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Review

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The Neural correlates of COVID-19-induced erectile dysfunction in males

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Abstract

Emerging evidence suggests that there are long-term complications after recovery from COVID-19, which involve multiple systems and lead to deterioration of the quality of life. Among these different complications, male sexual dysfunction, in particular erectile dysfunction, is one of the complications being identified recently. It was initially hypothesized that due to the presence of Angiotensin-converting enzyme II (ACE2) and transmembrane protease serine 2 (TMPRSS 2) in testes and Leydig cells, the male reproductive system is vulnerable to the infection of COVID-19, which may lead to a decrease in testosterone production and sexual dysfunction. However, evidence from a recent neurological study suggests that COVID-19 may be directly associated with dysregulation of the nervous systems at the central level in regions including the limbic system (e.g., hippocampus and amygdala), hypothalamus, brainstem, and the peripheral system (e.g., sympathetic nerves, olfactory bulb). As these affected regions are crucial for sexual behaviors, these observations may provide an alternate explanation for sexual dysfunction in COVID-19 survivors. To explore the potential involvement of the nervous system in sexual dysfunction induced by COVID-19, this review discusses the recent findings from the neurological perspective and states the possible research work that may be needed to delineate the underlying pathology.

Keywords: COVID-19, long COVID, sexual dysfunction, central nervous system, male reproductive system

INTRODUCTION

Since late 2019, the outbreak of coronavirus disease 2019 (COVID-19) has been a major health concern. Caused by a novel form of coronavirus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), multiple organs and tissues expressing the angiotensin-converting enzyme 2 (ACE2, a major receptor for SARS-CoV-2[1]) and the transmembrane protease serine 2 (TMPRSS2), which facilitates the fusion of the virus and cellular membranes[2]) are susceptible to coronavirus infection. ACE2 and TMPRSS2 are abundantly expressed in the respiratory system (e.g., nasal cavity), digestive system (e.g., esophagus, small intestine, large intestine, gall bladder), reproductive system (e.g., fallopian tube, testis), nervous system at central and peripheral level (e.g., cortex, substantia nigra, olfactory mucosa) , and other distinctive organs (e.g., heart, kidney[3,4]). The abundance of ACE2 and TMPRSS2 expression implies the relatively high risk of being susceptible to the infection of aSARS-CoV-2. Concurring with the expression level of ACE2 and RMPRSS2, signs and symptoms of COVID-19 are usually tied to the abovementioned organs, including respiratory (e.g., cough, and sore throat), gastrointestinal (e.g., diarrhea), olfactory (e.g., anosmia and ageusia) and neurological symptoms (e.g., headache and pain[5]). Due to the high expression level of ACE2 and SARS-CoV-2 in reproductive organs, it has been hypothesized that the reproductive function would also be affected by the COVID-19 infection. Testosterone, the male sex hormone produced by Leydig cells in the testis, was speculated to facilitate COVID-19 entry into testicular cells by augmenting the expression of ACE2 and TRMPRSS2[6]. The presence of COVID-19, in turn, damages the testis, induces hypogonadism, causes vascular damage in the penis, and ultimately leads to erectile dysfunction[7]. Since dysfunction of the reproductive system may not be the primary complaint of patients and not easy to observe in clinical situation, sexual dysfunction due to COVID-19 may be mainly reported by patients after recovery from the disease.

COVID-19 AS A CAUSE OF SEXUAL DYSFUNCTION

The aetiology of sexual dysfunction can have central or peripheral origins. Central causes of sexual dysfunction, such as erectile dysfunction, are common among individuals with spinal cord injury[8]. Additionally, peripheral sexual dysfunction can occur as a result of factors affecting the peripheral nervous system[9]. The neurological effects of COVID-19 at central and peripheral nervous system level may have negative implications for sexual function[10]. Presentations of central nervous system alterations caused by COVID-19 include dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizures, while peripheral nervous system manifestations include anosmia, dysgeusia, and nerve pain[11]. Neuronal damage detected in brain regions vulnerable to hypoxia, such as the neocortex, hippocampus, and cerebellum, has been observed in autopsies of COVID-19 patients[12], and alterations in certain areas of the brain such as the hippocampus, that is involved in sexual arousal, could also impact the erectile response[12,13]. On the other hand, reports of neurological complaints after recovering from COVID-19 point out the involvement of the peripheral nervous system[14]. For instance, disruption of the sensory nerves responsible for sending the local sensory signals to the brain can lead to erectile dysfunction[9]. Furthermore, fatigue associated with symptoms such as cardiovagal function, postural hypotension, tachycardia, and bladder, bowel and sexual dysfunction suggests the role of dysfunctional autonomic system responses associated with COVID-19[14], and autonomic dysfunction has been identified as an important factor in erectile dysfunction[15].

