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REVIEW ARTICLE

Mechanisms of new-onset psychosis during the COVID-19 pandemic: What ignited the fire?

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BACKGROUND: The coronavirus disease 2019 (COVID-19) pandemic has been associated with the emergence of various psychiatric illnesses, although very little literature has focused on the effect of COVID-19 on psychosis. Preliminary data have shown possible increases in new-onset psychosis.

METHODS: Using MEDLINE, we performed a review of the current literature to identify the mechanisms by which pandemics may increase psychosis risk and generate evidence-based recommendations to control surges of psychosis. We identified 85 relevant studies, of which 34 were case reports on psychosis during the COVID-19 pandemic.

RESULTS: Underlying mechanisms of psychosis include "direct viral mechanisms," such as neuroinflammation linked with the coronavirus, and "nonviral mechanisms," such as stress, isolation, and uncertainty.

CONCLUSIONS: Improvement of our understanding of the pathophysiology of psychosis related to COVID-19 along with implementation of strategies to fight against stress and social isolation in addition to awareness campaigns regarding new-onset psychotic symptoms are much needed to optimize early detection and management of psychosis.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) took the world by storm starting in December 2019. Strict lockdown measures were taken to limit the spread of the disease, resulting in complete isolation of people globally.[1] Although necessary, these measures have caused substantial stress, leading to the rise of an array of mental health disorders.[2] This is a trend that has also been observed in past pandemics, such as the 1917-1918 Spanish flu[3] and, more recently, severe acute respiratory syndrome (SARS).[4]

While depressive and anxiety disorders are known to be on the rise, psychotic disorders seem to have been left out of the discussion.[5]

This is especially curious considering that an increase in stress could increase the incidence of psychosis. Indeed, according to the diathesis-stress model, schizophrenia is the result of the interaction of environmental stressors with varying degrees of genetic predisposition, with individuals with life stressors being 3 times more likely to develop schizophrenia.[6]

The association of psychosis and viral infection is not new. In fact, influenza was not considered to be an isolated infection in the respiratory tract, but a continuum that spans the neuropsychiatric as well as the somatic systems.[7]

Several cases of psychosis, suicidality, and delirium were reported during the Russian,[8] Spanish[7,9,10] and Asian[11] influenza outbreaks. Preliminary research has shown that there has been a possible increase in first-episode psychosis in the COVID-19 pandemic.[12]

Considering this history linking pandemics and psychosis, it is necessary to look into the mechanisms responsible for this association and explore the interplay of psychosocial, environmental, immunological, media, and neurobiological factors and their effects on the emergence of new-onset psychotic symptoms in a pandemic context. In this narrative review, we navigate in-depth viral and psychosocial mechanisms associated with emergence of new-onset psychotic symptoms during the COVID-19 pandemic based on evidence collected from new cases of psychotic episodes published in the literature during the pandemic. Recommendations to prevent emergence of psychosis in vulnerable individuals are also discussed.

METHODS

We performed our review of the literature on December 28, 2020, using MEDLINE with the search strategy detailed in **TABLE 1**. We selected studies that included healthy individuals who developed new-onset psychotic symptoms/episodes during the pandemic. We excluded records on the effect of prenatal infection on the incidence of psychosis, as this has been discussed in a separate review.[13]

As such, we initially identified a total of 511 records. After removing duplicates, 508 records remained. After going through abstracts and titles, we excluded 423 records, leaving 85 relevant studies. Of these, 34 were case studies and case reports of psychosis developed during the COVID-19 pandemic, **TABLE 2**[14-29] summarizes studies that included participants with positive polymerase chain reaction (PCR) status, **TABLE 3**[30-43] summarizes studies that included participants with negative PCR status, and **TABLE 4**[44-47] summarizes studies that included participants with mixed PCR status. Additionally, 7 articles from the search results were experiments aiming to study the effects of various environmental factors on psychosis development during the pandemic. We identified additional records from the included articles' references. Based on the best available and most up-to-date evidence found in these studies, information on mechanisms was extracted and fell under 2 broad categories of "direct viral mechanisms" and "nonviral mechanisms," more specifically stress, isolation, and uncertainty.

VIRAL MECHANISMS UNDERLYING DEVELOPMENT OF PSYCHOSIS

Within the cases reviewed, psychosis was shown to emerge at different points across the course of the infection, be it at the initial presentation while being either symptomatic[14-17,19,23,24,27-29,46] or asymptomatic[15,18,20-22,25] or weeks after resolution of the infection.[26,45] Neuropsychiatric symptoms can be the only presenting symptoms of a COVID-19 infection.[48] In a nationwide surveillance study conducted in the United Kingdom on 153 individuals who contracted the infection, 10 (43%) of 23 patients presenting with neuropsychiatric disorders had new-onset psychosis.[49] Psychosis can thus be a core symptom of the infection.

