyelinating inflammatory polyneuropathy (CIDP), multifocal acquired demyelinating sensory-motor neuropathy, multifocal motor neuropathy, Myasthenia Gravis, Eaton-Lambert; and the degenerative group includes: amyotrophic lateral sclerosis, spinal muscular atrophies, hereditary neuropathies, muscular dystrophies, congenital myopathies, mitochondrial, metabolic myopathies, among others [35,36].

Disorders of taste and smell are commonly reported by patients with COVID-19. Recent reports indicate that anosmia or hyposmia are early markers of SARS-CoV-2 infection [37-39].

Some authors found in their casuistry that anosmia or hyposmia was required in 30% of patients. (86). In another case series, 85.6% had infection-related olfactory dysfunction. In another series, the authors specified olfactory dysfunction as the first manifestation of COVID-19 [38,40].

Subacute or Chronic Neuropsychiatric Sequelae in Relation to SARS-CoV-2 Infection

Studies of past respiratory viral pandemics suggest that various types of neuropsychiatric symptoms may arise in the setting of an acute viral infection, or after variable periods of time after infection. Reports from the 18th and 19th centuries suggest that influenza pandemics in particular have been characterized by a higher incidence of various symptoms, such as insomnia, anxiety, depression, mania, psychosis, suicidal tendencies, and delirium [41-43].

The lethargic encephalitis (EL) that was described by Von Economo in 1932, is an inflammatory CNS disorder, characterized by hypersomnia, psychosis, catatonia and parkinsonism, the incidence of which increased at the time of the early "Spanish" influenza pandemic of the 20th century.

During the most recent 2009 influenza (H1N1) pandemic and other coronavirus infections (SARS-CoV-1 epidemic in 2003, and the outbreak of the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, several Neuropsychiatric sequelae, including narcolepsy, epileptic seizures, encephalitis, encephalopathy, Guillain-Barré syndrome (GBS), and other neuromuscular and demyelinating processes [44-47].

In the first months of the current pandemic, reports of acute symptoms associated with the CNS in individuals affected by COVID-19, neurological manifestations and the mechanisms that have been postulated have already been compiled [6].

However, beyond acute infection, the delayed or chronic effects of this pandemic, particularly on mental health, will not be fully appreciated immediately. Therefore, timely and longitudinal investigations of possible neuropsychiatric outcomes associated with COVID-19 are essential in disease surveillance and evidence-based therapeutic strategies [41].

Long-term neuropsychiatric complications after SARS-CoV-2 infection are currently unknown and will be seen in the coming months or years. Following previous influenza pandemics and outbreaks of CoV, such complications have been described for highly variable periods of time, from weeks after acute respiratory symptoms in the case of neuromuscular and demyelinating processes, to decades after intrauterine exposure to viral infection [44,46,48].

Given the overall burden of COVID-19 infection, even if delayed neuropsychiatric sequelae are associated with a fraction of cases, the public health implications of such complications will be significant. Therefore, it is essential to understand the trajectory and characteristics of the neuropsychiatric outcomes derived from SARS-CoV-2 infection, and it will be essential to discover the pathogenic mechanisms that may support therapeutic interventions.

Depression and Anxiety

Depression, anxiety, and trauma-related symptoms of pandemics have been associated with outbreaks of CoV, but it is unclear whether the risks are attributable to viral infections per se or the host's immune response.

Although currently very limited data exist for COVID-19-related psychiatric symptoms, survivors of SARS-CoV-1 were clinically diagnosed with depression (39%), panic (32.5%), and obsessive-compulsive disorder (15.6%) at 31 to 50 months after infection, a dramatic increase in their pre-infection prevalence of any psychiatric diagnosis by 3% [49].

The main psychiatric manifestations related to the SARS-Cov-2 disease are considered to be due to anxiety, depression and stress. The confinement measures taken to curb the coronavirus, the harshness of the situation for the sick and health, as well as the loss of loved ones in isolation situations have generated severe damage to collective mental health.

Studies of health workers during the SARS-CoV-1 epidemic, the MERSCoV outbreak and the current SARS-CoV-2 pandemic suggest that the frequency and severity of psychiatric symptoms are associated with proximity to patients. infected with CoV [50-53].

It is considered by the authors who have reviewed the topic that the current health crisis represents a great psychological challenge for both health professionals and the population, since COVID-19 infection has compromised social, work and daily life.