The earliest concerns about COVID-19-associated sexual dysfunction can be traced back to mid-2020[16]. It was reported that the presence of orchitis and inflammation of testicles was found in about 20% of males with COVID-19 due to primary coronavirus infection or a secondary autoimmune response and testicular pain was a possible symptom in COVID-19 patients[17]. Subsequent case reports presented COVID-19 patients who experienced sexual dysfunction, including anorgasmia after recovery from COVID-19[18], Peyronie's disease with endothelial dysfunction[19], erectile dysfunction, and premature ejaculation[20]. As COVID-19 viral particles were found in testicular samples (but not in semen) and impaired spermatogenic function was shown in COVID-19 patients[21,22], these findings provide evidence to support the direct infection of testicular tissue by the coronavirus and the impact on the male reproductive function.

Later, studies on the prevalence of erectile dysfunction among COVID-19 patients provided further evidence to show the association between COVID-19 and erectile dysfunction. A study conducted by Sansone *et al.* (2021) found those patients infected by SARS-CoV-2 had a higher risk of developing erectile dysfunction[23]. Since the association observed did not imply any causal relationship, it is unclear whether COVID-19 causes erectile dysfunction or whether other underlying factors (e.g., age, ethnicity, and socioeconomic status) increase the risk of erectile dysfunction and COVID-19 simultaneously[24]. Other studies found similar findings. For instance, studies on COVID-19 recovery showed that erectile dysfunction was likely to be transient in subjects who recovered from COVID-19[25,26]. Estimations showed that the odds ratio of erectile dysfunction in COVID-19 patients was 3.3 times higher than in non-COVID-19 patients[27].

It was hypothesized that the male sexual dysfunction associated with COVID-19 was caused by several factors[28]. (1) Endothelial dysregulation: Since ACE2 and TMPRSS2 are abundantly expressed on the endothelial cell surface, COVID-19 may enter the endothelial cells in the penile tissue leading to endothelial dysfunction and subsequently affecting erection. (2) Hypogonadism: The infection of Leydig and Sertoli cells in the testis may disrupt the production of testosterone, which contributes to erectile dysfunction. (3) Psychosocial stress: Fear of transmission, awareness of social distancing, social isolation, and quarantine result in psychosocial stress, which would be another contributor to sexual distress and dysfunction. (4) Pulmonary impairment: A decrease in physical fitness due to pulmonary impairment may also affect sexual activity[29]. (5) Spinal cord damage: Spinal cord dysfunction due to spinal cord ischemia, epidural abscess, or demyelination has been observed in individuals after COVID-19 infection[30,31]. (6) Peripheral nerve damage: Dysfunctional autonomic system responses and aberrant sensory function associated with COVID-19 infection[11,14].

Although the reproductive damages of COVID-19 infection are still unclear, the presence of COVID-19 in the reproductive system (e.g., testis, which show high expression of ACE2) and the neuroinflammatory response indicate the impact of COVID-19 infection on sexual function[32,33]. Most male patients infected with COVID-19 present a cytokine storm that may lead to immune-mediated organ damage[33,34]. In other disorders, cytokines are known to pass the blood-brain barrier triggering a cytokine storm in the nervous system[32]. The cytokine storm (e.g., IL6, IL2R, IL10, TNFα, and MCP-2) can create dysfunction in different regions of the brain, including those responsible for the regulation of sexual functions (e.g., hippocampus and cerebellum) and lead to manifestations of neurological symptoms[12,32]. Central nervous system inflammatory lesions in COVID-19 patients have been previously reported suggesting the damage observed may be mediated by the cytokine storm[35,36]. The central nervous system to COVID-19-mediated lesions is more susceptible due to the increased vulnerability to hypoxia and a higher expression of ACE2 compared to the peripheral nervous system[32]. However, the peripheral nervous system is also affected. For instance, in peripheral nerves, COVID-19 spikes interact with GM1gangluoside leading to cross-reactivity and

production of antibodies against the antigens; this response induces peripheral nerve damage, which may lead to erectile dysfunction[37,38]. An elevated level of pro-inflammatory cytokines, including interleukin-6, may indicate a higher risk of developing erectile dysfunction[39]. As cytokine storm is a hallmark of COVID-19, infection severity would also serve as a predictor of erectile dysfunction[40]. Other predictors or post-COVID-19-related erectile dysfunction factors include but are not limited to age over 40 years and diagnosis of depression[41].