TABLE 1
Search strategy

For psychosis and schizophrenia
MeSH
Schizophrenic language
Schizophrenic psychology
Schizophrenia spectrum and other psychotic disorders
Delusions
Hallucinations
Auditory perceptual disorders
Alice in Wonderland syndrome
Keywords
Psychos?s
Psychotic*
Schizoph*
Schizoaff*
dementia praecox
Ultra-high risk
Clinical high risk
At-risk mental health
Prodromal schiz*
Capgras*
Ekbom*
Delusio*
Hallucinat*
For pandemics
MeSH
Pandemics
SARS-CoV-2
Coronaviridae infections
Coronaviridae
COVID-19
Pneumonia, viral
Influenza A
Influenza, human
Influenza 1918-1919
Keywords
Pandemic*
Coronavir*
hcov-*
SARS-CoV*
COVID*
Mers
Middle Eastern respiratory syndrome
1918 pandemic
1918 influenza
Spanish flu
Spanish influenza

Final search
1. exp Schizophrenic language/
2. exp Schizophrenic psychology/
3. exp "schizophrenia spectrum and other psychotic disorders"/
4. exp Delusions/
5. exp Hallucinations/
6. exp Auditory perceptual disorders/
7. exp Alice in Wonderland Syndrome/
8. Psychos?s.mp.
9. Psychotic*.mp.
10. Schizoph*.mp.
11. Schizoaff*.mp.
12. dementia praecox.mp.
13. Ultra-high risk.mp.
14. At-risk mental health.mp.
15. Capgras*.mp.
16. Ekbom*.mp.
17. Delusio*.mp.
18. Hallucinat*.mp.
19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp SARS-CoV-2/ or exp Coronaviridae infections/ or exp Coronaviridae/ or exp COVID-19/
21. exp Influenza, human/ or exp Pandemics/ or exp Influenza A virus/
22. exp Pneumonia, viral/
23. exp Influenza, human/
24. Pandemic*.mp.
25. Mers.mp.
26. Coronavir*.mp.
27. hcov*.mp.
28. SARS-CoV*.mp.
29. COVID*.mp.
30. 1918 pandemic.mp.
31. 1918 influenza.mp.
32. exp Influenza pandemic, 1918-1919/ or Spanish flu.mp.
33. Spanish influenza.mp.
34. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 19 and 34

MeSH: medical subject headings.

Neuroinvasion

Human coronaviruses have been found in brain tissue postmortem,[50] indicating a direct invasion of the CNS. The coronavirus has also been detected in the CSF for at least 1 year after the infection. This indicates possible latency of the virus in the CNS, potentially resulting in long-term psychiatric effects and potentially explaining the delayed onset of psychosis in certain patients after COVID-19 infection.[51]

Two main mechanisms are described in the literature to explain the virus' entry into the CNS. The first is via neuronal retrograde movement by entering through the cribriform plate through olfactory and enteric nerves.[52] The second route is the hematogenous route through angiotensin-converting enzyme 2 (ACE2) receptors localized on the brain, through endothelial cells via endocytosis, or via infected leukocytes, which then transmigrate through the blood brain barrier (BBB).[52] ACE2 receptor invasion causes accumulation of proinflammatory angiotensin II, promoting neuropsychiatric symptoms.[53]

Once in the CNS, this coronavirus has a propensity to invade the medulla, specifically the vagal nuclei such as the nucleus ambiguous and the solitary tract nucleus.[54] Some evidence shows that low vagal activity and dysfunction of the alpha-7 nicotinic acetylcholine receptor may be associated with increased inflammation and subsequent risk of developing schizophrenia.[55]

Neuroinflammation

Chronic neuroinflammatin and the coronavirus. Childhood and early-adulthood viral infections of the CNS have been found to be strongly associated with psychosis in adulthood.[56] Indeed, chronic inflammation is one of the mechanisms by which viral infections occurring early in life generally may prime the CNS into psychosis.[56] Priming occurs through microglial activation, whereby in response to certain brain insults, such as a single instance of viral interference, microglia release proinflammatory cytokines, causing neuronal insult.[57] These cytokines would then stimulate microglia to release more proinflammatory cytokines and chemokines, thus creating an inflammatory reaction altering neuronal function; synaptic plasticity;metabolism;andreuptakeofserotonin,noradrenaline, and dopamine in the brain, as well as activating the hypothalamus-pituitary adrenal (HPA) axis via increased release of corticotropin-releasing hormone (CRH).[58]

Cytokines such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) play a particularly important role in the development of psychosis, can also be released during peripheral or systemic infections, and have been shown to permeate through the BBB because of inflammation.[59] In addition, a recent review found that interleukins 1-beta, 7, and 8 and matrix metalloproteinase (MMP)-8 are important biomarkers predictive of transition from a prodromal or clinical high-risk for psychosis state to a full-blown first-episode psychosis.[60]

Seropositivity for the HKU1, NL63, and OC43 strains of coronavirus has been linked to the emergence of schizophrenia and other psychotic disorders.[61] This indicates an association between psychosis and neuroimmunoreactivity to the coronavirus. The coronavirus could thus induce chronic inflammation, leading to psychosis. It is not yet clear whether the direct viral infection or the secondary inflammatory response leads to psychosis.[62]

