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Letter to the Editor

The Effects of COVID-19 on Hypothalamus: Is it Another Face of SARS-CoV-2 That May Potentially Control the Level of COVID-19 Severity?

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Letter to the Editor

As we are all combating the COVID-19 pandemic , a war being imposed by an invisible enemy, each day we need to "spy" the new moves by our enemy in order to design our own strategy. This metamorphic menace has ways to amaze us and to bluff us by presenting in unexpected ways. Since we have never suffered from this novel viral infection before, there is no data to correlate and guide us regarding the possible ways of presentation of this virus. It has pushed us back in teaching ourself the basic science based on observation, building new words from the alphabets we find, and playing Columbus to discover the new faces through which SARS-CoV-2 may manifest itself while looking for the hallmark set of signs and symptoms. The tendency of masquerading itself of the SARS-CoV-2 , a virus that ruined the famous Venetian Carnival as it unveiled itself , has put all the researchers into a mayhem.

Sir, I really want to bring into your kind notice that we have found some signs and symptoms that are related with the central nervous system particularly the hypothalamus. It came into our observation that many patients with COVID-19 infection have presented to us with polyuria and polydipsia with and without polydipsia.

In a short study, we detected at least 27 patients who suffered from "unquenchable thirst" and "ravenous appetite". 7 of them were diabetic including 2 who were insulin dependent .Most of them did not develop severe COVID-19 . Polydipsia and polyphagia raise suspicion of hypothalamic infliction, since hypothalamus has centers of thirst, hunger and satiety [1]. The interplay between stimulation and inhibition leads to the normal hunger and thirst sensations. We further noted that 21 of them had other signs and symptoms related with peripheral nerves. They all suffered from dysosmia and dysgeusia as well. If we put all of these symptoms together and correlate it with the viral entry through the nose, it is quite simple to explain that SAS-CoV-2 affects the olfactory nerve and from there finds its way to the hypothalamus [2].

Addressing polyphagia and polydipsia separately, if we discuss polyphagia first in relation with hypothalamus , there can be various causes directly or indirectly related with the hunger and satiety centres in the hypothalamus. The most straight-forward mechanism of hunger and satiety is defined by the balance of signals coming from two hypothalamic centers: the lateral hypothalamus that responds to internal and external signals and cause one to feel hungry and the ventromedial hypothalamus that signals satiety. Secondly, polyphagia is It is also the part of the 3Ps of diabetes [3]. With an increasing experimental and clinical evidences showing hypothalamic dysregulation as one of the underlying mechanisms of abnormal glucose metabolism, it can be postulated that hypothalamic infliction is likely in SARS-CoV-2 that leads to polyphagia in both diabetic and non-diabetic patients as well as poor diabetic control in the diabetic patients. Koshiyama et al postulated several points to suggest the role of hypothalamus in causing diabetes mellitus noticeably an increased hypothalamic-pituitary-adrenal axis activity caused by extreme stress [4]. So a deranged hypothalamic function causing diabetic tendency and polyphagia can be one cause. Due to financial constraints, proper blood sugar level testing could not be performed in the non-diabetic patients, however, in the diabetic patients with COVID-19 it was evident that glucose control was poorer .The other important point regarding the causation of polyphagia is the direct effect on the hypothalamic centers for satiety. It is evident that mutations in several genes related with hypothalamic satiety signaling lead to polyphagia and the so called hypothalamic obesity [5]. This points towards a possibility of SARS-CoV-2 affecting hypothalamus not only directly but also via genetic mutations. In a study by Gu et al., neuronal histopathological changes were found in the hypothalamus who in the autopsies of 8 victims of SARS [6].

Nampootheri et al suggested SARS-CoV-2 invasion in the hypothalamus . Hypothalamus plays a key role in hypertension, diabetes, obesity and other risk factors for developing severe COVID-19 infection. They also suggested a non-respiratory system origin for respiratory failure. Hypothalamus being connected to brainstem cardio respiratory centers can cause respiratory arrest. They further showed that the human brain gene-expression analyses revealed that the hypothalamus with its associated regions express angiotensin-converting enzyme 2 and transmembrane proteinase, serine 2 which allows SARS-CoV-2 entry in the cell. They also showed that immunolabeling in human as well as in animal brains proves that the central role of the hypothalamus that by allowing SARS-CoV-2 brain invasion through multiple routes, influences brain susceptibility and various severe manifestation of the COVID-19 infections [7].

If we now discuss polydipsia then again we have various explanations via different causation pathways involving hypothalamus. The most straight forwards pathway is via Angiotens in II . Since SARS-CoV-2 also acts via the ACE2 receptors, somehow at any level whether central or peripheral , it is able to cause polydipsia[8]. Hypothalamus does have osmoreceptors that regulate thirst mechanisms.[9] So, basically, hypothathalamus plays a central role in thirst mechanism. Due to limited resources and an overwhelmed system, we were not able to follow any specific lab investigatory protocol. However, correlating with serum electrolytes and urine output records, none of them had either diabetes insipidus or dehydration. The only notable point was a poorer diabetic control during illness, but this can be from various different reasons, again hypothalamus does play a role in several of such mechanisms including blood sugar control.

Again, if we join all these pieces of information together, with patients presenting with polydipsia and polyphagia as well as signs involving olfactory nerve and other peripheral nerve signs and symptoms and provided the fact that SARS-CoV-2 does interact with the nervous pathways and it also interacts with ACE-II receptors, it is likely thatSARS-CoV-2 finds a way to the hypothalamus leading to the manifestations related with hypothalamic structures.

I believe there is a need to perform further research on this topic. This can be an important point to understand the level of severity of COVID-19 infection and may help in determining a proper management plan with monitoring as well as determining prognosis.

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