Research by Jianbo Lai *et al.*, From the Department of Psychiatry, Renmin Hospital, Wuhan University, evaluated the magnitude of mental health outcomes and associated factors among professionals treating patients exposed to COVID-19 in China. For this, they carried out a cross-sectional study, based on surveys

and stratified by regions, which gathered demographic data and psychological well-being evaluations of 1,257 health professionals in 34 hospitals. At the end of the study, the frequent manifestations of mental deterioration in the professionals were identified, which coincided with the manifestations previously mentioned [51].

Some authors consider that health personnel who directly care for patients with COVID-19 acquire stress for fear of becoming infested and this can cause damage to their health. If the psychological adjustment mechanisms do not compensate the situation, they may suffer from Burnout Syndrome (BOS) or post-traumatic stress disorder (PTSD), an entity that has been addressed by many authors, has been described more frequently in the nursing staff [54,55].

A vulnerable group is made up of patients with previous mental entities or those who have suffered special situations capable of developing psychological disorders such as post-traumatic stress, acute stress disorder, major depressive disorder, adaptive disorders or other anxiety disorders, as well as the development of somatic symptoms. In the case of patients suffering from mental pathology prior to infection by this virus, they are at greater risk of relapses or of worsening their symptoms in this situation. The high vulnerability to stress of these people will mean that their suffering may be greater than that of the rest of the population. Some authors even point out that suffering from mental illness increases the risk of contagion [56-60].

On the other hand, the scientific community has been alerted by the Spanish Psychiatric Society, about certain special groups such as patients with an Autism spectrum, patients with intellectual deficit, patients with Alzheimer's disease who have difficulty in adopting the indicated confinement measures, as well as personal hygiene and protection, suggested by the World Health Organization (WHO). In this sense, patients with schizophrenia may have exacerbation of symptoms and patients with addiction may increase the consumption of drugs such as alcohol, cigarettes, among other harmful substances [61,62].

Psychotic Disorders

Exposure to viral infections in utero, during childhood development, and into adulthood has been associated with an increased risk of developing schizophrenia [43,63,64].

While most studies have focused on the history of influenza and the risk of infection and psychosis, two studies have evaluated the presence of antibodies against various strains of coronavirus in individuals with psychosis. However, no association was reported between seropositivity for HCoV-NL63 and the history of psychotic symptoms in patients with mood disorders [65].

Furthermore, Severance *et al* found a higher prevalence of antibodies against four strains of HCoV in patients with a recent psychotic episode compared to non-psychiatric controls [66], suggesting a possible relationship between CoV infections and psychosis, which It can also occur in SARS-CoV-2.

Valdés-Florido *et al* report in the patients admitted to the Virgen del Rocío and Virgen Macarena University Hospitals (Seville, Spain), during the first two weeks of the mandatory quarantine at the national level, four patients who met the criteria for psychotic disorder in the Manual diagnosis and statistics of mental

disorders (DSM-5). In the authors' opinion, all the episodes were triggered by stress arising from the COVID-19 pandemic, and half of the patients exhibited severe suicidal behavior upon admission.

In turn, they consider that we may currently be witnessing an increase in the number of brief reactive psychotic disorders as a result of the COVID-19 pandemic. This type of psychosis, the authors comment, has a high risk of suicidal behavior and, although it is transitory, it has a high rate of psychotic recurrence and low diagnostic stability over time. Therefore, they are in favor of close supervision both in the acute phase and in the long-term follow-up of these patients [67].

In another order, it has been reported that patients with neurological diseases such as multiple sclerosis and other diseases of chronic evolution of the central nervous system, who suffer this nosological entity, can acquire depression, with decreased neurological functions and suffer new damage to the brain. All of which must be taken into account with a view to the comprehensive management of patients [67-69].

Conclusions

• SARS-CoV-2 infection shows evidence of nervous system involvement and therefore patients may present with neuropsychiatric manifestations.

• Acute symptoms include involvement of the central nervous system, skeletal muscle damage, and peripheral nervous system.

• The most significant central nervous system symptoms were dizziness, headache, impaired consciousness, cerebrovascular disease, ataxia, and epilepsy.

• Among the most significant clinical manifestations of the peripheral nervous system, anosmia and dysgeusia are reported.

• Psychiatric disorders that must be considered for their possible presentation are depression, anxiety, stress and psychosis.

• The possibility of the health personnel being affected by the stress of the pandemic and those who suffer from chronic diseases of the nervous system should be foreseen, which can worsen their symptoms and lead to suicide.

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