However, this chronic, low-grade inflammation alone may not be enough to explain the pathophysiology of acute psychosis induced by COVID-19, and an additional mechanism, the cytokine storm, has been proposed.[63]

Cytokine storm. A cytokine storm is the extensive systemic release of chemokines and interleukins such as IL-1 beta and IL-6.[63] This inflammation causes increased permeability of the BBB, leading to infiltration of cytokines, which causes neural injury.[63]

Indeed, COVID-19 has been theorized to cause cytokine storms, and it has been evidently implicated in the respiratory pathologies of the disease.[63]

The cytokine storm has been shown to be correlated with neuropsychiatric symptoms[64] and cognitive decline.[58] In one case report, COVID-19 was found to be associated with acute necrotizing encephalopathy, a rare complication of viral infections that is related to intracranial cytokine storms, resulting in BBB breakdown, without direct viral invasion.[65] Other case series looked at cytokine and inflammatory marker levels during psychotic episodes induced by COVID-19 infection; several studies showed increased C-reactive protein,[18,26,44,46] erythrocyte sedimentation rate, and D-dimer[44] and neutrophil-lymphocyte ratios indicative of IL-6 levels.[18] IL-6 and TNF-alpha levels were shown to be normal in another instance.[46] Future studies comparing longitudinal long-term changes in inflammatory biomarkers levels between COVID-19–positive patients who developed psychosis and COVID-19–positive controls are needed.

TABLE 2
Cases of psychosis associated with the COVID-19 pandemic with positive PCR status

Study	Country	Summary
Elkhaled et al[14]	Qatar	A 23-year-old man with no past medical or psychiatric history presented with auditory hallucinations and suicidal ideations. A brain MRI revealed an isolated oval-shaped lesion in the splenium of the corpus callosum suggestive of CLOCC. After a hospitalization associated with MODS and severe intra-abdominal and cerebral bleeding, he developed cardiac arrest and died on hospital Day 15
Ferrando et al[15]	United States	Three cases of recent-onset severe anxiety, psychomotor agitation, and delusions of persecution. One had hallucinations. All 3 tested positive for COVID-19, yet none showed any symptoms of COVID-19. Their delusions were not particularly centered around COVID-19–related fears. None of the 3 had a psychiatric history
Franchi et al[16]	Italy	A 36-year-old nulliparous woman at 35 weeks gestation presented with severe COVID-19 symptoms requiring ICU admission. Emergency C-section was performed, and the baby was in good health. Nine days after discharge, the patient presented with a manic episode with severe psychotic features. She also had a history of bipolar disorder
Gillett et al[17]	United States	A previously healthy 37-year-old male health care worker experiencing stress from the pandemic and his work presented with confusion, psychotic symptoms, and a suicide attempt after being diagnosed with COVID-19. After admission to the ICU, his physical and psychiatric symptoms eventually resolved
Huarcaya-Victoria et al[18]	Peru	Three cases of women with no psychiatric history presenting with delusions and auditory hallucinations unrelated to COVID-19. All 3 patients tested positive for COVID-19, though not all of them were symptomatic. Believed to be secondary to COVID-19 infection
Jaworowski et al[19]	Israel	Three cases of COVID-19–positive patients with psychotic symptoms that resolved after 2 days of varying doses of haloperidol. Only mild respiratory symptoms were present
Lanier et al[20]	United States	A 58-year-old male presented with acute psychosis and no symptoms associated with COVID-19. The patient had a medical history of coronary artery disease, chronic hepatitis C, polysubstance abuse (including cocaine and alcohol), liver disease, anxiety, and panic disorder. The patient was experiencing hallucinations and psychomotor agitation. He was tested for COVID-19 once he developed respiratory symptoms, leading to a positive result. He initially was treated with hydroxychloroquine before it was discontinued. The patient was treated with haloperidol and lorazepam, and symptoms resolved
Lorenzo-Villalba et al[21]	France	A 33-year-old woman was admitted to the ED with a 1-day history of auditory hallucinations and disorganized behavior. No other symptoms were reported. Blood testing confirmed elevated white cell count and C-reactive protein. The head CT scan was normal, but the chest scan showed right ground-glass opacities in the lower zones. The oropharyngeal swab was positive for SARS-CoV-2. The patient was given olanzapine 10 mg/d, and symptoms resolved after 2 weeks; antipsychotics were discontinued
Losee et al[22]	United States	This case report describes a patient with no psychiatric history who developed psychotic symptoms in the context of acute COVID-19 delirium without any other respiratory symptoms
Majadas et al[23]	Spain	A 63-year-old male with no psychiatric history presented with COVID-19–induced pneumonia, as well as delirium. He was treated with oxygen, lopinavir, ritonavir, tocilizumab, hydroxychloroquine, and a 3-day bolus of corticosteroids along with 3 mg of risperidone. He maintained the delusions up to 2 weeks after onset, and his dose was increased to 6 mg of risperidone, where he improved. Of note, the patient was still COVID-19 positive at readmission. Temporally, it is unlikely that the psychosis was drug-induced, so it is believed to have been associated with viral infection
Mirza et al[24]	United States	A 53-year-old COVID-19–positive male with no psychiatric or medical history presented after attempting to take his own life by drinking bleach. He was agitated. He then presented respiratory symptoms and fever requiring medical assistance. He took 3 doses of olanzapine, as well as oxygen supplementation, antibiotics, and hydroxychloroquine. He improved markedly on Day 12

