

COVID-19-induced psychosis: two case reports and narrative literature review

Pierwszy epizod psychotyczny indukowany COVID-19: dwa opisy przypadków i narracyjny przegląd literatury

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Abstract

Introduction: SARS-CoV-2 infection might be presented in many various specific and non-specific manifest and symptoms from different systems. Also, the psychotic symptoms are documented but the explanation for their pathophysiology remains debatable and a complex matter. The main objective of this paper is to present cases of patients without a history of psychiatric disorders who developed the first episode of psychosis during the SARS-CoV-2 infection.

Material and methods: Two cases of not-related patients with no previous psychiatric history developed psychotic episodes during COVID-19 infection. In both cases chronologically first they experienced symptoms of infection, secondly, delusions and psychomotor agitation that required psychiatric hospitalization. Full remission was observed after antipsychotic treatment in both cases.

Results: Even though the pathophysiology of the post-COVID-19 psychiatric symptoms remains unclear, some reports that indicate associations between the infection and the onset of such symptoms. The infection itself, by the induction of cytokine storm followed by the excessive release of pro-inflammatory cytokines, is considered to stimulate the potential onset of the psychosis, however, other factors such as medications used during treatment (with a particular emphasis on glucocorticosteroids) or psychological factors should be considered as well.

Conclusions: Patients infected with SARS-CoV-2 might develop serious psychotic episodes even without a prior psychiatric history. Besides, psychiatric symptoms might be the first the even the only manifestations associated with the active SARS-CoV-2 infection which seems to be very challenging especially in cases of rapid psychotic episodes without any clear respiratory symptoms.

Keywords: COVID-19, SARS-CoV-2, central nervous system, psychosis, psychotic episode

Streszczenie

Wstęp: Zakażenie SARS-CoV-2 może manifestować się objawami z różnych układów. Zostało także udokumentowane występowanie objawów psychotycznych, ale wyjaśnienie ich patofizjologicznego podłoża pozostaje dyskusyjne i złożone. Celem głównym pracy jest przedstawienie przypadków pacjentów bez wywiadu psychiatrycznego, u których rozwinęła się

psychoza w trakcie zakażenia SARS-CoV-2.

Materiał i metody: W artykule przedstawiono 2 opisy przypadków niespokrewnionych ze sobą osób bez wcześniejszego wywiadu psychiatrycznego, u których rozwinął się I epizod psychotyczny podczas zakażenia COVID-19. Chronologicznie w pierwszej kolejności ujawniły się objawy infekcji, następnie urojenia i pobudzenie psychoruchowe wymagające hospitalizacji psychiatrycznej. Po włączeniu do terapii leków przeciwpsychotycznych uzyskano pełną remisję.

Dyskusja: Chociaż patofizjologia objawów psychotycznych współwystępujących z COVID-19 pozostaje nie do końca wyjaśniona, uważa się, że sama infekcja, poprzez wywołanie burzy cytokinowej, po której następuje nadmierne uwalnianie cytokin prozapalnych, stymuluje potencjalny początek psychozy, jednak inne czynniki, takie jak stosowane leki w trakcie leczenia (ze szczególnym uwzględnieniem glikokortykosteroidów) lub czynniki psychologiczne należy również wziąć pod uwagę.

Wnioski: Pacjenci zakażeni SARS-CoV-2 mogą rozwinąć ciężkie epizody psychotyczne nawet bez wcześniejszego wywiadu psychiatrycznego. Poza tym objawy psychiczne mogą być pierwszymi, a nawet jedynymi objawami związanymi z aktywną infekcją SARS-CoV-2, co wydaje się być dużym wyzwaniem, zwłaszcza w przypadku nagłych epizodów psychotycznych bez wyraźnych objawów ze strony układu oddechowego.

