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Viral Pandemics as Possible Psycho-immunological Causes of Psychiatric Symptoms: From Past to Present

Psikiyatrik Belirtilerin Olası Psikoimmünolojik Nedenleri Olarak Geçmişten Günümüze Viral Pandemiler

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ABSTRACT
Human history has witnessed a wide variety of viral outbreaks from past to present, following these outbreaks, there has been an increase in the frequency of neuropsychiatric, neurodegenerative, neurobehavioral, and autoimmune disorders. Dramatic increases in psychotic disorder, anxiety disorder, depression, mania, and suicide cases after viral pandemics in the 19th and 20th centuries caused great debate. Trying to explain this increase in psychiatric disorders only with panic and trauma experienced by the populations who are caught unprepared for viral outbreaks will be incomplete without addressing the underlying infectious agents and the inflammation triggered in the host. Recent studies show that viral infections and inflammatory mechanisms triggered by them cause uncontrolled activities in microglia and impaired neurotransmitter functions, which leads to many psychiatric disorders based on genetic predisposition. In this review, we discusscase presentations and clinical studies in the literature related to acute psychiatric findings, which are thought to be associated with SARS-CoV-2(the virus that causes COVID-19), the underlying etiological mechanisms, and possible psychoimmunological reflections of these acute symptoms, by considering past viral outbreaks.
Keywords: COVID-19, SARS-CoV-2, pandemic, inflammation, psychiatric symptom

ÖZ
İnsanlık tarihi geçmişten günümüze çok çeşitli viral salgınlara tanık olmuş, bu salgınların ardından, etkilenen toplumlarda nöropsikiyatrik, nörodejeneratif, nörodavranışsal ve otoimmün bozuklukların görülme sıklığında artış meydana gelmiştir. 19. ve 20. yüzyıllarda viral pandemilerin ardından psikotik bozukluk, kaygı bozukluğu, depresyon, mani ve intihar olgularında görülen dramatik artışlar büyük tartışmalara yol açmıştır. Psikiyatrik bozukluklarda görülen bu artışın viral salgınlara hazırlıksız yakalanan toplumların yaşadığı panik ve bunun neden olduğu travma ile açıklanmaya çalışılması altta yatan enfeksiyöz ajanları ve konakçıda tetikledikleri inflamasyonu ele almadan eksik kalacaktır. Son dönemde yapılan çalışmalar, viral enfeksiyonların ve tetikledikleri enflamatuvar mekanizmaların mikroglialarda kontrolsüz aktivitelere ve nörotransmitter fonksiyonlarında bozulmalara neden olduğu, bu durumun da genetik yatkınlık zemininde birçok psikiyatrik bozukluğa yol açtığını göstermektedir.Bu derlemede, SARS-CoV-2'nin (COVID-19 etmeni) neden olduğu düşünülen psikiyatrik bulgularla ilgili literatürde yer alan vaka sunumları ve klinik çalışmaları, altta yatan etiyolojik mekanizmaları ve sebep olduğu akut tabloların ileri dönemdeki olası psikoimmünolojik yansımalarını, geçmiş viral salgınları da göz önünde bulundurarak tartıştık.
Anahtar Kelimeler: COVID-19, SARS-CoV-2, pandemi, inflamasyon, psikiyatrik belirti

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INTRODUCTION

The previous years have dramatically witnessed the great viral pandemics of 1889 Russian H2N2, 1918 Spanish H1N1, 1957 Asian H2N2, 2009 swine flu H1N1 (1). Again Ebola, Chikungunya, and Zika infections in different geographic places, sporadic infections with H5N1 and H7N9 viruses in South-East Asia, and the widespread H5N2 IAV outbreak in North America had a tremendous impact on every facet of individuals' lives (2). Finally, the coronavirus disease 19 (COVID-19) pandemic, which affects the whole world, continues to spread and so far approximately 3 million cases have occurred globally. According to the World Health Organization COVID-19 situation reports, the United States, Spain, and Italy are currently among the most affected countries (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation reports).