TABLE 2 (continued)

Study	Country	Summary
Noone et al[25]	United States	Two case reports of adult patients with COVID-19 infections who presented with severe psychosis and mania with no psychiatric history and in the absence of notable medical symptoms. One was a 49-year-old man presenting 3 weeks after diagnosis of COVD-19. He was given haloperidol 2 mg as needed for agitation and received trials of olanzapine 2.5 mg/d and then quetiapine up to 150 mg, which were then tapered off after 2.5 weeks because of improvement. CT and EEG were clear. The second was a 34-year-old woman with bizarre behavior and paranoid ideation. She was given 1 mg of risperidone, after which she improved
Parra et al[26]	Spain	Isolated 10 cases of post–COVID-19 psychosis in patients with no history of mental health issues. All had the infection at least 2 weeks since developing the symptoms. No patients had any family history of infection. Five (50%) patients had been admitted to the ICU, which, according to the authors, could have played a role in the symptoms of confusion
Saje et al[27]	Slovenia	A case of a middle-aged male suffering from acute psychosis while quarantining for COVID-19. The patient required urgent hospital admission because of his psychosis. After recovery, the patient experienced spontaneous virus reactivation a few weeks later that additionally resolved with antipsychotics
Smith et al[28]	United States	A 36-year-old African American woman working at a nursing facility with a remote history of erythema multiforme and no psychiatric history was diagnosed with COVID-19 with symptoms of rhinorrhea and congestion. Four days into her illness, she developed persecutory delusions. She was given 2 daily doses of olanzapine 2.5 mg and 5 mg without any improvement. She was then switched to an eventual dose of risperidone 3 mg with improvement
Subramanyam et al[29]	India	Case series of 3 women of low SES and no psychiatric history presenting for postpartum psychosis in the context of positive COVID-19 PCR tests. Laboratory workup and neuroimaging were negative. Patients had uneventful pregnancies and deliveries. All 3 developed auditory hallucinations, paranoia, and aggression, and 1 patient tried to harm her newborn infant. All 3 were treated with antipsychotics, and symptoms resolved

CLOCC: cytotoxic lesion of the corpus callosum; ED: emergency department; ICU: intensive care unit; MODS: multiple organ dysfunction syndrome; PCR: polymerase chain reaction; SES: socioeconomic status.

Additionally, the cytokine storm seems to precipitate or co-occur with coagulation cascade activation, which is possibly associated with psychosis after COVID-19 infection.[26]

Hypercoagulability and endothelial injury

Hypercoagulability in association with inflammation is thought to be an underlying pathophysiological mechanism leading to schizophrenia.[66] Defects in coagulation pathways have been shown to be possible trait biomarkers of psychosis even before the onset of a first episode.[67] Patients with schizophrenia are found to be more prone to hypercoagulability; they have increased levels of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which may lead to endothelial injury, which usually co-occurs with inflammation.[68]

There is a possible link among COVID-19, schizophrenia, and hypercoagulability.[69] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is known to cause hypercoagulability by binding to ACE2 receptors expressed by endothelial cells, thereby causing endothelial injury and leading to an inflammatory response.[70] Endothelial injury generally activates the complement and coagulation pathways.[71] Considering that SARS-CoV-2 causes endothelial injury, COVID-19 infection may trigger psychosis via the coagulation cascade.[26] Small clots generated secondarily to SARS-CoV-2 invasion could travel across the CNS vasculature, leading to mild ischemia and hypoxia that further perpetuate neuroinflammation and psychosis.[26,63] Coagulation factors may thus be future biomarkers to survey.

Autoimmunity and viral receptor interference

Considering that several autoimmune neuropsychiatric diseases have occurred in association with SARS-CoV-1,

TABLE 3
Cases of psychosis associated with the COVID-19 pandemic with negative PCR status

