COVID

Editorial

Post-COVID-19 Neuropathology and Perspectives of Protective Roles of Estrogens

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Epidemiological data revealed that COVID-19 (Coronavirus disease 2019) is more prevalent and lethal among the elderly population. Likewise, COVID-19 also affects men more severely than women. Several lines of evidence indicated that SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) can infect neuronal cells, and a variety of neurological symptoms can be associated with COVID-19. However, the long-term consequences of COVID-19 have not been fully investigated. The gender disparity is also observed in neurodegenerative diseases, such as Alzheimer's disease (AD), and studies suggest that in both pathologies sex hormones play an important role in the clinical outcome.

COVID-19 is a disease caused by the coronavirus SARS-CoV-2, an enveloped virus with a single-stranded RNA genome that belongs to the Coronaviridae family [1]. For the virus infection they use the S protein, which binds to the enzyme ACE2 (Angiotensin-Converting Enzyme 2). Several cell types (including neuronal cell lines) are permissible to SARS-CoV-2 infection [2]. Another protein, TMPRSS2, is important for viral infection [3], and oestradiol is able to alter their gene expression [4,5].

This topic is gaining major interest, yet relevant to COVID-19 studies, because until now more than 670 million people have been infected by SARS-CoV-2 (according to Johns Hopkins Coronavirus Resource Center; https://coronavirus.jhu.edu/map.html, accessed in 21 September 2024). The coronavirus can infect many cell types [2], and the central nervous system (CNS) has been reportedly affected, generating great concern among neurologists. The post-COVID symptoms, or long COVID, include dizziness, headache, impaired consciousness, and seizure, also considering that 36% of acute COVID-19 patients develop neurological symptoms [6]. Interestingly, Heneka et al. (2020) launched an editorial with a viewpoint about neurological disorders related to COVID-19, raising some questions about how COVID-19 could affect CNS and promote brain disorders including cognitive decline [7].

In another study, Crunfli et al. (2022) found symptoms such as anxiety and cognitive impairment in COVID-19 patients, which could be associated with altered cerebral cortical structures. Not only can neurons be affected by SARS-CoV-2 but also astrocytes, which can promote energy imbalance that can alter neuronal energy supply, resulting in association to neuronal viability [8]. These recent studies raise some questions about how the brain is affected by SARS-CoV-2, also regarding the neurotransmission and subcellular alterations. Ramani et al. (2020) have noticed that neurons in brain organoids are susceptible to

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SARS-CoV-2 infection, despite the low level of ACE2 [9]. Of note, the neuron infections are associated with hyperphosphorylation of tau and cell death, and the authors discuss whether this could be a direct action of the SARS-CoV-2 or a secondary effect of neuronal stress. In our view, both hypotheses could be considered, as the oxidative stress is a well-known promoter of protein aggregation (for review [10]). Evidence from another study with herpes simplex virus type I (HSV-1) has associated the virus infection to AD's risk factor, since it induced hyperphosphorylation of tau in neurons [11].

Senile plaques (or amyloid plaques, which are composed mainly by the aggregation of β-amyloid peptide, generally with 40 or 42 amino acids) and neurofibrillary tangles are being associated with the aggregation of hyperphosphorylated tau proteins [12]. AD is the most prevalent neurodegenerative disease associated with aging in the world, wherein the main symptoms are the gradual loss of memory and dementia, with higher prevalence in women than in men [13]. Many studies have been carried out in an attempt to clarify the role of estrogens in AD (for review [14]). Several authors suggest that the beneficial effects of hormonal therapy on memory in menopausal women are dependent on the time of life that it was given and the duration of this therapy [15,16].

So far, not much evidence could possibly prove the association of COVID-19 to the prevalence of AD, because those illnesses take years to develop until reaching the dementia diagnosis. However, some developing ongoing research is in a roll for new evidence that could possibly link COVID-19 to AD's risk factor. For example, The Alzheimer's Association has launched a study searching data from more than 30 countries on this topic. This Consortium was evaluating data from more than 22 million COVID-19 cases with follow-up evaluations, to better understand the long-term cognition and brain function compromise [17,18]. In addition, the known data from another data bank research analysis, with a systematic review cohort of UK Biobank revealed clues that indicate COVID-19 as a susceptibility factor associated with dementia or AD, which is in turn an age-independent risk factor for severity and death of COVID-19 patients [19]. Overall, this evidence and the increasing interest of the scientific community in associating dementia to COVID-19 must be fueled by upcoming epidemiological data that will soon come out and may be deeply explored, and some studies suggest that long COVID-19 could enhance cognitive impairment. For example, in the beginning of the pandemic it was reported impaired consciousness in COVID-19 patients [6], and new studies review works on the neurological sequelae of long COVID-19 [20]. Many viruses are able to impair human cognition, causing long-term memory decline (reviewed by [21]). Moreover, being able to recognize the patterns or pathogenesis of long COVID-19 would help to understand this phenomenon.