Słowa kluczowe: COVID-19, SARS-CoV-2, ośrodkowy układ nerwowy, psychoza, epizod psychotyczny

1. Introduction

COVID-19 is an infectious disease induced by a new virus named SARS-CoV-2 from the Coronaviridae family. The first cases of COVID-19 were reported in December 2019 in the capital of Hubei province – Wuhan, China [1]. 11th March 2020 WHO announced COVID-19 as a pandemic. This disease in most cases manifests in form of mild to moderately severe symptoms primarily from the respiratory system, however, among the elderly and those with other conditions and diseases, COVID-19 course might be very rapid and severe leading to serious symptoms of pneumonia and even death [2]. Researchers also noticed that many patients experience neurological symptoms during infection, ranging from headache and dizziness to acute cerebrovascular disease, impaired consciousness, encephalitis, and Guillain-Barre syndrome [3,4].

The relationship between some viral infections and the induction of psychoses has been noticed in the XVIII century during the pandemic of the Spanish Flu [5,6]. During the epidemic of the SARS disease induced by the SARS-CoV dating back to February 2003 [7] it was noticed that a statistically greater risk of psychosis was among the individuals infected with SARS-CoV-2 compared to the control groups. It might be explained primarily by the toxicity of glucocorticosteroids used in high doses during infections with severe symptoms of infection but also because of stress and anxiety induced by the infection itself along with the individual's susceptibility of the patient [7]. Studies conducted by Severance et al. (2011) also indicate that infections induced by coronaviruses statistically increase the probability of psychoses (based on the studies on four coronaviruses - 229E, HKU1, NL63, and OC43) [8]. Numerous reports claim that also COVID-19 might, via numerous mechanisms, predispose to the

induction of a psychotic state [9,10,11,]. Yoa et al. in 2020 observed that patients with clinically stable schizophrenia have experienced worsening psychotic symptoms after COVID-19 [12].

Rentero et al. (2020) drew attention to the increasing number of patients without previous history of any psychiatric treatment in a psychiatric hospital in Madrid; those patients presented psychotic symptoms and at the same time they turned out to have COVID-19. The researchers suggest that further speculations regarding the relationship between the infection with a novel coronavirus and a greater risk of psychoses might lead to the introduction of a completely new disease entity [13].

The mechanisms that might hypothetically lead to the induction of psychosis among patients with COVID-19 can be divided into three major subgroups:

- 1) Biological – studies on the *Coronaviridae* family indicate that coronaviruses might attack the central nervous system (CNS) via the synaptic route through earlier infected peripheral nerves [14]. The viruses might also penetrate through the cribriform plate of the ethmoid and move further into various parts of the brain [15]. Studies conducted so far suggest that the penetration of the coronaviruses into the CNS might also happen through the blood [15]. It was reported that within the brain, the ACE2 receptor, which is crucial for the penetration of the SARS-CoV-2 [15], might be expressed and this can explain the neurological and psychiatric conditions in patients with COVID-19.

1.1 Cytokine storm

The symptoms of neuro-infection could also be the results of the so-called 'cytokine storm' induced by SARS-CoV-2 [6,16]. A strong response of the immunologic system can lead to serious, sometimes even lethal complications from the

respiratory and cardiovascular systems; it is hypothesized that it can also be related to the induction of neuropsychiatric symptoms [17,18]. It was reported that patients with COVID-19 present a significant increase in pro-inflammatory cytokines including IL-6, IL-8, IL-10, IL-2R, tumor necrosis factor, and CRP. Furthermore, an increase might be associated with the severity of infection [19,20]. Fernando et al. (2020) described a case series of three patients with COVID-19 and psychotic symptoms among whom an increased level of CRP and IL-6 could reflect the importance of the so-called 'cytokine storm' in the etiology of psychosis [21].

- 2) Drug-induced - Numerous studies indicate that the induction of psychosis among patients with COVID-19 might be due to high doses of drugs used in order to treat the infection.

