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Pulmonary Edema in COVID19—A Neural Hypothesis

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ABSTRACT: In COVID-19, lung manifestations present as a slowly evolving pneumonia with insidious early onset interstitial pulmonary edema that undergoes acute exacerbation in the late stages and microvascular thrombosis. Currently, these manifestations are considered to be only consequences of pulmonary SARS-CoV-2 virus infection. We are proposing a new hypothesis that neurogenic insult may also play a major role in the pathogenesis of these manifestations. SARS-CoV-2 mediated inflammation of the nucleus tractus solitarius (NTS) may play a role in the acute exacerbation of pulmonary edema and microvascular clotting in COVID-19 patients.

KEYWORDS: *COVID-19, Nucleus tractus solitarius, Catecholamine storm, Brain trigger zones, Neurogenic pulmonary edema, Microvascular clotting*

INTRODUCTION

We had proposed a hypothesis that SARS-CoV-2 may cause inflammation of the nucleus tractus solitarius (NTS) through the axons of cranial nerves VII, IX, and X.[1] Autopsy studies have now reported lesions in the NTS of COVID-19 patients.[2]

Recently, autopsies were conducted on six patients who had died of COVID-19. The brains showed localized perivascular and interstitial encephalitis. Neuronal cell loss and axon degeneration were found in the dorsal motor nuclei of the vagus nerve, trigeminal nerve, nucleus tractus solitarii, dorsal raphe nuclei, and fasciculus longitudinalis medialis. There were no territorial infarctions. It was reported that the lesions could be a result of virus invasion or due to an immune response.[2]

The findings also included lymphocytic pan encephalitis and meningitis. But no conspicuous endothelitis was reported in these six cases even though the SARS-CoV-2 virus has been reported to infect endothelial cells in earlier reports. Patients older than 65 years had a history of comorbidities and died because of cardiorespiratory failure. Patients younger than 65 years died of either massive intracranial hemorrhage or pulmonary embolism and exhibited diffuse petechial hemorrhage in the entire brain.[2]

It has also been reported that acute activation of the sympathetic nervous system can simultaneously trigger both the coagulation and fibrinolysis pathways within minutes, resulting in net hypercoagulability as a part of normal human physiology. Plasma levels of thrombin-antithrombin III complex (TAT) and D-dimer indicate the augmented formation of thrombin and fibrin, respectively.[3] Elevated plasma D dimers and cardiac enzymes are found in COVID-19.[4]

Neurogenic pulmonary edema (NPE) is a form of acute respiratory distress syndrome, characterized by marked, acute-onset, extravascular accumulation of interstitial pulmonary fluid. NPE is diagnosed by exclusion of any primary pulmonary or cardiac lesion.[5]

From an anatomical standpoint, the cerebral sites regarded as NPE trigger zones are mainly found in the posterior hypothalamus, the ventral medulla including the A1 catecholaminergic group neurons, and the dorsal medulla comprising the solitarius tractus nuclei, the medial reticulated nucleus, and the dorsal motor vagus nucleus.[6] Autopsy reports have also shown lesions in most of these sites.[2]

Damage to these trigger zones can result in a catecholamine storm leading to an intense pulmonary vasoconstriction initially that causes an increase in pulmonary hydrostatic pressure and an increase in the permeability of pulmonary capillaries. This is followed by a loss of vasomotor tone and neurogenic hypotension. It can also cause a systemic inflammatory response that further induces an increase in the permeability of pulmonary capillaries.[6]

OUR HYPOTHESIS

SARS-CoV-2 causes pneumonia in the lungs. It also causes accumulation of interstitial fluid from leaking pulmonary capillaries, microvascular thrombosis, and cytokine storm. Currently, all these manifestations are considered to be only consequences of the lung infection caused by SARS-CoV-2.

We propose that SARS-CoV-2 may also cause inflammation of the NTS through the axons of the VII, IX, and X cranial nerves (Figure 1). This can also play a major role in aggravating the pulmonary edema, cytokine storm and microvascular clotting in COVID 19 patients.