Study	Country	Summary
Anmella et al[30]	Spain	A 42-year-old woman working as a general practitioner responsible for a COVID-19 unit came in with what was later diagnosed as "brief reactive psychosis." This started as extreme anxiety 2 days prior that was treated with lorazepam. She had delusions of persecution along with paranoid ideation that she would be forced to the ICU against her will. She was given olanzapine 10 mg and showed improved behavior. She had no psychiatric history, and urine drug screen was negative
Chandra et al[31]	India	First case is a 34-year-old woman with no psychiatric history presenting for delusions surrounding COVID-19, claiming the president would save her. Second case is of a 24-year-old woman with no psychiatric history presenting with postpartum psychosis with disorganized speech and fears of having COVID-19 and passing it to her child. She was very anxious before the episode due to being pressured to give birth to a boy
D'Agostino et al[32]	Italy	All 6 patients were previously healthy. Mean age was 53. All patients had varying degrees of delusions surrounding anxieties relating to COVID-19 or having COVID-19
de Burgos-Berdud et al[33]	Spain, United States, Italy, France	Four case reports of psychosis in health care workers. The first, done in Boston, Massachusetts, described 3 incidences of stress-induced brief psychotic disorders; 2 were health care workers and 1 was housekeeping staff. The second study, done in Seville, Spain, looked at another case of psychosis in a frontline health care worker, and the third study, done in Barcelona, Spain, described another case of brief psychotic disorder. Geoffroy et al recently reported preliminary data on a psychological support system, the Covid-Psy hotline, for health care workers during the COVID-19 outbreak in Paris, France. In their first characterization analysis of calls, the authors identified 3 individuals who sought help for psychotic symptoms related to stress and overwork
Elliott[34]	United States	In the first case, a 40-year-old physician with no medical or psychiatric history displayed erratic and bizarre behaviors at work along with increasing consumption of news on coronavirus. His symptoms decreased with lorazepam. The second case was a nurse in her mid-40s with hopelessness and suicidal thoughts from the belief that she had caught the virus, despite being negative. She improved on lorazepam and antipsychotics. The third case was of a 40-year-old female hospital custodian with a history of anxiety coming in for agitation and delusions that she had caught the virus and people were chasing after her because of this. She partially responded to lorazepam
Finatti et al[35]	Italy	Three patients (mean age 37) who were all previously healthy with no history of psychiatric disorders. All 3 were diagnosed with brief psychotic disorder. All 3 admissions occurred in less than 1 week, starting 10 days after severe quarantine procedures. They were treated with risperidone (range 2 to 5 mg), diazepam (range 2 to 6 mg), and paroxetine (20 mg in case 3), with a complete remission of acute psychotic symptoms within a few days. Themes of delusions included being trapped, of guilt, and of the quarantine being a conspiracy
Huarcaya-Victoria et al[36]	Peru	A 38-year-old female patient with no psychiatric history developed severe insomnia-inducing anxiety after an encounter with her dentist, who was not wearing a mask. She went on to develop auditory hallucinations regarding fears of having the COVID-19 virus, eventually leading her to attempt to kill her family. She was given quetiapine 500 mg and clonazepam 1 mg, and improved
Lazzari et al[37]	Italy	Six previously healthy patients presenting with stress-induced psychotic and manic symptoms along with agitation. The symptoms responded to typical antipsychotics and antidepressants
Ovejero et al[38]	Spain	Patient known to have bipolar disorder presented with mania and delusions centering around COVID-19
Rivas et al[39]	Spain	A 60-year-old male health care worker isolated himself at home while reading about the COVID-19 pandemic on social media. The patient became very anxious and developed dissociative symptoms as well as delusions. He was hospitalized and given olanzapine 10 mg/d, with quick improvement

TABLE 3 (continued)

Study	Country	Summary
Shanbour et al[40]	United States	Three patients, all COVID-19 negative and with no psychiatric history, were displaying delusions and auditory hallucinations. All 3 cases were precipitated by anxieties and delusional thoughts surrounding the pandemic
Valdes-Florido et al[41]	Spain	Four patients, ranging in age from 33 to 49, who were admitted during the first 2 weeks of compulsory nationwide quarantine. In just 2 weeks, 4 patients met DSM-5 criteria for a brief reactive psychotic disorder. All of the episodes were directly triggered by stress derived from the COVID-19 pandemic, and 2 (50%) of the patients presented severe suicidal behavior at admission. Two (50%) of the patients were previously healthy with no previous psychiatric history, while 1 patient had experienced 2 other previous brief psychotic episodes and the other had adjustment disorder
Weise et al[42]	Germany	A 60-year-old woman with no previous psychiatric history presented with delusional disorder
Zhang et al[43]	China	20-year-old male who caught fever at the beginning of lockdown developed psychotic symptoms. PCR tests done at several instances were negative. Patient recovered on antipsychotics and was given diagnosis of acute and transient psychotic disorder

ICU: intensive care unit; PCR: polymerase chain reaction.

psychiatric symptoms in coronavirus infections may be brought on by molecular mimicry (ie, cross-reactivity between SARS-CoV-2 and self-antigens).[54] A case of psychosis was reported in a patient with COVID-19–induced anti-*N*-methyl-D-aspartate (NMDA) encephalitis,[72] though other cases of COVID-19–induced psychosis had no antibodies in the CSF.[46] More studies on CSF for autoantibodies in COVID-19–induced psychosis are necessary to elucidate the role of molecular mimicry.