2.1 Glucocorticosteroid hypothesis

The fact that there is a relationship between glucocorticosteroid intake and the risk of induction of psychosis is relatively well documented in the literature; e.g. it is confirmed in the study by Dubrovsky et al. (2012) [22]. The results of a retrospective study by Lee et al. (2004) on patients who survived the infection by SARS-CoV-2 indicate a relationship between post-covid psychosis and treatment with high doses of glucocorticosteroids. Since glucocorticosteroids are often used during COVID-19 treatment, further observations regarding the influence of glucocorticosteroids on psychosis must be done also in the case of SARS-CoV-2.

2.2 Antiviral treatment hypothesis

Cheng et al. (2004) performed a study on patients with SARS-CoV who developed psychosis which confirmed that treatment with antiviral drugs can also induce psychosis in patients with SARS infection [23].

Cytokine storm and drug-induced hypotheses can be confirmed by the case study of a 43-year-old patient, previously untreated, who developed symptoms of psychosis. The patient expressed grandiosity delusions-he claimed to have 'direct contact with God', was aggressive towards family members, showed psychomotor agitation, and confirmed auditory hallucination. Before the development of psychotic symptoms, the patient was hospitalized for 8 days for bilateral pneumonia related to COVID-19 infection. He was treated for eight days with oral lopinavir-ritonavir and hydroxychloroquine, followed by high-dose methylprednisolone. For 4 days

after discharge, the patient was to take 32 mg of methylprednisolone orally daily. (In MRI examinations of the head - no changes. In laboratory tests - hyperglycemia is associated with the use of glucocorticosteroids [24]. As the authors comment, the consequences of COVID-19 infection and the resulting treatment with high doses of glucocorticosteroids and antiviral drugs may cause serious psychopathological symptoms in the course of various mechanisms.

- 2.3 Other medications used in COVID-19 infection that may potentially trigger psychosis or cause psychotic symptoms:

Hydroxychloroquine can cause agitation, emotional lability, and a tendency to irritation [25].

Dextromethorphan and pseudoephedrine (components of painkillers and antipyretics):

- Although those substances are a component of over-the-counter drugs, they can cause neurological and psychiatric symptoms, such as euphoria, ataxia, dissociative symptoms, slurred speech, and nystagmus. In the study by Schadel and Sellers (1992) on dextromethorphan, cases of psychosis were reported rarely and only when the dose exceeded 600 mg/day [26,27].
- Similar conclusions can be drawn from the case report described by Roberge et al. (1991), where after the administration of a drug containing dextromethorphan and pseudoephedrine, psychotic symptoms developed in a two-year-old boy [28].

2. Psychological

So far, it has not been possible to prove the overwhelming importance of any of the mentioned mechanisms that can potentially contribute to the development of psychosis in the case of COVID-19 infection. It is known that several psychological factors contribute to the increased likelihood of developing psychotic symptoms in people with SARS-Cov2 infection. It should be taken into account that any regulations aimed at limiting the spread of the pandemic (including temporary closure of schools, work in the so-called 'home office' system, isolation, and quarantine of people after contact with COVID-19 infected, etc.) may increase anxiety, depression, and loneliness [29].

On the other hand, according to Cheng et al. (2004), people with psychotic symptoms are less adhered to the principles of disinfection and social distancing, which may contribute to an increased risk of infection in their case [23].

The case report of a 31-year-old from Malaysia, with no history of mental illness, indicates that the most likely cause of psychosis in his case was severe stress and anxiety related to the reception of media information about the SARS-CoV-2 pandemic [30]. The works of Stevense (1987) confirm the correlation between stress caused by, inter alia, diseases or death in the family and the occurrence of short-term psychotic episodes [31].

3. Case report 1

Mr. B, a 47-years-old policeman, married, father of two children, without a history of psychiatric disorders or somatic disease. He denied drug or excessive alcohol usage. On the 28th of November 2020, Mr. B was admitted to Regional Psychiatric Hospital on the COVID-19 ward in assist of police officers due to severe agitation, depersonalization, and grandiosity delusions.

