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PREVENTION OF NEUROLOGICAL COMPLICATIONS OF COVID-19 BY PHYSICAL EXERCISE

Hagiu Bogdan-Alexandru[1], Craciun Liviu Ciprian[2]

[1] Department of Physical Education and Sport, Faculty of Physical Education and Sports, "Alexandru Ioan Cuza" University of Iasi, Romania

[2] Bayfront Medical Center , St. Petesburg, USA

E-mail: bogdan_hagiu@yahoo.com

Abstract: *The paper hypothesizes that atherosclerosis and / or heart failure may favor the neurological complications of COVID-19 via cerebral hypoxia -with the most affected structures being those that naturally express increased amounts of ACE2 in the brain and those adjacent to them. The hypothesis is supported by clinical and imaging arguments, as well as by the higher incidence of neurological complications of COVID-19 in patients with pre-existing neurological pathology and congestive heart failure. Prevention could be done once the SARS-CoV-2 infection has set in by multiple means e.g. medically (e.g. vasodilators, ACE2 blockers), use of oxygen therapy (however, the effectiveness and safety of administration are debatable) but especially before diagnosing the infection, by moderate intensity physical exercise, that activate genes /metabolic pathways promoting resistance of neurons to hypoxia. Aerobic exercise combined with breathing exercises can also prevent the expression of NRP1 and therefore the infection of astrocytes. Moderate intensity exercise could also be an effective secondary prophylaxis method, as it has been shown that COVID-19 could be a trigger for the atherosclerotic process.*

Key Words: Neurological Complications, COVID-19, Atherosclerosis, Heart Failure, Physical Exercises.

INTRODUCTION

The coronavirus spike (S) protein attaches to angiotensin converting enzyme 2 (ACE2) receptors [1]. In the early stages of hypoxia, ACE2mRNA increases in the smooth muscle cells of the pulmonary artery [2]. Based on the above, hypoxic cells may have increased susceptibility to SARS-CoV-2 infection. In fact, in a previous paper [3], we hypothesized that the hypoxia of vascular endothelial cells during intense physical

activity may favor their infection with the virus. In order to provide new data on the pathogenesis of COVID-19 and the therapeutic possibilities, we aim to analyze this pathophysiological mechanism in the cells of the central nervous system. This is because ACE2 is relatively highly expressed in several peculiar brain locations, such as the choroid plexus and paraventricular nuclei of the thalamus and also in some non-neuronal cells (mainly astrocytes, oligodendrocytes, and endothelial cells) in the human middle temporal gyrus and posterior cingulate cortex, even as few ACE2-expressing nuclei were found in a hippocampal dataset [4]. Chronic cerebral hypoperfusion and hypoxia could be caused by several factors, including atherosclerosis and heart failure [5], insufficient blood flow being associated with hypoxia [6].

The structures of the central nervous system that express ACE2 and those adjacent to them are the most exposed to SARS-CoV-2 infection

Atherosclerosis and / or heart failure, through hypoxia caused in the central nervous system, may favor the neurological complications of COVID-19, being co-factors that favor SARS-CoV-2 infection with predilection for the central nervous system structures that naturally express increased amounts of ACE2. Hypoxia may also contribute to this phenomenon by favoring the infection of the endothelium of the vessels that irrigate the brain. The access of the virus to the central nervous system is done through the transcribial route, and the infection of the capillary endothelial cells takes place first, and the involvement of the neurons is secondary [7]. The fact that olfactory sensory neurons and those in olfactory bulbs do not appear to be attacked by the SARS-CoV-2 virus [8] can be explained by the fact that those neuronal populations does not express ACE2 [9, 10]. There have been reports of both central nervous system involvement (e.g. encephalopathy – including haemorrhagic necrotizing encephalopathy, encephalitis stroke, epileptic seizures) and also peripheral nervous system involvement (e.g. rhabdomyolysis and Guillain-Barre syndrome) [11]. Increased expression of ACE2 by the choroid plexus [4] may help explain this variety of lesions (encephalopathy, encephalitis, necrotizing hemorrhagic encephalopathy) including disseminated ones [12]. On the other hand, the paraventricular nuclei of the thalamus also express ACE2 [4] and are anatomically neighboring with transcribrial route. Due to the anatomical proximity, the case of rhombencephalitis appeared as a complication of COVID-19 [13].