Viruses that interfere with specific receptors can lead to various sequences of inflammatory and autoimmune events, which are implicated in several multifactorial diseases, such as diabetes, schizophrenia, and coronary artery disease.[73] For instance, influenza has been involved in inducing schizophrenia through interference of the functioning of serotonin and NMDA receptors.[74] Indeed, viruses can co-opt cell surface molecules for cell entry by altering their own envelope to resemble the target ligand.[73] This will have 2 effects: first, this may alter receptor function owing to the residual viral epitope affecting affinity or causing antagonism or agonism; second, because of the residual nonself, immunogenic viral component incorporated into the host receptor, an immune response is elicited that is unable to distinguish between self and nonself components, thereby causing autoimmunity.[73]

Coronaviruses interfere with the ACE2 receptor,[75] leading to an increase of the proinflammatory angiotensin II.[37] Angiotensin-converting enzyme 2 has a possible role in mood regulation.[76] Therefore, interference by SARS-CoV-2 with ACE2 receptor could presumably be an additional explanation for neuropsychiatric symptoms and merits further investigation.[73] No data exist yet to demonstrate whether ACE2 receptors are implicated in psychosis specifically, which merits further investigation.

It is important to note that SARS-CoV-2 was still able to penetrate through the olfactory bulb, even in ACE2-receptor–negative mice, stipulating that the virus may be interfering with other receptors relevant to psychosis, such as serotonergic or dopaminergic receptors.[52] Therefore, it would be imperative to investigate whether the coronavirus may also interfere with neurotransmitter receptors in the brain, accounting for neuropsychiatric symptoms.[52]

Coronavirus, genes, and psychosis

A sequence from the SARS-CoV-2 ORF1b gene was found in the human netrin G1 (NTNG1) gene, located on chromosome 1p13.3. The human NTNG1 encodes a preproprotein that is responsible for axon growth during neuronal development. Mutations of this gene have been implicated in the pathophysiology of psychosis and schizophrenia.[77]

In addition, another study of a sample of COVID-19 patients found that 9 genes implicated in causing psychosis were found to be altered after coronavirus infection.[78] These were AKT serine/threonine kinase 1 (AKT1), euchromatic histone lysine methyltransferase 1 (EHMT1), FKBP prolyl isomerase 5 (FKBP5), methylenetetrahydrofolate reductase (MTHFR), synapsin II (SYN2),

TABLE 4
Cases of psychosis associated with the COVID-19 pandemic with mixed PCR status

Study	COVID PCR status	Country	Summary
Chacko et al[44]	Positive IgG antibodies, negative PCR	China	A 52-year-old man with no psychiatric history presented with paranoia and suicidality leading to a suicide attempt. Patient was found to have IgG antibodies for coronavirus but was COVID-19–negative. He was also found to have elevated LFTs and inflammatory markers (erythrocyte sedimentation rate: 40; C-reactive protein: 1.5; D-dimer: 1,003). His symptoms resolved with 6 sessions of ECT
Correa-Palacio et al[45]	Previously positive, negative at presentation	Spain	A 43-year-old man with manic psychosis 8 days after being discharged from treatment for COVID-19 with corticosteroids and hydroxychloroquine. He was no longer taking corticosteroids at the time. He had no encephalitis or increased inflammatory markers
Lim et al[46]	Positive at presentation, then negative	England	A 55-year-old woman who presented with severe COVID-19 respiratory symptoms as well as delirium and psychosis. Eventually, only psychotic features remained. At Day 14, symptoms persisted while she was receiving haloperidol 0.5 mg, so she was switched to risperidone. Symptoms persisted until approximately Day 52, when there was finally improvement. Her TNF-alpha was perpetually elevated, even when viral traces were gone from the patient. She was not given steroids. Her brain MRI, EEG, CSF examination, and autoimmune panel were all normal
Tuna et al[47]	Negative and positive	Turkey	Two cases, both previously healthy. The first was a COVID-19–negative 34-year-old male refugee who stabbed himself in the leg and believed he was the source of COVID-19. He was treated with olanzapine 20 mg/d and lorazepam 1 mg/d. The second patient was a COVID-19–positive 46-year-old woman who had tried to throw herself off a balcony. She was administered haloperidol 10 mg/d and biperiden 5 mg/d with partial resolution of symptoms

ECT: electroconvulsive therapy; IgG: immunoglobulin G; LFT: liver function tests; PCR: polymerase chain reaction; TNF-alpha: tumor necrosis factor-alpha.

apolipoprotein L2 (APOL2), apolipoprotein L4 (APOL4), SET domain-containing 1A, histone lysine methyltransferase (SETD1A), and Chitinase-3 like-1 (CHI3L1).[78]

It is important to note that this study also found increased expression of several inflammatory markers after SARS-CoV-2, such as TNF, IL-1 beta, and interferon gamma (IFN-gamma), among others.[78] This is noteworthy, considering the role of neuroinflammation in psychosis.