On the 23rd of November, he complained about symptoms of infection - strong fatigue, fever, creeps, and cough. He decided not to get tested for COVID-19 because of feeling similar symptoms as in the previous year. He stayed at home and treated himself with paracetamol, other medication containing dextromethorphan, pseudoephedrine not exceeding therapeutic dosage, and homemade treatments such as drinking milk with garlic and honey. Body temperature was oscillating around 38.5 degrees of Celsius, however, the highest temperature of over 40.0 degrees was noted the day before hospital admission. Three days later from the information provided by the wife, Mr. B for the first time in his life was crying and believed that the world was coming to the end. He thought that the first effect of infection was emerging and 'the world was spinning around'. He started to believe he ended up being in a vegetative state, and he did not want to live to be a burden to the family.

On the 28th of November he was under the impression to be an alien, a person from outer space. He manifested belief to be in a different reality, in possession of supernatural powers, and expressed delusional thoughts: 'I am an alien', 'everywhere are aliens', and 'I am in space'. He couldn't explain his power, but he was under the belief to be able to do anything even 'conjure up money'.

His wife described him as an introvert, always calm, and composed man. That day he presented psychomotor agitation, verbal and physically aggressive behavior; he snatched the phone from his son, shattered the chandelier. Despite the imposed quarantine he went outside, and try to talk to random strangers.

Mr. B's wife called a family member for help and they went to the police station where he was examined with an extended urine drug screening panel which came up negative. With help of police officers, he was taken by ambulance to Regional Psychiatric Hospital to the COVID-19 ward.

During the admission to this ward, the patient was disoriented in time, place and delusional, presenting psychomotor agitation, aggressive and vulgar behavior toward medical staff and police officers. There was a need for mechanical restraint by straps of the patient. He continued to express delusional thoughts; therefore, he was given haloperidol 5 mg i.m. Later he started to be partly critical of his previous thoughts and behavior.

On the second day of hospitalization rt-PCR test for COVID-19 was performed and confirmed SARS-Cov-2 infection. The patient becomes calm, in logical contact, fully oriented, without any delusions.

During hospitalization, he could be irritable and had a problem with sleep. On the 4th of December, haloperidol was withdrawn and till the end of the hospitalization, the psychotic symptoms did not appear. He did not experience any severe symptoms from COVID-19 infection during hospitalization and the temperature, saturation was in a normal range. Laboratory results showed kidney function as normal, test for hepatitis B and C negative, morphology typical for COVID-19 infection with elevated neutrophils and lower lymphocyte counts. Inflammatory markers and d-dimer, aspartate transaminase (AST), alanine transaminase (ALT) needed to be monitored because of elevated levels. The hepatoprotective treatment was introduced. Laboratory results are shown in table 1.

On the 15th of December, after two negative COVID-19 tests, the patient was transferred to the psychiatric ward in the 1st Department of Psychiatry, University Hospital. Where extended diagnostic was performed. Hypertension

Table 1. Mr. B's laboratory results.

Laboratory parameters	Date of test				
	18.11.20	02.12.20	11.12.20	16.12.20	31.12.20
AST (u/l)	31	52	80	21.1	12.2
ALT (u/l)	26	74	198	92.6	21.8
CRP (mg/l)	79.3	48.2	1.6	0.8	
D-dimer (ng/ml)	637	410	312	215	
Fibrinogen (mg/dl)	596		382		312
Potassium (mmol/l)	3.2	3.6	4.7	4.32	4.31

was noted and an elevated level of antibodies of types IgM and IgG against *Borrelia burgdorferi* was detected. Vitamin D3 was at a low concentration almost at the deficiency level (20.5 ng/ml). Abnormality was found in electroencephalography – changes in the form of generalized theta-delta wave discharge attacks, activated by hyperventilation and basic activity with a low beta wave ratio. In Magnetic Resonance Imaging of the head, everything was normal except the presence of retention cysts of the right maxillary sinus.

