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Mini Review

A Review of COVID-19 with Evidence of Neuropsychiatric Complications

Ciro Visone*

Department of Psychology, Northcentral University, United States

***Corresponding Author:** Ciro Visone, Department of Psychology, Northcentral University, United States.

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Abstract

COVID-19 has claimed the lives of over 2.1 million people across 224 countries. There have been 98 million conferred cases since Chinese health officials first identified the zoonotic RNA virus. The virology of SARS-COV-2 is a primary reason why an individual's respiratory system decompensates, affecting cellular processes governed by angiotensin-converting enzyme 2 (ACE2). Importantly, ACE2 enzymes are abundant throughout the body's major organs, including lungs, kidneys, cardiovascular system and intestines. Proper ACE2 functioning is important for amino acid transportation and can help regulate blood pressure, gut dysbiosis and pulmonary hypertension, while reducing the risk of heart failure, lung disease and diabetes mellitus. Research suggests an over active inflammatory response resulting in a cytokine storm responsible for severe and fatal effects. This macrophage activation syndrome (MAS) attacks healthy cells and organs in an attempt to rid the body of bacteria, resulting in chronic inflammation akin to other inflammatory disorders. Research now also suggests the vulnerability of the central nervous system. ACE2 enzymes exist most notably in the cortex, brainstem, striatum, and hypothalamus. Recent studies show neurologic and neuropsychiatric susceptibility, with enduring symptoms beyond recovery. A UK study of 125 patients found 62% to present with ischemic stroke, while 31% of patients exhibited altered mental state, personality, behavior and new onset psychosis, with roughly an equal number of patients below and above the age of 60 experiences neuropsychiatric symptoms and disorders. A separate study of 402 patients in Milan found 60% to have at least one neuropsychiatric diagnosis 15 days post discharge, despite a reduction in neuroinflammatory markers, suggesting potentially enduring effects on the brain and central nervous system.

Keywords: *COVID-19; Neuropsychiatric Complications; Macrophage Activation Syndrome (MAS); Angiotensin-Converting Enzyme 2 (ACE2)*

Introduction

Chinese health officials in Wuhan, China reported the initial case of human contacted COVID-19 in early December 2019 [1]. By mid-January 2020, the virus was identified has having a zoonotic origin; contrasting the popular perspective that perhaps it had been constructed in a laboratory. A worldwide pandemic quickly ensued, with global economies resorting to complete lockdowns of businesses, schools, and nearly all public establishments, in addition to mandated wearing of masks to prevent further spread in the context of growing numbers of those infected and total deaths. Practices of "social distancing", "social isolation" and "quarantine", became as prevalent in spoken languages across the globe as common greetings. Now, a year later, what was initially thought to subside through misinformed theories of "herd immunity", COVID-19 has claimed the lives of over 2.1 million people, with nearly 98 million confirmed cases, across 224 countries [1]; a stark reality.

Pathophysiology and virology

Although the purpose of this article is not to divulge the biochemical properties of COVID-19, it is important to elucidate how the virus infiltrates human cells to foster a basic understanding of the symptoms produced. In doing so, it is first necessary to articulate COVID-19's pathophysiological structure, beginning with its given name. COVID-19 is the disease abbreviated name for "coronavirus 2019", assigned

by the Coronavirus Study Group of the International Committee on Taxonomy of Viruses (ICTV) [1]. While the name is often used interchangeably with the term "coronavirus", it is important to note that COVID-19 is the disease, whereas the virus is actually marked by a severe acute respiratory syndrome (SARS). The virus shares similar properties to the 2003 SARS outbreak, also known as SARS-COV-1. As such, the official virus classification is SARS-COV-2; an ode to the pathophysiological corona or crown-like structure when viewed at the microscopic level under.

The virology of SARS-COV-2 is a primary reason why an individual's respiratory system decompensates. The virus is a type of ribonucleic acid (RNA) with the potential to influence cellular processes and functions. Method of entry into the cell is via the angiotensin-converting enzyme 2 (ACE2) [2]. Once permeated, cellular mechanism are altered, triggering some of the acute and chronic damage being see in certain organs, which may result in hypoxia, thrombosis, and viral proliferation throughout the body. ACE2 is an enzyme widely expressed throughout the lungs, kidneys, intestines, heart, and arteries [3]. In the central nervous system, ACE2 exists be in abundance in the cerebral cortex, striatum, brainstem, and hypothalamus [4]. Importantly, healthy ACE2 functioning is responsible for lowering blood pressure, transporting amino acids, an reducing the risk of heart failure, diabetes mellitus, and lung disease [5]. ACE2 functioning has similarly been shown to improve gut dysbiosis and pulmonary hypertension [5].