Gut microbiome

The role of dysbiosis in schizophrenia is unclear. Several studies have found distinct types of microbe imbalances characteristic of schizophrenia. A model was proposed[79] to explain the link between pathogens, dysbiosis, gut inflammation, CNS inflammation, and psychosis. According to Severance et al,[79] the model indicates that pathogens and gut dysbiosis together may cause inflammation in the gut and systemically. Defects in the blood-gut barrier as well as in the BBB may allow the passage of pathogens and toxins from gut bacteria and inflammatory mediators to the brain, leading to changes in astrocyte and microglia signaling and subsequent psychosis.[79]

Angiotensin converting enzyme 2 receptors are expressed by gut epithelium; enteric nerves are a proven point of access of coronaviruses. In addition, the virus has been shown to cause gastrointestinal (GI) symptoms and has been isolated in stools, indicating ample activity in the GI tract.[54] Following the model proposed by Severance et al,[79] infection caused by the coronavirus could interact with gut dysbiosis, leading to CNS inflammation and eventual psychosis.

INDIRECT ENVIRONMENTAL MECHANISMS (NONVIRAL)

Stress

The concept of "stress-induced psychosis" is not new and can be explained in the context of the diathesis-stress

model.[6] Although not a diagnosis of its own, stress has been introduced as a specifier in the ICD-10 as follows: "acute and transient psychotic disorders" "with associated acute stress" (F23.x1) and in DSM-5 as follows: "brief psychotic disorder" (BPD; 298.8) "with marked stressor(s)."[80]

Our search identified 16 case reports and series of COVID-19–negative patients who developed psychosis following exposure to stress from the pandemic.[30-33,35-43,47] Interestingly, several of these cases responded to benzodiazepines.[30,34] Additionally, COVID-19–positive patients tended to have delusions that were unrelated to the pandemic, in contrast to COVID-19–negative patients with psychosis.[30-33,35,36,38-42]

Several "vulnerability factors" have been identified in the literature as predictors of the development of psychosis secondary to stress.

One study in China found that measures of paranoid ideations and psychoticism were substantially elevated in a sample of 1,060 patients during the pandemic compared with data retrieved from a different large Chinese group from before the beginning of the pandemic.[81] Being older than age 50 or younger than age 18, being divorced or widowed, having a lower education level, being a migrant agricultural worker, and being a health care worker were all predictors of worse mental health outcomes, including psychosis.[81]

Several studies[30,33,34] highlighted the increased vulnerability of health care workers to psychosis given their high exposure to the stressful consequences of the virus on patients, as well as the stressful fear of catching the virus.[30,33,34] Other groups considered at increased risk of paranoid ideations linked to stress are minority groups[82] as well as people of lower socioeconomic status (SES) and victims of discrimination.[82]

Another study indicated that students and employed individuals were more likely to have paranoid symptoms compared with controls. One explanation might be that this population is obligated to leave their homes and commute.[82]

Interestingly, the news seems to play an important role in amplifying COVID-19–related stress. Exposure to COVID-19–related news has been shown to have a moderating role in the effect of "political trust" and "fear of COVID" on developing psychotic symptoms. These variables have otherwise no effect on patients who are not exposed to the news.[82]

Isolation

Studies have consistently demonstrated the positive correlation between social isolation and psychotic symptoms.[83]

The prodromal phase preceding schizophrenia is often characterized by social withdrawal and isolation. The social marginality theory stipulates that isolation of communities increases the amount of pseudoscientific beliefs and illusions.[84] Pseudoscientific beliefs belong to a psychotic continuum/psychotic phenotype that increases the risk of developing full-blown psychosis.[84] In addition, loneliness has been shown to have direct effects on brain biology; a study of 8,780 adults age ≥50 demonstrated that higher levels of social engagement and living with someone were associated with lower levels of CRP, fibrinogen, and white blood cell counts, while lower levels of loneliness were associated with higher levels of IGF-1.[85] Another study of 319 adults age 61 to 82 showed that higher loneliness scores were associated with smaller gray matter volumes, specifically the left amygdala/anterior hippocampus, the left posterior parahippocampus, and the left cerebellum.[86] Of note, hippocampal reduction is a common brain finding in schizophrenia.[87]

In that vein, 174 Spanish individuals completed the Community Assessment of Psychic Experiences (CAPE-42) questionnaire to assess pseudoscientific and psychotic behaviors pre- and postquarantine. Social quarantine in this sample showed increased levels of magical thinking, pseudoscientific beliefs, and anomalous perceptions. Additionally, there was a notable increase in paranoid thoughts, derealization/depersonalization, and positive psychotic experiences.[84] These data are contradicted by other studies that failed to find any association between self-isolation and the development of paranoia.[82]

The internet is a possible link between isolation and paranoia. Conspiracy theories are likely to arise as a coping mechanism to the pandemic, often discussed on the internet. Indeed, the internet can be instrumental in the formation of "echo chambers," which are spaces in which sets of homogenous ideas are repeated. This, combined with a lack of opposition and challenging of beliefs, can accelerate the formation of beliefs that are not necessarily rooted in reality, eventually evolving into delusions.[88] This was evident in a series of 3 patients identified in this review, 1 of whom, a 23-year-old male, believed recently installed cellphone towers were spreading the virus.[40] This was a conspiracy widely available on the internet, and symptoms began shortly after the patient's roommates vacated; the authors believe this timing suggests

the delusion had more room to grow in an environment where the patient's thoughts could not be challenged.[40]