Researchers claim that chronic conditions caused by viral infections can lead to numerous disorders, including neurodegenerative, psychiatric and neurobehavioral disorders, autoimmune diseases, and other conditions (3). Studies from the 19th and 20th centuries have showed an increased percentage of psychosis, depression, mania, anxiety, suicide, insomnia, and delirium. Although the viral pandemia, which affects the populations quickly and catches up unprepared, is a source of trauma in itself, viral load and cytokine storm can lead to psychiatric symptoms with the contribution of a genetic basis (4).

Possible Mechanisms of Psychiatric Manifestations in Viral Infections:

There might be particular mechanisms altering the harmful effects of infectious agents. Many studies have published that the harmful effects of prenatal viral infections depend on direct infection of the fetal brain and placenta (5). The influenza A virus has been detected in the central nervous system of immunodeficient mice at seventeen-months, post-inoculation, and with limited destruction to tissues (6). The influenza A virus has also been detected in fetal brain three-days after prenatal infection and continued up to ninety-days postnatally (7). Coronaviruses (CoV) and influenza viruses are potentially neurotropic and may invade the brain through the olfactory neural pathway. It has been also hypothesized that the neuroinvasive potential of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), especially of medullary structures related to respiration (nucleus ambiguus, solitary tract nucleus), might partly cause respiratory failure currently seen in COVID-19 (8).

In the central nervous system, virus-infected monocytes can trigger neuroinflammation and cause neuropsychiatric symptoms, by spreading inflammatory cytokines, and by increasing microglial activation. There is also data that leukocytes can remain persistently contaminated by CoV (4). Although low-level neuroinflammation induced by viruses is claimed to cause neuropsychiatric symptoms (9), there is also a hypothesis that peripheral inflammation due to deterioration in the blood-brain barrier, leading to peripheral immune cell movement into the central nervous system, and interruption of neurotransmission (10).

For over a century, it was thought that waste and toxins that accumulate in the intestinal tract can affect a person by leading in depression or psychosis. The relation between the gut microbiome and the first-onset of schizophrenia (SCZ) was recently discovered. Patients experiencing their first episode of psychosis had changed intestinal bacteria composition. It seems that the gut flora altered in these patients, probably as a result of inflammatory effects (11). Viral spilling in feces of COVID-19 continues for about five weeks post-infection. Although the degree and mechanisms of viral infiltration of gut epithelium by SARS-CoV-2 are unknown, angiotensin-converting enzyme 2 (ACE2) is expressed by gut epithelial cells, and approximately 40% of COVID-19 patients apply with gastrointestinal signs (4).

Psychiatric Disorders:

1. Schizophrenia Spectrum and Other Psychotic Disorders:

It has been reported that there is a relationship between SCZ and many autoimmune diseases, and there is an increased prevalence by about 45% of the

existence of an autoimmune disease. Furthermore, viral infections exposed in the embryonic and early childhood years lead to delays in fetal brain maturation and excessive synaptic pruning through adolescence, are among the potential risk factors of psychosis (12). There is limited evidence for transplacental passage and persistence of the virus in the offspring brain. More likely to be relevant are the effects of infection-induced maternal immune activation on the developing brain. Many studies also concentrate on biomarkers of the earlier infection (usually IgG antibodies to particular pathogens, including influenza) in adults with psychotic disorders, with exposure to several microorganisms related to increased SCZ risk (13). An association between aggressiveness and inflammation was also shown in an examination of inpatients diagnosed with SCZ. Elevated c-reactive protein (CRP) levels were related to increased aggressive behavior compared to inpatients with normal levels of CRP (14). The patients who are a high predisposition for psychosis and SCZ also have a moderate increment in the inflammatory microglial activity (15).