Brainstem Infection by SARS-CoV-2 can be done both at vascular and neuronal level - the corresponding signs and symptoms being appetite loss, vomiting, and nausea [14]. Furthermore, the anatomical vicinity with the posterior cingulate cortex – a structure whose neurons express ACE2 [4] may explain posterior hemorrhagic reversible encephalopathy syndrome that appeared as a complication of COVID-19 [15]. The same pathogenetic mechanism may also be the basis of an epileptic focus located in the left temporo-parietal lobe, described in a patient with COVID-19 [16]. Unfortunately, the areas of the central nervous system most vulnerable to hypoxia are hippocampus and striatum [17], that are anatomically adjacent structures with the transcribrial route (the pathway through which the virus enters) and with neural areas expressing ACE2. So it can be considered that the virus reaches the brain on the transcribrial route, and from here the infection can occur both via vascular and cellular pathways, with predilection to regions exposed to hypoxia and whose cells (neurons and glial cells) express large amounts of ACE2. Fig. 1. shows the anatomical vicinity of the brain areas known to express relatively large amounts of ACE2 by neurons and glial cells and regions for which the clinic and imaging have argued the infection with SARS-CoV-2 was highlighted.

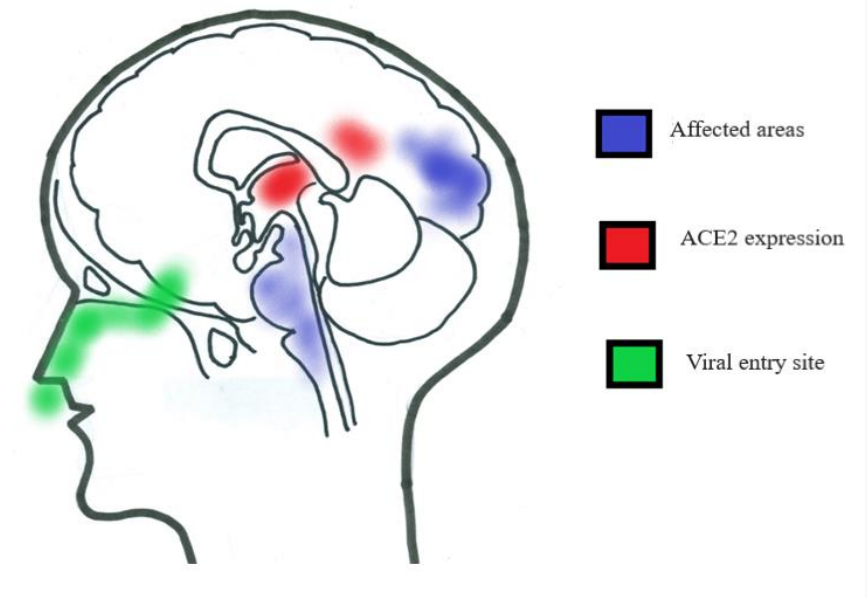

Fig. 1. Brain areas with ACE2 expressed at the cellular level (red), adjacent to regions involved in SARS-CoV-2 infection- as suggested by clinical and imaging arguments (blue).

The correlation between cerebral atherosclerosis and neurological complications of COVID -19

At the top of the list of comorbidities of COVID-19 patients suffering from neurological and psychiatric complications are neurological diseases [18]. It is known that for neurological diseases (recurrent ischemic stroke) an important risk factor is intracranial and systemic atherosclerosis [19]. The argument is also supported by the fact that patients with cerebral atherosclerosis are prone to COVID-19 (brain damage could contribute to the inflammatory cascade). This possibility is suggested by the fact that microglia reactivity may contribute to individual response to COVID-19 infection and subsequently to the severity of the disease [20]. Thus one can conclude that the risk of COVID-19 is higher in those with vascular dementia [21]. It is known that there is an association between midlife atherosclerosis and development of vascular dementia [22]. Furthermore, even patients with schizophrenia are prone to develop arterial stiffness [23], it is known that these patients have an increased risk for COVID-19 and a worse prognosis [24].