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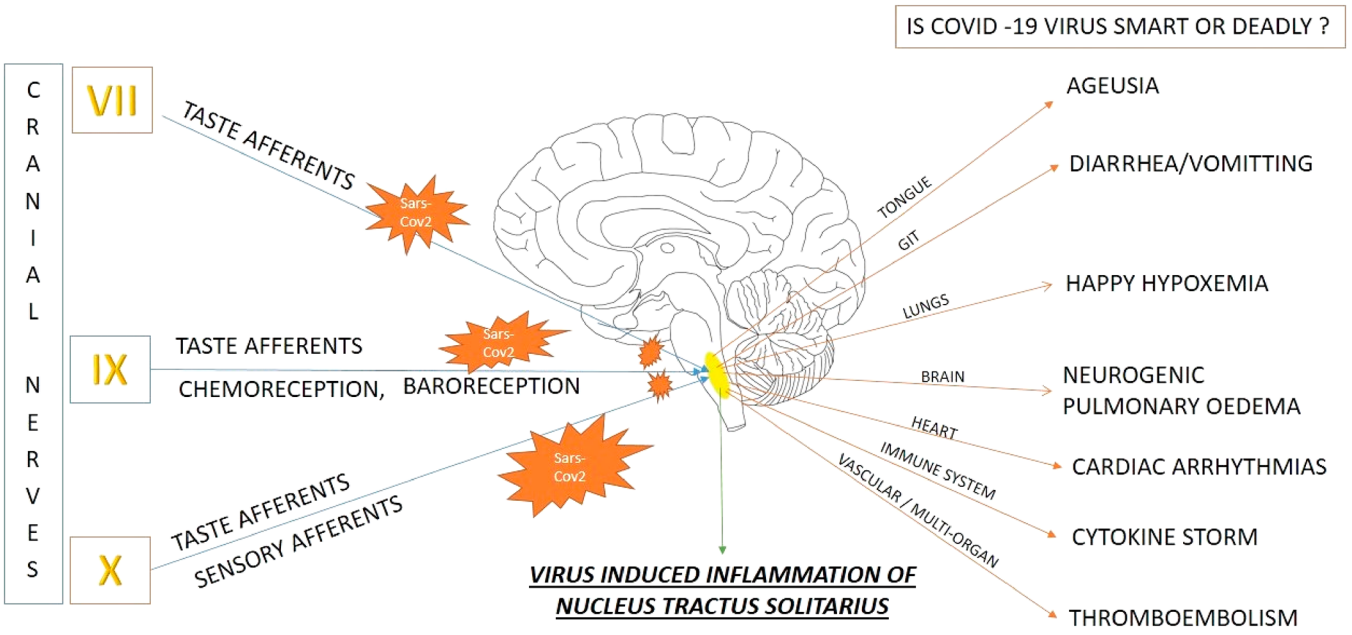

Figure 1. Virus entry to the NTS through the axons of the VII, IX, and X cranial nerves and its clinical implications.