IMPACT OF THE PANDEMIC ON THE SEXUAL FUNCTIONING

The impact of the COVID-19 pandemic is not only on those who contracted SARS-CoV-2 but also on people with no COVID-19 infection[42]. During the epidemic, deteriorated sexual functioning including erectile dysfunction, diminished ejaculation control ability, and decreased sexual satisfaction were observed in people who were not infected by COVID-19[43]. Increased anxiety and depression are implicated in the sexual issues observed in people without COVID-19[43,44]. The increase in the prevalence of erectile dysfunction may be indirectly reflected by the increase in sales of and interest in phosphodiesterase-5 inhibitors, which are common erectile dysfunction medications[45,46]. In a study on admission to urology clinics, the number of patients with erectile dysfunction and varicocele increased significantly during the pandemic, and psychogenic factors rather than viral infection were underlying causes of sexual dysfunction in people without COVID-19 infection[47]. Erectile dysfunction was also reported in healthcare professionals working in COVID-19 settings due to the stressful working environment that affected their psychological well-being[48]. It is important to acknowledge that the incidence of depression and anxiety in COVID-19 patients is notably higher than in those without the infection[49,50]. As a result, it is reasonable to hypothesize that depression and anxiety may contribute to sexual dysfunction in COVID-19 patients as well. The heightened psychological distress experienced by this population, in conjunction with the direct and indirect effects of the virus, may amplify the risk of developing sexual dysfunction.

Unlike patients infected with COVID-19, the impact of the pandemic on the sexual functions of uninfected individuals is likely due to psychosocial factors including stress, concerns about virus transmission and social distancing as well as personality traits, which are not directly related to factors associated with sexual dysfunction in COVID-19 patients[51,52]. Evidence from cross-sectional studies showed that during the pandemic, sexual desire and sexual activity were suppressed due to social distancing concerns, and sexual activities that can be carried out by isolated individuals (e.g., pornography consumption) were increased[53-55].

SEXUAL FUNCTIONING IS REGULATED BY THE NERVOUS SYSTEM

Though most of the current perspectives on COVID-19-induced sexual dysfunctions focus on direct infection of the reproductive tissues with SARS-CoV-2, it is highly plausible that the dysfunction is not only caused by the dysfunction of the reproductive system but also by alterations in the central nervous system. For instance, erection is a spinal reflex in which penile tissues (e.g., corpora cavernosa), the autonomic nervous system, and cortical tissues participate[56]. Apart from the reflex arc at the spinal level, sensory information including visual, tactile, and olfactory stimulation and sexual imagination, which are processed by the cortex, are important in supraspinal control of erection[56]. Since ACE2 and TMPRSS2 are expressed in relatively high abundance in different regions of the brain, including the olfactory bulb, cerebral cortex, striatum, hypothalamus, hippocampus, and brainstem[57-60], COVID-19 infection in these cortical and subcortical regions may interfere with the supraspinal control of penile erection[61]. In the following section, the role of these cortical/subcortical regions involved in sexual functioning is discussed, as well as the possibility of their contribution to COVID-19-induced sexual dysfunction.

Medial preoptic area of the hypothalamus

Medial preoptic area (MPOA) is a key region that regulates sexual behaviour[62]. This region receives input from the olfactory system via the bed nucleus of the stria terminalis, amygdala, and hippocampus[63]. When the MPOA was lesioned, substantial, long-term suppression of sexual behavior, including fewer mounts, intromissions and ejaculations, was observed[64]. On the other hand, stimulation of the MPOA promoted penile erection[65]. The MPOA is suggested to integrate hormonal and sensory signals for sexual behavior, process relevant information and redistribute this information to downstream structures like the paraventricular nucleus and caudal spinal cord nuclei, which control erections[66]. As the hypothalamus expresses ACE2 and TMPRSS2, it is also a potential target for SARS-CoV-2, which may invade different hypothalamic circuits of the olfactory system. The coronavirus may be transmitted trans-synaptically and ultimately spread to interconnected brain regions[67].