Heart failure and risk for neurological complications of COVID-19

Hypoxia from heart failure could stimulate the expression of ACE2 in the endothelium of the blood vessels that irrigate the brain and in the neurons and glial cells that already express this receptor. This correlation is supported by the fact that congestive heart failure is on the list of comorbidities of COVID-19 patients suffering from neurological and psychiatric complications [18]. Patients with heart failure have a worse prognosis when exposed to COVID-19 and ACE2 may be up-regulated in cardiac patients receiving treatments with ACE inhibitors or angiotensin receptor blockers (ARB) [25]. Therefore, in the case of heart failure, the risk of hypoxia is compounded by the risk of ACE2 overexpression when using ACE inhibitors or angiotensin receptor blockers. Predisposition to COVID-19 and poorer prognosis can be determined by transmembrane ACE2 expression in vascular endothelial cells under the action of hypoxia [3].

Drug prophylaxis and oxygen therapy of neurological complications of COVID-19

Administration of cerebral vasodilators and ACE2 inhibitors may be considered in COVID-19 patients with atherosclerosis and / or heart failure in order to prevent or improve cerebral hypoxia - if they do not contradict the treatment regimen of the

underlying condition. Actually, for many patients suffering from these diseases, these drugs are already part of the therapeutic scheme. However, ACE2 blockers are controversial in their effect on SARS-CoV-2 infection because they increase ACE2 receptor expression, and a potential benefit is prevention of severe lung damage [26]. Cerebral vasodilators have not been discussed as prophylactic agents of brain damage by SARS-CoV-2, but it should be borne in mind that the pathophysiological chain of COVID-19 predisposes to stroke [27] and it is likely that SARS-CoV-2 infection potentiates the cerebral effects of atherosclerosis. The strokes are mainly ischemic type and the association is multifactorial –additional factors are cardiovascular, proinflammatory and prothrombotic risk factors) [28]. Oxygen therapy may be indicated as prophylaxis of neurological complications in COVID-19 patients who have cerebral atherosclerosis and / or heart failure as comorbidities.

Physical prophylaxis of neurological complications of COVID-19

Under hypoxic conditions, the genes responsible for long-term adaptation to low pO2 are activated in the neuronal mitochondria of the cerebral cortex [29]. On the other hand, physical training stimulates mitochondrial biogenesis in the brain [30]. Thus it is assumed that exercise increases the hypoxia resistance of brain neurons and subsequently they will no longer express such large amounts of ACE2, SARS-CoV-2 receptors. Of course, these are moderate-intensity physical exercises [3] performed prophylactically by people suffering from hypertension of atherosclerotic etiology and / or heart failure, while avoiding development of hypoxia during physical activity. In this regard, although patients with heart failure are recommended a combination of resistance training and inspiratory muscle training to aerobic training [31] and perhaps it would be good for resistance exercises to be monitored in order to avoid hypoxia. Aerobic exercises are indicated for cases with difficult to control hypertension [32].

DISCUSSIONS

The usefulness of secondary prophylaxis can also be addressed, as it has been suggested that COVID-19 may be a trigger for the atherosclerotic process [33]. ACE2 is involved in both the pathogenesis of atherosclerosis and COVID-19, requiring the balance of the enzyme and its receptor [34]. In vitro, the influence of hypoxia on ACE2 expression in

brain endothelial cells depends on its severity, after 48 hours ACE2 is increased at 8% oxygen but decreased at 2% [35]. From the above, an effective and risk-free secondary prophylaxis of cerebral atherosclerosis in individuals with post-COVID-19 neurological sequelae, with the possibility of recurrences of neurological and psychiatric complications in case of reinfection, can be achieved through moderate-intensity exercise. Moreover, physical exercises stimulate the activity of PGC-1α/FNDC5/Irisin pathway, which increases the chances of neuron survival [36]. SARS-CoV-2 also infects astrocytes, the NRP1 (neuropilin-1) receptor being involved [37]. In the tumor microenvironment, NRP1 is expressed in increased amounts by the action of hypoxia [38], this being also possible in the brain tissue. At least in pregnant women, aerobic exercise combined with breathing exercises improve blood oxygenation [39], so here is a direct way to prevent infection through NRP1 as a co-receptor.

CONCLUSSIONS

1. Physical exercises of moderate intensity can be a risk-free means of prophylaxis of neurological and psychiatric complications of COVID-19, by avoiding cerebral hypoxia that stimulates ACE2 expression.
2. Aerobic exercise combined with breathing exercises seems to have the ability to improve blood oxygenation, thus avoiding the expression in large quantities of the co-receptor NRP1 for SARS-CoV-2. The infection of astrocytes can be prevented in this way.

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