The analysis of the Minnesota Multiphasic Personality Inventory scales indicated that the subject may deny or minimize the problems. The profile may be inaccurate due to the strong tendency to contradict and dissimulate, which can be related to the professional position of Mr. B. as a policeman, he wanted to do well in the study, and may deny his fears or aggressive impulses, but that did not mean that he was hiding psychotic experiences.

Throughout the further hospitalization, the patient did not receive any antipsychotic medication and the maximum dosage of additional medication was: trazadone 25mg, hydroxyzine 40mg, metoprolol tartras 47.5 mg, ramipril 5mg, furosemide 40mg, kalipoz prolongatum, enoxaparin sodium 40mg, captopril 25mg, ketoprofen 50mg, vitamin d3 2 000 UI.

On the day of the discharge, the patient was in good general condition. He was in logical contact, fully oriented, in a balanced mood and psychomotor drive, without delusional thoughts, with good insight to the illness. He denied the occurrence of suicidal thoughts - he scored 0 points on the Suicidal Scale of the Mini-International

Neuropsychiatric Interview (MINI-scale).

4. Case report 2

Mrs. L 28-years old dental assistant, married, lives with a family. She had never had any somatic or mental illness. She denied drug or excessive alcohol usage. Her mother suffers from a neurotic disorder, her father from alcohol dependence, and her cousin committed suicide. On the 10th of December 2020, Mrs. L is admitted to Regional Psychiatric Hospital on the COVID-19 ward after the intervention of the family doctor due to delusional thoughts. The doctor diagnosed acute psychosis in the course of SARS-CoV-2.

Before hospitalization, on the 4th of December 2020 patient was diagnosed with COVID-19 infection. She became restless, sleepless and from a general practitioner she received citalopram 10mg and alprazolam 0.25mg by teleconsultation, after which her symptoms escalated. At the time of admission to the hospital, the patient was in difficult verbal contact, bizarre in behavior, circled with her right lower limb and upper limbs, probably under the influence of auditory hallucinations. She was not fully oriented (especially to time and place) and in psychomotor agitation. She expressed nihilistic delusions ('my family is dead', 'I'm in hell'). She would climb on another patient's bed and put her mask on the patient's face, throw a book and a cup at the doctor. Mechanical restraint in the form of straps was used and 5 mg of olanzapine was administered p.o.

During the stay, pregnancy was excluded and

Table 2. Mrs. L's prolactin results.

Laboratory parameters	Date of test			
	18.12.20	12.12.20	26.01.21	08.02.21
Prolactin (ng/mg)	127.71	148.47	29.72	32.17

pharmacological treatment was optimized to 20mg of olanzapine. Within a few days, the patient's condition gradually improved. The patient became calmer, became less bizarre in behavior, and stopped spontaneously uttering delusional content. She became partially critical of her mental condition. Lack of appetite and fear of eating (suspected delusions of poisoning) were observed. Increased levels of prolactin have also been noted. During her stay, her COVID-19 infection was poorly symptomatic.

Later on, on the 17th of December the patient was referred for further treatment and diagnostics to Ist Department of Psychiatry, University Hospital.

The patient was oriented autopsychically, not oriented to time, correctly oriented to the place, in a depressed mood, and psychomotor agitation. She expressed disturbance in concentration and attention. She uttered delusions of reference and persecutory delusions:

'Someone was watching me through the cameras, I felt threatened.' It also confirmed the occurrence of auditory hallucinations. She denied suicidal thoughts and scored on the MINI scale 2 points – low risk of suicide.

