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REFERENCES

1. D'Adamo H, Yoshikawa T, Ouslander JG. Coronavirus disease 2019 in geriatrics and long-term care: the ABCDs of COVID-19. J Am Geriatr Soc. 2020; 68:912-917.
2. Lloyd-Sherlock PG, Kalache A, McKee M, Derbyshire J, Geffen L, Casas FG. WHO must prioritise the needs of older people in its response to the covid-19 pandemic. BMJ. 2020;368:m1164.
3. Morley JE, Vellas B. Editorial: COVID-19 and older adults. J Nutr Health Aging. 2020;24(4):364-365.
4. Kunz R, Minder M. COVID-19 pandemic: palliative care for elderly and frail patients at home and in residential and nursing homes. Swiss Med Wkly. 2020;150:w20235.

Neurological, Cognitive, and Behavioral Disorders during COVID-19: The Nitric Oxide Track

To the Editor: Coronavirus disease 2019 (COVID-19) exhibits a wide range of clinical signs, especially in older adults.[1] Alkeridy et al recently reported an interesting case of delirium with lower limb sensorimotor disorders in a 73-year-old man with otherwise asymptomatic COVID-19.[1] The mechanism proposed by the authors was based on the invasion of the nervous system by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, as previously described in a COVID-19 case with encephalitis.[2] Although acknowledging the value of this assumption, we discuss here the likely role of a third player, namely nitric oxide (NO), to explain the onset of neurocognitive disorders in patients with COVID-19.

NO, originally known as an endothelium-derived relaxing factor, is a gaseous membrane-soluble neurotransmitter synthesized endogenously from L-arginine, oxygen, and nicotinamide adenine dinucleotide phosphate by various nitric oxide synthase enzymes.[3-5] Studies in experimental animals have well documented the synthesis of NO in the brain and its role in a variety of neuronal functions including learning and memory processes or locomotor activity.[3]

Although it plays an important role in cell signaling in the brain, NO was described as an "unconventional" neurotransmitter. Indeed, it is neither stored in synaptic vesicles nor released upon membrane depolarization; it is directly released upon synthesis.[4] Also, NO does not mediate its action by binding to some membrane-associated receptors, but it diffuses from neuron to neuron to act on intracellular components.[4] NO functions as a neurotransmitter by stimulating soluble guanylyl cyclase to form a second messenger molecule, cyclic guanosine monophosphate (cGMP), in target cells. The cyclic nucleotide cGMP relaxes vascular smooth muscles with consequent vasodilation and increased blood flow. Increased intracellular cGMP level was shown to contribute to excessive neuron excitability and locomotor activity.[6] The decrease in NO concentrations in the brain was consistently found to induce cognitive and behavioral disorders in various experimental animals.[5]

On this basis, we propose that some of the neurological signs in patients with COVID-19 are associated with the virus-induced decrease in NO levels in the brain. The production of NO is tightly linked to the renin-angiotensin system (RAS), precisely targeted by SARS-CoV-2[7] that was described to overactivate the RAS by interacting, via its spike (S) glycoprotein, with the metallopeptidase angiotensin-converting enzyme 2 (ACE2) receptor,[7] expressed at the surface of numerous cell types including cerebral neurons.[8]

In RAS, angiotensin II, by acting on the vasoconstrictor type 1 angiotensin II receptor (AT_1R), reportedly diminishes the production of NO,[9] leading to an expected decrease in NO concentrations in the brain during COVID-19, which needs to be compensated to prevent neurological cognitive and behavioral disorders. Because NO is basically too reactive (with a very short half-life of 5 seconds) to constitute an appropriate therapeutic target, a strategy would be to counterbalance RAS overactivation and thus maintain the appropriate NO levels in the nervous system. Interestingly, previous work to increase NO concentrations in the brain with specific agents known to elevate NO production was found to improve memory in experimental animals.[5]

In human COVID-19, proposed chemotherapeutic drugs to limit/counterbalance the overactivation of RAS could be ACE inhibitors (to prevent the production of angiotensin II from angiotensin I), blockers/antagonists of AT_1R such as losartan and derivatives, and also some natural candidate peptide drugs that belong to the so-called counterregulatory RAS (i.e., angiotensin 1–7, angiotensin 1–9, alamandine, angiotensin A, and/or angiotensin IV).[10] All these molecules are expected to counteract the SARS-CoV-2-induced overactivation of RAS, to maintain NO production, and to reverse, to some extent, the associated neurological cognitive and behavioral disorders in COVID-19.