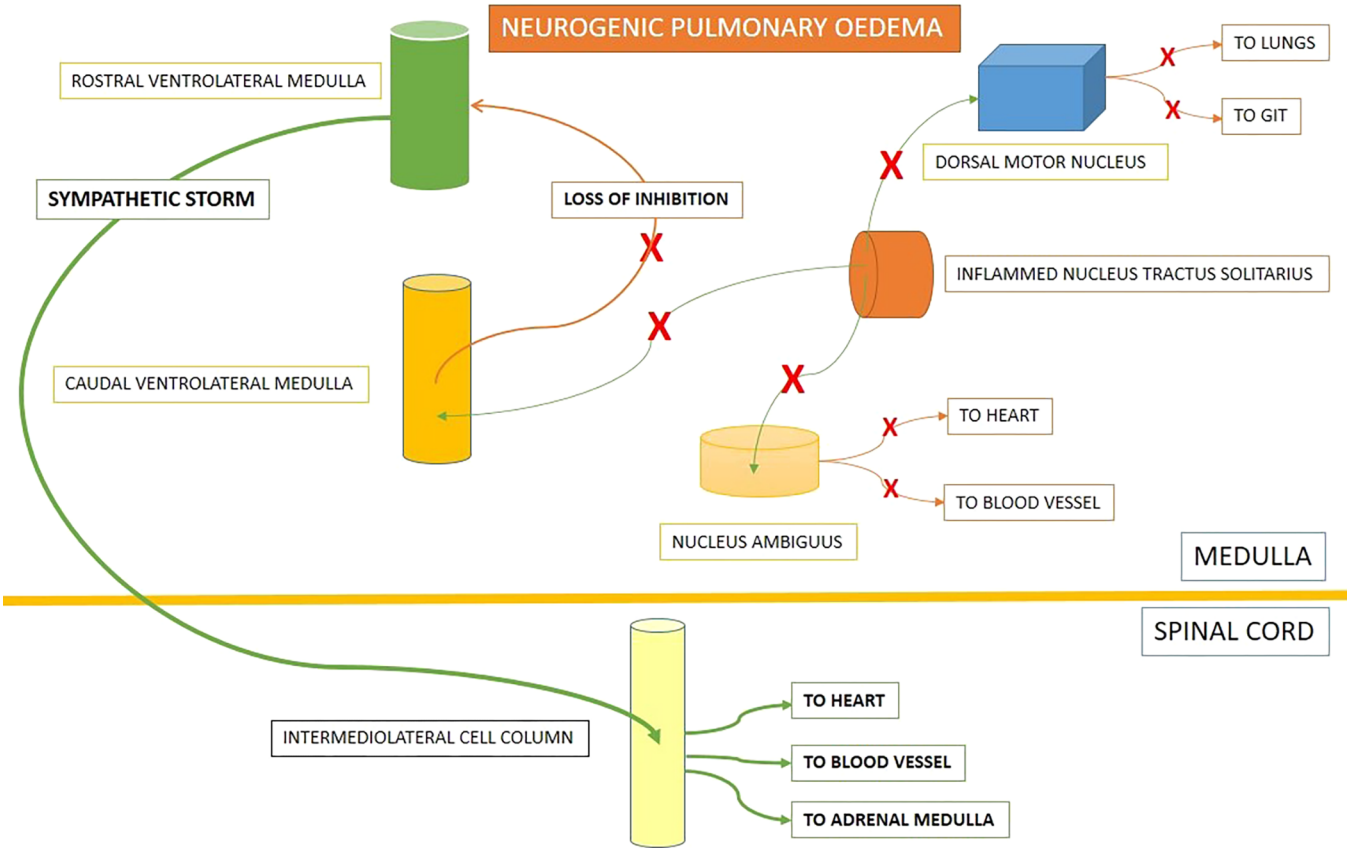

Figure 2. Inflamed NTS with loss of relay to the vagal parasympathetic nuclei and loss of inhibition of rostral ventrolateral medulla.

NTS is one of the trigger zones for neurogenic pulmonary edema. Damage to the NTS can lead to loss of inhibition of the rostral ventrolateral medulla and loss of relay to the vagal parasympathetic nuclei (Figure 2). This can lead to an intense sympathetic outflow that can initially cause vasoconstriction, leading to an aggravation of pulmonary edema due to increased hydrostatic pressure. This may also explain the hemorrhages in the brain and the reporting of high altitude pulmonary edema findings in COVID-19 patients. The hypertensive state may be followed by a loss of vascular tone and hypotension. This may explain why some patients decompensate when vasodilators are given.

The sudden surge in catecholamines can cause elevation of cardiac enzymes. The sympathetic hyperactivity can trigger the

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coagulation and fibrinolysis pathways and cause microvascular clotting as a response. This can result in elevated plasma D-dimers. The intense inflammatory response following the catecholamine release can be aggravated by the presence of SARS-CoV-2 infection in the lung. This can result in a severe cytokine storm.

As the virus attacks the pharynx and upper respiratory tract earlier, the neural inflammation may occur early in the disease. Therefore, in COVID-19, a neurogenic form of pulmonary edema can coexist with SARS-CoV-2 pneumonia due to inflammation of the nucleus tractus solitarius, in contrast to the classic NPE. The degree of neurogenic insult may play a role in the progression and manifestation of COVID-19.

Most of the patients infected by SARS-CoV-2 are either asymptomatic or exhibit minimal symptoms. Only a small subset of COVID-19 patients develop life threatening complications. Therefore, the SARS-CoV-2 virus is proving to be more of a smart virus that targets specific sites (Figure 1) rather than being a deadly virus that affects all organs.

CONCLUSION

Neurogenic insult caused by SARS-CoV-2 mediated inflammation of the nucleus tractus solitarius may also play a major role in the acute exacerbation of pulmonary edema and microvascular thrombosis in COVID-19 patients. The neurogenic insult may aggravate the local tissue damage caused by the primary pulmonary SARS-CoV-2 infection. Early intervention to treat both the pulmonary and neurogenic pathologies may be necessary. Further studies are required.

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Author Contributions

Both the authors have contributed equally to the work

Notes

The authors declare no competing financial interest.

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