In the initial period of therapy, the patient was disorganized in thinking, ambivalent, and reported difficulties in concentrating due to internal experiences. She was restless, distracted, and anxious. Mood and psychomotor drive were lowered, and the insight into the disease was incomplete. She had no sense of smell and taste, reported decreased appetite and trouble falling asleep. The clinical picture showed delusions of poisoning, persecution, olfactory and visual hallucinations: 'I can see colors on the legs of a person, they evoke emotions: blue good, red bad, green neutral', 'I was afraid to eat because something could have been poisoned'.

According to the patient's report, the psychotic

symptoms disappeared on December 21, 2020. Later in the hospitalization period, facial numbness, headaches, difficulties with concentration and memory occurred. During hospitalization, modification of pharmacotherapy was started. Due to hyperprolactinemia, olanzapine was reduced, and aripiprazole 15 mg and quetiapine 100 mg were added. The patient also received vitamin D (2000 units daily). In addition, neurological and neuropsychological consultations, head and pituitary gland MRI examinations were performed. The treatment resulted in a significant improvement of the mental state in the form of reduction of anxiety, withdrawal of psychotic symptoms, and improvement of sleep and appetite. The patient gained insight into her disease.

5. Discussion

A possible link between viral infections and the onset of psychiatric disorders has been widely investigated in recent years but because of various possible explanations and limitations of the current studies, the discussion and debate about a such possible relationship are still ongoing. Crow (1978) indicates that an interest in this matter has primarily risen because of the discovery of a transmissible agent as a causation of the Creutzfeldt-Jakob disease and since that day, psychiatrists worldwide became interested in other biological factors such as viruses [32]. Viruses such as retroviruses, herpesviruses (primarily cytomegalovirus, Herpes Simplex virus, or Epstein-Barr virus), or influenza viruses are currently reported to be associated with various psychiatric disorders namely schizophrenia, autism spectrum disorder, bipolar disorder, or major depressive disorder [33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48]. The results of the meta-analysis by Khandaker et al. (2012) show that childhood infections of the central nervous system (CNS) might be associated with an increased risk of adult psychotic illnesses [49]. Besides, an association between viral respiratory infections and the onset of spontaneous psychoses has been already reported in the literature [50]. Among those viruses, coronaviruses have been described probably in the most detailed way and the outbreak of the COVID-19 pandemic induced by the newly described SARS-CoV-2 reactivated the researchers' interest in this matter.

Since the outbreak of the COVID-19 pandemic and throughout its duration, the researchers and clinicians were continually describing the newer and newer specific and non-specific manifestations and symptoms [51]. Except for common symptoms such as fever, cough, or shortness of breath, the patients were reported to present other less specific ones like olfactory and gustatory dysfunctions, as well as ophthalmic, gastrointestinal, dermatological, or cardiovascular manifestations. Besides, since SARS-CoV-2 presents neurotropic

properties, some patients were also reported to present various neurological manifestations including conscious disturbance, acute cerebrovascular disease, confusion, or corticospinal tract signs [52,53]. Further, a relationship between the infection with SARS-CoV-2 and the onset of various mental disorders including depressive major disorder, bipolar disorder, schizophrenia, or dementia was reported [54]. The growing evidence also suggests a role of the SARS-CoV-2 infection in the onset of spontaneous psychosis even among individuals without any previous episodes or even psychiatric history.

One of the earliest reports regarding the possible link between spontaneous psychosis and the infection with the SARS-CoV-2 was published by Varatharaj et al. (2020); the researchers showed that among 125 patients with confirmed SARS-CoV-2 infection, 10 of 23 patients with neuropsychiatric disorders developed a new onset psychosis [55]. However, there are also cases of COVID-19 patients without any prior psychiatric history who developed severe anxiety and/or psychotic symptoms as a side effect of the SARS-CoV-2 infection [56,57]. Quite a recent study on a population of 236,379 survivors of COVID-19 found an increased risk of psychotic, mood, and anxiety disorders due to the SARS-CoV-2 infection [58]. Parra et al. (2020) reported 10 patients without previous psychiatric history who developed psychotic symptoms primarily confusion with structured delusions [59]. Ferrando et al. (2020) reported three cases of patients with COVID-19 who developed psychotic symptoms at the same time lacking any respiratory symptoms that could indicate an active disease [60]. Therefore, it should be noted that psychosis might not only be the first but also the only symptom of the infection. Even though such cases are not very common, clinicians and psychiatrists should also take them into consideration to provide the quickest and most appropriate treatment for such patients.