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See the Reply by Alkeridy et al.

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REFERENCES

1. Alkeridy WA, Almaghlouth I, Alrashed R, et al. A unique presentation of delirium in a patient with otherwise asymptomatic COVID-19. J Am Geriatr Soc. 2020;10.1111. https://doi.org/10.1111/jgs.16536.
2. Zhou L, Zhang M, Gao J, Wang J. Sars-Cov-2: underestimated damage to nervous system. Travel Med Infect Dis. 2020;101642. https://doi.org/10.1016/j.tmaid.2020.101642.
3. Susswein AJ, Katzoff A, Miller N, Hurwitz I. Nitric oxide and memory. Neuroscientist. 2004;10:153-162.
4. Garthwaite J, Boulton CL. Nitric oxide signaling in the nervous system. Annu Rev Physiol. 1995;57:683-706.
5. Paul V, Ekambaram P. Involvement of nitric oxide in learning & memory processes. Indian J Med Res. 2011;133:471-478.
6. Tseng K, Caballero A, Dec A, et al. Inhibition of striatal soluble guanylate cyclase-cGMP signaling reverses basal ganglia dysfunction and akinesia in experimental parkinsonism. PLoS One. 2011;6:e27187.
7. Cao Z, Wu Y, Faucon E, Sabatier JM. SARS-CoV-2 & Covid-19: key-roles of the 'renin-angiotensin' system/vitamin D impacting drug and vaccine developments. Infect Disord Drug Targets. 2020;20:1.
8. Doobay MF, Talman LS, Obr TD, Tian X, Davisson RL, Lazartigues E. Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. Am J Physiol Regul Integr Comp Physiol. 2007;292:R373-R381.
9. Dasgupta C, Zhang L. Angiotensin II receptors and drug discovery in cardiovascular disease. Drug Discov Today. 2011;16:22-34.
10. Annweiler C, Cao Z, Wu Y, et al. Counter-regulatory 'Renin-Angiotensin' System-based candidate drugs to treat COVID-19 diseases in SARS-CoV-2-infected patients. Infect Disord Drug Targets. 2020. https://doi.org/10.2174/1871526520666200518073329.

Reply to: Neurological, Cognitive and Behavioral Disorders During COVID-19: The Nitric Oxide Track

To the Editor: We read with great interest the letter of Annweiler et al.[1] They propose an intriguing mechanism for cognitive impairment related to coronavirus disease 2019 (COVID-19). We would like to clarify a couple of points related to our case. First, although we wanted to exclude COVID-19 encephalitis as a possibility, this was not possible without cerebrospinal fluid analysis and magnetic resonance imaging, which was refused by our patient. Our patient fulfilled the Confusion Assessment Method criteria for delirium on admission, which was our working diagnosis.[2] In fact, the rapid improvement in his cognitive function might argue against COVID-19 encephalitis. Second, our patient's usual medication included lisinopril, an angiotensin-converting enzyme 2 inhibitor, for treatment of hypertension in the context of diabetes mellitus, type II. Possibly, the mechanism proposed by Annweiler et al[1] pertaining to the nitric oxide track could explain the rapid improvement in our patient's cognition following just a brief period of supportive management.

It is important to emphasize that delirium is a heterogeneous entity caused by multiple causative factors and complex underlying pathogenesis.[3-5] In fact, nitric oxide has long been implicated in the pathogenesis of delirium and cognitive impairment.[6,7] Whether the nitric oxide track will prove to have a central role in the acute manifestations of COVID-19–related cognitive impairment remains to be seen. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection could activate multiple downstream molecular pathways affecting each individual distinctly.[7] We propose that the underlying mechanism of COVID-19 central nervous system manifestation or delirium depends on the interaction between SARS-CoV-2 activated molecular pathways and the individual related factors, including age, COVID-19 severity, individual's underlying genetic susceptibility, vascular risk factors, premorbid cognitive function, use of certain medication, and comorbidities.

Several other mechanisms have been linked to COVID-19 neurological and cognitive manifestations.[8,9] However, the retrospective design of the study by Mao et al limits our ability to infer the causal mechanism of cognitive decline in COVID-19 patients.[8] We propose possible mechanisms of COVID-19–related cognitive dysfunction (Table 1), which could help researchers in studying the specific pathways associated with each possible mechanism. Finally, the core message of our study is for clinicians to proactively screen for delirium in hospitalized older adults.[10] Once delirium is identified, a comprehensive individualized assessment should

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