CoV cause infections varying from common colds to SARS.Psychiatric symptoms such as auditory and visual hallucinations, manic and depressive symptoms have been reported in researches about SARS infection (16). When Severance et al. measured the IgG level of 4 human coronavirus (HCoV) strains (229E, HKU1, NL63, and OC43) in 106 patients with a recent onset of psychotic symptoms and 196 nonpsychiatric controls,they found that the patient IgG levels were higher than controls for HKU1, NL63, and OC43 strains (17). Consequently, the expanding spread of COVID-19 has proposed serious fear that, in addition to the acute psychiatric symptoms related to the current condition, the psychiatric outcomes of the disorder especially in the context of the rising frequency of SCZ, may become visible in following years (4).

2. Depressive Disorder and Bipolar and Related Disorders:

The Danish researchers showed that the patients who were diagnosed with autoimmune disorders had a 45 % increased risk for a mood disorder. The authors also found that the patients who had been hospitalized for the previous infection had an approximately 62 % increased risk for bipolar disorder (BD) or major depressive disorder (MDD) (18). Fetal exposure to influenza virus leads to a four-fold increase in the risk of BD and MDD reported related to Borna disease virus and members of the herpesvirus family (HSV-1, HHV-3, and HHV-4) (19). Prusty et al. reported that molecular evidence for active HHV-6A and HHV-6B infection in Purkinje cells of the human cerebellum in BD and MDD (20). Mazaheri-Tehrani et al. showed a high prevalence of subclinical Borna disease virus infections in Iran as reported for central Europe and provided again an indication for the correlation of Borna disease virus infection and mood disorders (21). Again Tanaka et al. published that an increase in C-reactive protein, IgM classantibodies against cytomegalovirus (CMV), and IgG class antibodies against HSV-2 were found in BD (22).

A new study shows that viral infections can trigger brain endothelial and epithelial cells to produce a cytokine that damages neuronal firing in the hippocampus, leading to depressive-like behavior and cognitive impairments (23). Several pathogens that cause persistent infections have been related to MDD. Human papillomavirus (HPV) has been associated with depressive symptoms in human immunodeficiency virus (HIV)-infected patients (24, 25). Throughout the 12 year follow-up of study with nurses, including above 43,000 participants, the development of MDD was increased in nurses who had higher inflammatory markers (26).

When the publications about CoV are reviewed, it was seen that seropositivity for HCoV strain (NL63) has been related to a history of mood disorder, although not with its polarity or with a history of suicide attempts (27). Again, the COVID-19 outbreak erupts in China, an online survey was conducted by Ahmed et al. on a sample of 1074 Chinese people, the majority of whom from Hubei province. They evaluated depression, anxiety, mental well-being, and alcohol consumption behavior with self-reported measures. Based on the Beck Depression Inventory

more than one-third ofparticipants (37.1 %) were having different forms of MDD (mild 10.2 %, moderate 17.8 %, and severe 9.1 %) (28).

3. Anxiety Disorders, Trauma and Stress-Related Disorders, And Obsessive-Compulsive and Related Disorders:

It is still unclear whether the symptoms associated with anxiety or trauma- and stress-related disorders (TSD) in previous CoV pandemics are due to the virus infection itself or the host immune system (4). Some study results published that infectious diseases could be related to specific anxiety disorders. Obsessive-compulsive disorder (OCD) is related to low-grade inflammation, neuro-inflammation, and autoimmune disorders. In some groups of patients diagnosed with OCD, autoimmunity may be activated by viral,bacterial, or parasitic agents with overlapping surface antigens in the central nervous system (29). Group A streptococcal infections seem to be related to OCD and/or tic disorders (Pediatric autoimmune neuropsychiatric disorders associated with streptococci (PANDAS)) (30). During earlier outbreaks like influenza, SARS, and the middle east respiratory syndrome (MERS)the aggravation of OCDhas been observed particularly within 6–12 months of post-infection (31).