The pathophysiology of post-COVID-19 psychiatric symptoms remains unclear. As previously mentioned, there are three major theories describing this phenomenon including biological causation, drug-induced, as well as psychological factors. It is currently widely documented that SARS-CoV-2 is known for its ability to penetrate the CNS and stimulate hyperinflammatory responses via the induction of the cytokine storm. It has been found that among patients infected by the viruses from the Coronaviridae family, those who presented psychotic symptoms had also an increased prevalence of IgG antibodies against three viral strains [61]. After-corticosteroid psychosis is a well-documented phenomenon that usually occurs within 1-2 weeks after the initiation of treatment [62]. The fact that corticosteroid administration is widely used to treat the SARS-CoV-2 infection, might be one of the explanations for the possible

onset of psychosis even among those patients without prior psychotic episodes or any psychiatric history. Further, also psychological factors should be considered while analyzing the development of psychotic episodes among COVID-19 patients. Tizenberg et al. (2021) pointed out that the severity of the SARS-CoV-2 infection along with the intensity of psychological trauma associated with the fact of having COVID-19 might be associated with the onset of psychoses among COVID-19 patients.

In the following paper, we have described two cases of patients who got psychosis in the course of the infection by the SARS-CoV-2; both of the patients have never experienced any psychotic symptoms and had no psychiatric history. The explanation why both patients developed psychiatric disorders can be narrowed to biological and psychological theories, as both patients did not use any antiviral medications. At the end of 2020, there was not much available information about the virus, and a lot of restriction measures were introduced which increased the level of stress in patients. Especially in the case of Mr. B with a very stressful job as police officer additionally with a high fever the cytokine storm could play an important role in the development of psychotic symptoms.

6. Conclusions

The ongoing research regarding any relationships between COVID-19 and related SARS-CoV-2 infection with the onset of various psychiatric symptoms and disorders is highly recommended since knowledge in this matter is relatively scarce and primarily based on case reports or series of cases with a minimum number of longitudinal large-scale observations. What has recently become obvious for the researchers, based on the current studies and observations, is a link between psychotic symptoms and infection by the SARS-CoV-2. Nevertheless, the etiology and the process of this phenomenon remain unclear and too complex based on the current state of knowledge. All of the aspects mentioned in this study, namely biological, pharmacological, and psychological factors should be taken into consideration while dealing with a COVID-19 patient with psychotic symptoms.

Conflict of interest

The authors have declared no conflict of interest.

