J Med Sci 2023;43(3):147-148
DOI: 10.4103/jmedsci.jmedsci_271_21

LETTER TO EDITOR

Both Immunological Reaction and Complex Posttraumatic Stress Disorder Might be Involved in the Symptoms Manifestation of Long COVID

Dear Editor,

We read the review article summarized influences from COVID-19 on cardiovascular system published in Volume 41 Issue 3 of Journal of Medical Sciences. The authors discussed the possible role of dysregulated immune response in cardiovascular involvement and myocardial injury by coronavirus-19. A collective term "long COVID" has been used for describing lasting or newly-developed clinical manifestations even after the viral infection. Both physical and mental health could be impacted. The relationships between long COVID, immune system, and related psychological symptoms are worthy of exploration.

Long COVID could cause long-term effects in multiaspects. Common symptoms including fatigue (58%), headache (44%), attention disorders (27%), hair loss (25%), and dyspnea (24%).[1] Chest pain and myalgia had also been reported.[1] Symptoms of long COVID resembled symptoms of fibromyalgia much. Fibromyalgia, characterized by widespread chronic pain, was said to be associated with mast cell and dysregulation of immune response.[2] It had been speculated that long COVID pathophysiological mechanisms might be related to sequelae of organ damage, postviral syndrome, postcritical syndrome, chronic inflammation, or immune response.[3]

The COVID-19 pandemic has been widely considered a traumatic event. In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), core diagnostic features of posttraumatic stress disorder (PTSD) are symptoms following exposure to traumatic events, including at least one intrusion symptom, one avoidance symptom, two negative cognitive or mood alternations, two arousal, and reactivity alternations, with functional impairment and duration longer than 1 month. Prevalence of PTSD was about 20% in confirmed population. Historically, overall postpandemic PTSD prevalence after outbreaks of sudden acute respiratory syndrome, H1N1, Ebola, Zika, etc., was about 22.6%, which raised the concern of mental hygiene indeed.[4] Stress could not only influence the glucocorticoid secretion but also influence immune response. Previous studies had discussed that PTSD was probably a result of inflammatory state and immune imbalance of stimulatory and inhibitory immune mediators.[5] Serum level of enhanced proinflammatory cytokines such as interleukin-6 had been detected in patients with fibromyalgia, PTSD, or mice infected by COVID-19.[2,6] Higher prevalence of PTSD was seen in fibromyalgia patients. Prior study had implied traumatic events as mediator of fibromyalgia developing to PTSD.[7] Elevated leukocytes and inflammatory activities following stress with downregulated glucocorticoid system were found, by which rheumatic disorders would be caused.[8] Adrenaline might increase neutrophils and reduce lymphocytes whereas noradrenaline might increase both neutrophils and B cells numbers.[9] Moreover, glucocorticoids could redistribute T cells in the bloodstream.[9] Under stress, catecholamine and glucocorticoids would be initially enhanced with elevated leukocytes. We could speculate a bidirectional relationship that not only dysregulated hypothalamic-pituitary-adrenal axis with increased corticotropin-releasing hormone and subsequently resulting decreased glucocorticoid level had been found in PTSD patients; however, disrupted circadian rhythm, sleep deprivation in PTSD could, in turn, fail to reduce nocturnal catecholamine secretion, sympathetic drive, inducing further immune-inflammatory responses.[10]

The type of trauma and time since trauma might also influence the change of cytokine level.[5] Chronic PTSD, defined as PTSD symptoms lasting more than 6 months, was also commonly seen. Chronic inflammatory state might associate with worsening elevated cytokine level. Complex PTSD (CPTSD) after exposure to multiple interpersonal traumatic events over a prolonged period of time with physical and mental impacts, also possibly happened during the pandemic, especially in groups of children and adolescents. Somatization symptoms including stomachaches and headaches were examples. CPTSD, categorized as a PTSD subtype in DSM-5, had been proposed by the International Classification of Diseases 11th version as a separate diagnosis. CPTSD was featured by symptoms in three key domains, including affective dysregulation, negative self-identity, and disturbed relationship. Higher somatization than PTSD was also noticed in CPTSD.[11] Cognitive, emotional symptoms were similarly seen in fibromyalgia.[7] The persisting pandemic could expose people to chronic and complex trauma type. Victims would also be at higher risk of having long-lasting negative influences on immune, nervous system, or other chronic diseases.[12] The mechanism of involving mental outcome in COVID-19 might be shared through immune pathway.[6]

Immune dysregulation and chronic inflammation might play an essential role in the mechanism of PTSD during and postpandemic. Persistent infection might lead to chronic inflammatory state, in turn, making patients more

susceptible to developing PTSD.[5] Preventive measures such as self-regulation for stress coping, seeking help to mental health professionals when necessary are suggested. Follow-up of survivors of COVID-19 psychiatric condition and resilience might be helpful for their long-term well-being.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Received: July 29, 2021; Revised: September 26, 2021; Accepted: October 06, 2021; Published: November 19, 2021;

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How to cite this article: Lin CC, Yeh CB. Both immunological reaction and complex posttraumatic stress disorder might be involved in the symptoms manifestation of long COVID. J Med Sci 2023;43:147-8.