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The Anticipated explanation for Sudden deaths due to Stroke of young people infected with SARS-CoV-2

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Question Addressed: Why do SARS-CoV-2 symptoms vary in severity from slight to fatal?

Abstract

The SARS-CoV-2 virus attacks several organs in the human body but mainly targets three—the brain, lungs, and gastrointestinal tract—whichever is first infected. This determines the incubation period, symptoms, severity of the injury, and the course of the injury inside the body. This explains why, with the use of anticoagulants and respirators, treatment can fail and a stroke may develop.

Does SARS-CoV-2 work as an angiotensin-converting enzyme inhibitor?

As of 27 April, 2020, there have been more than 2,921,201 confirmed SARS-CoV-2-positive infected patients and more than 203,289 deaths worldwide. The most common symptoms of infected individuals with COVID-19 are fever, dry cough, fatigue, dyspnea, and myalgia. Some patients may suffer from anosmia, headache, olfactory or gustatory alteration, vomiting, abdominal pain, diarrhea, nausea, and lymphopenia RNAaemia (1,2). The virus genome consists of 30 kb nucleotides which mainly encode four major proteins containing, from the outside to inside, the spike protein (S), membrane protein (M), envelope protein (E), and nucleocapsid protein (N). The spike protein works as a receptor that binds to Angiotensin-Converting Enzyme 2 (ACE2) to gain entry into patients' cells, which is considered part of the Renin–Angiotensin System (RAS) (3). High levels of

ACE2 expression have been observed in lung, renal, cardiovascular, and gastrointestinal tissues, and low expression has been found in bone marrow, testes, thymus, skin, lymph nodes, liver, spleen, and brain. ACE2 appears to be more expressed in males than females, as well as in elderly individuals (4). ACE2 converts a monocarboxypeptidase that can degrade angiotensin II to Ang-(1–7), whereas fission of Ang I is conducive to the formation of Ang-(1–9) (5). ACE2 is considered to be a fundamental regulator of cardiac function and blood pressure control, maintaining electrolyte and fluid homeostasis, as well as protecting an individual from severe acute lung damage, which can prompt acid aspiration; sepsis; Severe Acute Respiratory Syndrome (SARS) and the lethal avian influenza A genotypes H5N1 and H7N9 infections (6, 7); and post infection regulation, which includes immune response, cytokine secretion, and genome replication of virus. ACE2 possibly acts in parallel with ACE1 (8). Downregulation of ACE2 may cause extreme Ang II accumulation, specifically at the glomerular level in the kidneys, causing an increase in albuminuria and glomerular damage (9).

What occurs in the Brain?

SARS-CoV-2 could infect the olfactory receptors in the neuroepithelium in the early stage of the disease, leading to anosmia and olfactory or gustatory alteration in some patients, and spread to the olfactory bulb and various brain structures, specifically the medulla oblongata in the brainstem, leading to acute respiratory failure based on previous studies (10,1). The RAS in the brain is a necessary regulator for physiological homeostasis and diseases in the cerebrovascular system, such as ischemic stroke. Overactivation of ACE in the brain and the Angiotensin II type 1 receptor (AT1R) axis was revealed to contribute to the development of hypertension, thrombogenesis, and atherosclerosis, which raises the probability of ischemic stroke. Further, brain Ang II levels have been revealed to be increased in

the ischemic tissues after stroke, thereby contributing to neural damage through elevated oxidative stress levels, agitating the inflammatory response in the ischemic hemisphere through AT1R. In addition, the infected medulla oblongata in the brainstem has been found to lead to acute respiratory failure, based on a previous study by Netland et al. (10). This may explain the severity of symptoms and death within a few days, despite the use of blood-thinning treatments to prevent blood clots.

ACE2 transforms Ang II to Ang-(1-7), and Ang-(1-7) binds with its receptor Mas, producing beneficial effects in cerebrovascular disease by interacting with nitric oxide and bradykinin. Ang-(1-7) could weaken the development of hypertension and the pathological progression of atherosclerosis. Further, its antithrombotic activity also halts thrombogenic events, which may assist in reducing the risk of ischemic stroke. In addition, after ischemia injury, ACE2–Ang-(1-7)–Mas has been shown to reduce the cerebral infarct size and improve neurological deficiency via its antioxidative and anti-inflammatory effects. Taken together, activation of the ACE2–Ang-(1-7)–Mas axis may become a novel therapeutic target in the prevention and treatment of ischemia stroke, something which requires further investigation (11).

What occurs in the lungs?

SARS-CoV-2 infection employs ACE2 receptors for viral attachment and penetration into cytosol; thus, swift replication of SARS-CoV-2, like SARS-CoV, may reduce the ACE2 surface expression, which may increase the acuteness of the inflammation and the severity of the pathogenicity of disease (12). On the other hand, the virus's ORF8 expression protein and surface glycoprotein could manage binding to the porphyrin, respectively. In conjunction with orf1ab, ORF10, and

ORF3a proteins, they could together cooperate to attack the Heme in the 1-beta chain of hemoglobin to break up the iron to form the porphyrin. The attack could lead to a clear decrease in the level of hemoglobin below the ability to carry oxygen and carbon dioxide, leading to extreme intensification of lung cell inflammation due to the loss of the ability for oxygen and carbon dioxide exchange (13). The onset of this disease may lead to progressive respiratory failure due to alveolar damage; increased plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα; cytokine storm; acute cardiac injury; and even death (14). This mechanism may interfere with brain vessels, leading to stroke as well.

What occurs in the gastrointestinal tract?

Evidence from SARS-CoV-2-infected individuals shows that the virus can replicate in the gastrointestinal tract via fecal–oral transmission based on positive stool samples and rectal swabs, even after such individuals' respiratory samples were negative. Disease onset includes vomiting, diarrhea, and abdominal pain (15, 16), though such patients may show milder symptoms (17), including minor respiratory symptoms (18). Another study indicated that on day 7 of the illness, SARS-CoV-2 genomic RNA could be detected in patient stool samples by using reverse transcription real-time polymerase chain reaction (19). It was observed that patients with initial gastrointestinal symptoms may experience the duration of viral infectivity with a complete lateness viral conversion rate (20).

In conclusion. SARS-CoV-2 attacks several organs, but it mainly targets three—the brain, lungs, and gastrointestinal tract—whichever is first infected. This determines the incubation period, symptoms, severity of the injury, and the course of the injury inside the body. This explains why, with the use of anticoagulants and respirators, treatment can fail and a stroke may develop.

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