Inflammatory response

The aforementioned implications of ACE2 enzymes are significant, given the propensity for SARS-COV-2 to permeate a cell at the ACE2 receptor site, triggering uncontrolled endocytosis and impeding normal cellular regulatory processes. The result is a massive cascade of inflammatory cytokines known as the "cytokine storm" [6]. In summary, inflammation under normal operating circumstances can clear and eliminate pathogens and injury. In the same way inflammation causes a paper cut to heal, internal structures also recuperate from illness. Nevertheless, inflammation beyond injury recovery can lead to greater harm. COVID-19 however, appears to trigger a greater than needed inflammatory response, potentially using inflammation to further injury the internal organs. McGonagle., *et al*. [7] refer to this increased cytokine response as a macrophage activation syndrome (MAS); describing a life threatening response shared by a variety a systemic inflammatory disorders. In COVID-19 patients with SARS, cytokines trigger inflammation to fight off pneumonia in the lungs. Under normal circumstances, this inflammation is well regulated. In contrast, COVID-19 patients exhibit chronic inflammation affecting healthy cells and surrounding tissues and organs. Although the lungs are most prominently affected because of the abundance of ACE2 receptors, other areas with ACE2 concentrations can equally be damaged.

Neuropsychiatric complications

While common symptoms of COVID-19 are typically the result of lower respiratory infections, research suggest individuals may experience secondary effects on the heart, kidney, and liver [8]. Now, there is emerging research demonstrating central nervous system vulnerability and a growing likelihood of neuropsychiatric complications. Mao., *et al*. [9] found roughly 36% of a study of 214 patients with severe COVID-19 to experience neurological symptoms, including cerebrovascular, impaired consciousness, dizziness, headache and ataxia. A United Kingdom (UK) study of 125 patients reported ischemic stroke in 62% of patients and altered mental state in the context of a neuropsychiatric diagnosis in 31% of patients [10]. Moreover, those with neuropsychiatric diagnoses included alterations in personality, behavior and cognition. Additional psychiatric symptoms in severe COVID-19 include new onset psychosis, neurocognitive syndromes mimicking dementia, and mood and affective disorders. Unlike a variety of other severe COVID-19 symptoms affecting the heart and lungs, the UK study found a roughly even distribution of patients exhibiting neuropsychiatric symptoms to be below 60 (49%) or above 60 (51%).

Psychiatric complications appear to be persistent, at least for a subset of individuals, even after recovery from COVID-19. Mazza., *et al*. [11] found enduring presentations of anxiety, depression, obsess compulsive symptoms, insomnia, and post-traumatic stress disorder

in a study of 402 patients (mean age 57) at the San Raffaele Hospital in Milan even in the context of reduced inflammatory markers post discharge. In total, nearly 60% of patients scored in the pathological range of at least one clinical diagnosis on measures of psychiatric pathology 15 days post discharge.

In patients presenting with neurological and neuropsychiatric symptoms, COVID-19 appears to have a neuroinvasive potential affecting the central nervous system through a number of ways, which permeate the blood-brain barrier and ultimately affecting the brainstem. Briguglio., *et al*. [12] identified five potential routes of entry: neuronal route, pericellular route, hematogenous route, lymphatic route, and Trojan route, respectively. In in depth discussion of each identified central nervous system route is beyond the scope of this review however, the following is a brief discussion.

The neuronal route of entry provides an entry point through the olfactory receptors in the nasal cavity, the enteric nervous system of the gastrointestinal tract, and the pulmonary network [12]. The olfactory entry point is an important point, considering the constellation symptoms associated with alteration of smell; dysosmia, anosmia and hyposmia. The pericellular route also involves the olfactory system. Entry via this route is hypothesized to be via the cleft between the olfactory sensory neurons and associated ensheathing cells responsible for eliminating axonal debris and bacteria, as well as dispersion between the respiratory mucous layer or cerebrospinal fluid [12]. The hematogenous route provides direct access for viral proliferation to surrounding nervous tissue, likely by permeating the blood brain barrier through neuroinflammation [12]. Closely related, the lymphatic route provides direct viral access through the lympathic system, allowing infection to spread to cells in close contact with surrounding blood flow [12]. Lastly, researchers hypothesize a novel Trojan route in which the virus recruits inflammatory leukocytes, thereby infecting them en route to the central nervous system [12].

Conclusion and Final Thoughts

This conclusion was intended to be a review of the above information. Instead, it takes on a more perusable, human approach aimed at touching the everyday individual. SARS-COV-2 is a zoonotic RNA virus responsible for the lives of 2 million people worldwide. What began as a nationally televised outbreak of what appeared to be a controllable virus, has turned into the largest global pandemic in nearly 100 years. If nothing else, COVID-19 has taught humanity that even in the 21st century, the very biology of human functioning is susceptible to compromise in the absence of a well-prepared medical network. Hospitals have turned to sport stadiums, libraries, schools, and open parking lots to care for the sick. Physicians, nurses, and other healthcare professionals have been cross-trained to support an enduring effort of a bonafide medical emergency. At their peak, COVID-19 treatments were no longer objectively trying to minimize symptomology, but rather control a growing number of global deaths; a somber thought for what is still a significant portion of the world that perhaps, still doubts the severity of such a complex and ever-mutating disease. With newer and deadlier variants emerging over the last several months, the promises of vaccines and developing treatments provide light at the culmination of a tunnel which appears ever so distant. But perhaps even more daunting has been the growing presence of politics, social media opinionated posts and other forms of opposition or disbelief about COVID-19's severity. The growing presence of arm-chair medical professionals vouching for nearly the exact opposite of medical testimony and epidemiological evidence should be concerning. Nevertheless, the world owes its current state of existence, in spite of the enumerating loses, to the millions of professionals dedicating their livelihoods to ensuring a return to normality once again.

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