Other researchers have found increased rates of TSD in HIV positive patients over different sociodemographic and cultural backgrounds (32). TSD has also been examined to identify markers of inflammation. A study showed that patients diagnosed with post-traumatic stress disorder (PTSD) had increased levels of immune molecules in their blood. The authors also suggested that low-grade inflammation might be a potential new target for the pharmacological treatment of PTSD (11, 33). Lam et al. reported that the patients who have recovered from the disease of SARS-CoV-1 were diagnosed with PTSD (54.5%), MDD (39%), pain disorder (36.4%), panic disorder (32.5%), and OCD (15.6%) through 31 to 50 months post-infection and they also found that a dramatic rise of prevalence of any psychiatric disorders as 3% according to the patient's pre-infection period (34).

In the literature on SARS-CoV-2, Ahmed et al. published that 29% of the 1074 Chinese participants, whose anxiety levels were measured with the Beck Anxiety Inventory, showed different anxiety levels (mild 10.1%, moderate 6.0%, and severe 12.9%) since they were locked up at home due to the curfew caused by COVID-19 outbreak (28). In a web-based study, the data obtained from 7,236 self-selected participants who evaluated with socio-demographic and COVID-19 related information, generalized anxiety disorder (GAD), depressive symptoms, and sleep quality from February 3 to February 17, 2020. A high prevalence of GAD and poor sleep quality in the Chinese public during the COVID-19 outbreak was reported in this cross-sectional study (35).

4. Suicidal Behavior:

In recent studies, inflammation-related gene polymorphisms found significantly different in patients with psychiatric disorders with suicidal behavior (SB) than a patient without SB or control group (36). There was also some research showed that besides genetic factors, due to the infection, the level of inflammatory markers may increase in the serum, cerebrospinal fluid, and postmortem brain tissues of individuals with SB. The authors recognized higher levels of inflammatory markers in patients with suicide risk compared to healthy participants. They deduced that IL-1β and IL-6 could predictably distinguish patients with SB from the non-suicidal control group (37).

Specific infectious agents might infect the brain directly, others may reach the brain from the periphery, and even others can produce molecular mediators of inflammation that pass from the periphery into the brain and so increase the risk of SB. Examples of infectious agents infecting the brain are the influenza B virus and the Toxoplasma Gondii, which have been associated with SB (38). When Nissen et al. evaluated the association between HSV-1 infection and CRP levels, and psychiatric disorders and SB among 1,504 Danish psychiatric patients, 353 suicidal cases, and controls were frequency-matched by age and sex, they reported that HSV-1 was associated with suicidal behavior and first psychiatric

disorder whereas no association between CRP and psychiatric disorders or SB was found (39).

Psychiatric problems related to COVID-19 have already cost a person's life in India, it was claimed that a 50-year-old man committed suicide in the Chittoor district of Andhra Pradesh (40). Suicide news, thought to be related to SARS-CoV-2 infection, started to appear in Turkish media. A 67-year-old man diagnosed with renal failure in Salihli district of Manisa, committed suicide by jumping from the 3rd floor of the hospital where he was quarantined due to COVID-19, accompanied by high fever after dialysis. Again in Kutahya, a 29-year-old woman, who had previously locked her room and attempted suicide by drinking medicines, committed suicide by jumping from the window of her house for fear of transmitting the CoV to her relatives (41, 42).While case presentations, which are claimed to be suicides due to the fear of being infected with COVID-19 or spreading others, have started to be reported, the comments regarding the relationship of suicide with inflammation due to viral infection seem to be early.

CONCLUSION

The studies on the acute psychiatric effects of COVID-19 pandemic, which can be a source of great panic, anxiety, and delusional drafts all over the world, is gradually entering the literature. However, we know that decades after past epidemics, there has been an increase in the frequency of psychiatric disorders associated with inflammation. Chronic exposure to low-level inflammation was considered the cause of psychiatric disorders when evidence of viral particles could not be detected in the serum, cerebrospinal fluid, and postmortem brain samples of patients. Although anxiety, mood disorders, psychotic symptoms, SB, and sleep disturbances have already been linked to social isolation, curfews caused by the COVID-19 outbreak, or news related to this issue in the press and social media, it will take a while to understand the role of inflammation on these psychiatric symptoms.

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