Another study was conducted on university students based on data collected in October 2018 and in April 2020 during the beginning of the COVID-19 pandemic.[89] The authors demonstrated that psychotic experiences were significantly correlated longitudinally with worse negative affectivity, especially depression. They found that psychotic experiences did not increase proportionally with time spent in quarantine. However, the authors found a significant correlation between psychotic experiences and loneliness, as well as perceived stress. Those 2 factors were predictors of psychosis cross-sectionally and longitudinally.[89] In addition, some authors argue[84] that quarantining may not yield sufficient levels of isolation to show psychotic symptoms because of the availability of the internet and other modes of communication. According to Escola-Gascon et al,[84] this theory may explain why several studies conducted during the pandemic did not replicate the studies done on isolated communities.

Other studies have confirmed that loneliness, rather than isolation from quarantine, may be at play. Four hundred thirty-two Hong Kong residents were surveyed for mental health disorders, including psychotic symptoms. Results showed that an exorbitant 22.5% of respondents had psychotic symptoms.[90] The authors contrasted this with a prevalence of 4% of psychotic symptoms in a sample of youths seeking help in the United States before the pandemic. Results also showed that all mental health symptoms were mediated by loneliness, but not by social network size (ie, number of social roles and number of people in the social network), indicating that quality rather than quantity of social interaction is important in the pathogenesis of psychosis.[90]

Uncertainty

Reed et al[91] looked at the effect of expected vs unexpected uncertainty in the development of paranoia and delusions. Expected uncertainty is defined by an outcome that may be surprising but does not require updates in belief systems. Unexpected uncertainty is defined as an outcome that was not within the predicted variations and calls for revision of belief systems. The authors found that a higher degree of expected uncertainty (ie, this was an expected variation) did not entail belief revisions, whereas increased unexpected uncertainty caused belief revisions. This belief change can entail recategorization of allies as enemies, one of the evolutionary theories of paranoia. The authors also found that paranoid individuals were more likely to make decisions based on their expectation of volatility rather than their experience.[91]

Indeed, the Scientific Unexplained Beliefs Model (SUB) claims that magical thinking is done to re-establish control in the face of uncertain challenges,[84] whereas the cognitive theory of magical beliefs indicates that causal illusions are made to attribute causes to problems that are beyond expectation, such as a global pandemic, to better know how to assess them and tackle them, thereby ensuring survival.

CONCLUSIONS

Based on this review and data on the risk of psychosis in previous pandemics, we anticipate a strong association between the COVID-19 pandemic and emergence of new-onset psychosis, notably in at-risk individuals. Several factors tied to the pandemic in general, and the virus in particular, have been identified in this article, many of which can be modified to curb the psychosis wave.

Early interventions in vulnerable populations are needed, notably in individuals younger than age 18 and older than age 50, health care workers,[30,33,34] foreign workers, people of low SES, divorced or widowed individuals,[81] and members of minority groups.[92] These groups would benefit from specific governmental and nongovernmental subsidies, as well as mental health interventions with the goal to provide psychological assistance, support, and guidance.[81] Awareness and psychoeducation campaigns about psychotic symptoms and prodrome can be implemented in school curricula for adolescents and young adults, community centers for certain minorities, or via hospitals for health care workers to enhance early detection.

Fear of contamination, lockdown measures, and social isolation may hinder access to mental health services.[93] Telepsychiatry has emerged as an efficient tool to enhance early detection of psychosis transition. Indeed, mobile interventions, such as psychoeducation phone calls, are a cost-effective strategy found to be associated with a marked decrease in the severity of psychotic symptoms compared with controls.[94]

The news was shown to mediate psychotic symptom development.[92] As such, media outlets can control

the narrative of the pandemic to dispel fallacies and fake news while giving more control to the viewer (eg, proper care to limit contagion, resources for support).[40]

There should also be attempts to educate people using easy and nonsensationalized terms about the nature of the pandemic for the sake of dispelling false notions and decreasing fears.[81]

As demonstrated earlier, loneliness plays an important role in the evolution of psychotic symptoms during quarantine.[89,90,92] It is thus important to defeat loneliness by creating strategies to increase social cohesion on a wide scale, mostly through the use of technology.[90]

Although funds dedicated to mental health research are currently reduced, given the priority of research directly related to the pandemic, there are many gaps in knowledge in our understanding of the exact pathophysiology of psychosis triggered by SARS-CoV-2.

The inflammatory theory underlying psychosis needs to be further explored at different timepoints of the infection or the pandemic to elucidate the roles of cytokines and other markers in prediction of psychosis risk and prognosis.

A better understanding of the pathophysiology of the disease may lead to the development of more effective intervention strategies and pharmacological treatments. For example, within the inflammatory theory of psychosis related to SARS-CoV-2, tocilizumab, an IL-6 receptor monoclonal antibody, may represent a promising alternative to treat psychosis in addition to COVID-19–related respiratory symptoms.[52] ■

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