Paraventricular nucleus of the hypothalamus

The paraventricular nucleus (PVN) receives projection from the MPOA and is an important supraspinal control center of erection[66]. PVN contains premotor neurons that project directly to the caudal spinal cord, which in turn contains neurons connected to the corpus carvernosum[66]. Stimulation of the PVN by different agonists including oxytocin and glutamate elicits penile erection[68], while a lesion of this region leads to fewer noncontact erection and increased latency to erection[69]. As a supraspinal erectile control center, PVN is another vulnerable area susceptible to COVID-19 infection due to the high expression of ACE2 in this region[70]. Interestingly, the infection of the PVN may be expected to affect the physiological status leading to fatigue, anxiety and changes in the circadian rhythm[71,72]. However, there is still a lack of studies on the connection between PVN and sexual dysfunction in the context of COVID-19.

Thalamus

The thalamus has been traditionally regarded as a sensory gateway to higher cortical regions, which relay sensory information, apart from chemosensation, to the cortex[73]. Similar to other sensory modules, the sexual stimuli from peripheral nerves of the penis are relayed by the thalamus and sent to higher cortical regions[74]. Deep brain stimulation of the thalamus was shown to influence penile erection[75]. Due to the complex interaction with the cortex and other subcortical regions, the involvement of the thalamus in sexual functioning can be observed in multiple aspects. The thalamus expresses high levels of ACE2[76]. Therefore, the thalamus may be another possible affected site by the coronavirus.

Amygdala

The amygdala has a widespread connection with other cortical and subcortical regions, and it has a close connection with the olfactory system and also sexual functions[77]. It is involved in the processing of olfactory and pheromonal signals which are transmitted from the olfactory bulb and the olfactory tract[74]. Through the integration of various stimuli, the amygdala regulates social, emotional and sexual functions. For instance, stimulation of the amygdala evokes orgasm-like sensations[78]. Disruptions in this region may induce functional impairment at different levels, including emotional functions, sexual functions, and resilience to stress. Thus, potential neuroinvasion into the amygdala may affect sexual functioning from the psychosocial/stress aspect to neural pathways associated with sexual function. Though ACE2 and TMPRSS2 expression is not particularly high in the amygdala, its close connection with the olfactory system may render vulnerability to this area through trans-synaptic transmission.

CONCLUSIONS

A proportion of COVID-19 patients may develop post-acute COVID Syndrome (Long COVID). Sexual dysfunction has been proposed as a possible characteristic of Long COVID[79], which could have a significant impact on the quality of life for patients after recovery. While the pathophysiology underlying

COVID-19-induced sexual dysfunction remains unclear, it is essential to consider various factors that may contribute to this condition. Recent findings suggest the potential for neuroinvasion by the virus[80], but it is crucial to examine traditional sources of erectile dysfunction (ED) alongside COVID-19-related factors. This review acknowledges the need for further research to establish a strong link between CNS-induced ED, COVID-19, and Long COVID.

Research to understand the impact and mechanism of long COVID on sexual dysfunction is still limited. Critical questions in this field include: What neural mechanisms can be targeted to restore sexual function after COVID-19? How do the neural correlates of COVID-19-induced sexual dysfunction associate with other physiological mechanisms relevant to sexual function? How do neural correlates affect the long-term prognosis of sexual dysfunction associated with long COVID? Therefore, further studies are needed to delineate the causal relationship between COVID-19 and sexual dysfunction to identify targets for treatment to improve the quality of life of the patients. Considering these conditions, it becomes essential to rigorously examine conventional etiological factors associated with erectile dysfunction in parallel with investigating the potential connection between Long COVID and sexual dysfunction. This integrative research approach will enable a deeper comprehension of the pathophysiological underpinnings of COVID-19-related sexual dysfunction and clarify its potential contribution to Long COVID. Ultimately, the insights gained from these investigations will facilitate the development of targeted and effective therapeutic interventions to address this significant clinical concern.

DECLARATIONS

Author's contribution

Study conception and design: Lau BWM, Lee JCD, So KF
Literature search and review: Lau BWM, Sanchez-Vidaña DI, Chan JNM
Draft manuscript and preparation: Lau BWM, Lee JCD, Sanchez-Vidaña DI, Chan JNM
Review and revision of paper: Lau BWM, Lee JCD, Sanchez-Vidaña DI, Chan JNM, Lau WKW, So KF
Approval of final version: Lau BWM, Lee JCD, Sanchez-Vidaña DI, Chan JNM, Lau WKW, So KF

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Conflicts of interest

The authors declare that they have no conflicts of interest regarding the publication of this manuscript. All authors have read and approved the final version of the manuscript.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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