Regarding the neuroprotective role of oestradiol, it has been shown that, in transgenic mice for AD (3xTg-AD), treatment with oestradiol is able to reduce the deposition of β-amyloid proteins [22], in addition to improving the loss of memory and survival in this model treated with ERβ-selective phytoestrogens [23]. In addition, it has been shown that in the hippocampus of patients with AD, ERα is localized and interacts with the tau protein [24]. In addition, considering that tau is an aggregate-prone protein, one of the promising therapeutic strategies for the treatment of neurodegenerative diseases, through the removal of protein aggregates, is the modulation of autophagy [25]. Additionally, evidence shows that estrogenic signaling may be involved in the autophagic pathway. Estrogen receptors (mainly ERα) can regulate autophagy by overexpression of the BAG3 protein [26], and the selective GPER1 antagonist (G15) induces an increase in autophagosomes in oral carcinoma cells [27]. Finally, treatment with 17β-estradiol in EGFP-tau WT overexpressing cells increased clearance of phosphorylated and total tau protein [28]. Thus, these results show that the autophagy induction mediated by 17β-estradiol has an important role in

dysfunctional tau protein degradation to prevent the formation of neurofibrillary tangles, characteristic of AD and other tauopathies.

Although the primary site of action of steroid hormones is the reproductive system, they have an important role in the CNS. Oestradiol is a steroidal hormone derived from cholesterol that modulates its activity through its binding to estrogen receptors, including estrogen receptor ER-α, ER-β (with genomic actions), and G-protein-coupled estrogen receptor (GPER1) [29]. When it binds to GPER1, the signaling pathway can induce intracellular calcium mobilization from intracellular stores, along with the production of cyclic AMP. These second messengers activate signaling pathways that may involve the phosphorylation of transcription factors, leading to the modulation of gene expression [30,31]. Costa et al. have shown that GPER1 can also participate in SARS-CoV-2 infection, and the overexpression of this receptor reduces virus load in human bronchial epithelium cell line [32]. Regarding viral infections, particularly Ebola virus (EBOV), a study published by Zhao et al. (2016) tested selective estrogen receptor modulators (SERMs) and observed that toremifene led to a reduction in viral infection in HEK293T cells [33]. In experiments carried out with mice infected with EBOV, treatment with clomiphene resulted in a survival of 90%, and with toremifene, 50% [34]. In addition, it has been demonstrated that toremifene has the ability to block viral infections, such as MERS-CoV, SARS-CoV, and EBOV in cell lines [34,35].

Considering the recent data about COVID-19 and estrogen, a few analyses of clinical records have been performed. As an example, Seeland et al. (2020) analyzed a database health record for a large cohort and was able to correlate the reduced COVID-19's fatality risk in those aged above 50 years with oestradiol therapy [36]. Additional a study was performed by Costeira et al. (2020) using the "COVID Symptom Study Group" data collected from women taking the combined oral contraceptive pill and Hormone Replacement Therapy (HRT), which found that the HRT treatment can be positively correlated with COVID-19 symptoms and disease severity [37]. However, considering the systemic actions of oestradiol and HRT, an interaction between the peripheral nervous system (PNS) and CNS should be considered while investigating the protective effects of estrogens.

Due to the urgency of studies and products to combat the COVID-19 pandemic, several emergent models (in silico, in vitro, in vivo, etc.) were generated on a fast-track scale, with an unprecedented effort demonstrated by the scientific community. The most popular, important, and widespread product, which has tremendously reduced the number of deaths by COVID-19, was the mass population vaccination. With great success, it reduced the mortality rate and partially solved the problem of the pandemic, which was considered a short-term priority. However, many questions are still open. What are the long-term consequences of post-COVID-19, and could it be related/associated with chronic-developing diseases? Moreover, considering the gender bias in COVID-19 and AD, what is the role of steroids hormones in neuropathological conditions related to long COVID-19?

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