References

- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in *lancet*. *Lancet*. 2020; 395 (10223), 497–506.
- World Health Organization. Novel coronavirus (2019-nCoV) situation report - 1. *WHO Bull*. 2020.
- Losy J. SARS-CoV-2 infection: symptoms of the nervous system and implications for therapy in neurological disorders. *Neurology and therapy*. 2021;10(1):31–42.
- Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in wuhan, China. *JAMA Neurol*. 2020;77(6):683–690.
- Kepińska AP, Iyegbe CO, Vernon AC, et al. Schizophrenia and influenza at the centenary of the 1918–1919 Spanish influenza pandemic: mechanisms of psychosis risk. *Frontiers in Psychiatry*. 2020;11(72).
- Szcześniak D, Gładka A, Misiak B, et al. The SARS-CoV-2 and mental health: From biological mechanisms to social consequences. *Prog. Neuropsychopharmacol. Biol. Psychiatry*. 2021;104:110046.
- Lee DTS, Wing YK, Leung HCM, et al. Factors associated with psychosis among patients with severe acute respiratory syndrome: a case-control study. *Clinical Infectious Diseases*. 2004;39(8):1247–1249.
- Severance EG, Dickerson FB, Viscidi RP, et al. Coronavirus immunoreactivity in individuals with a recent onset of psychotic symptoms. *Schizophr. Bull*. 2011;37 (1):101–107.
- Chacko M, Job A, Caston 3rd F, et al. COVID-19-Induced psychosis and suicidal behavior: case report. *SN Compr Clin Med*. 2020;1–5.
- Watson CJ, Thomas RH, Solomon T, et al. COVID-19 and psychosis risk: real or delusional concern? *Neurosci. Lett*, 2021;741:135491.
- Tariku M, Hajure M. Available evidence and ongoing hypothesis on corona virus (COVID-19) and psychosis: is corona virus and psychosis related? A narrative review. *Psychol. Res. Behav. Manag*. 2020;13:701–704.
- Yao H, Chen JH, Xu YF. Patients with mental health disorders in the COVID-19 epidemic. *Lancet Psychiatr*. 2020;7(4):e21.
- Rentero D, Juanes A, Losada CP, et al. New-onset psychosis in COVID-19 pandemic: a case series in Madrid. *Psychiatry Res*. 2020;290:113097.
- Li YC, Bai WZ, Hirano N, et al. Neurotropic virus tracing suggests a membranous-coating-mediated mechanism for transsynaptic communication. *J. Comp. Neurol*. 2013;521:203–212.
- Baig AM, Khaleeq A, Ali U, Syeda H. 2020. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem. Neurosci*. 2020;11:995–998.
- Clark IA, Vissel B. The meteorology of cytokine storms, and the clinical usefulness of this knowledge. *Semin. Immunopathol*. 2017;39(5):505–516.
- Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395:1033–1034.
- Troyer EA, Kohn JN, Hong S. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain Behav Immun*. 2020;87:34–39.
- Wang C, Pan R, Wan X. A longitudinal study on the mental health of general population during the COVID-19 epidemic in China. *Brain Behav Immun*. 2020;87:40–48.
- Wang L. C-reactive protein levels in the early stage of COVID-19. *Med Mal Infect*. 2020;50:332–334.
- Ferrando SJ, Klepacz L, Lynch S, et al. COVID-19 Psychosis: A Potential New Neuropsychiatric Condition Triggered by Novel Coronavirus Infection and the Inflammatory Response?. *Psychosomatics*. 2020;61(5):551–555.
- Dubovsky AN, Arvikar S, Stern TA, Axelrod L. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. *Psychosomatics*. 2012;53:103–115

23. Cheng SK-W, Tsang JS-K, Ku K-H, et al. Psychiatric complications in patients with severe acute respiratory syndrome (SARS) during the acute treatment phase: a series of 10 cases. *Br. J. Psychiatry*. 2004;184(4):359–360.
24. Correa-Palacio AF, Hernandez-Huerta D, Gómez-Arnau J, et al. Affective psychosis after COVID-19 infection in a previously healthy patient: a case report. *Psychiatry research*. 2020;290:113115.
25. Mascolo A, Berrino PM, Gareri P, et al. Neuropsychiatric clinical manifestations in elderly patients treated with hydroxychloroquine: a review article. *Inflammopharmacology*. 2018;26:1141–1149.
26. Schadel M, Sellers E. Psychosis with Vicks Formula 44D. *Can Med Assoc J* 1992;147:843 – 844.
27. Miller SC. CASE REPORT Dextromethorphan psychosis, dependence and physical withdrawal *Addiction Biology* 2005;10,325–327.
28. Roberge RJ, Hirani KH, Rowland PL, et al. Dextromethorphan and pseudoephedrine-induced agitated psychosis and ataxia: case report. *The Journal of Emergency Medicine*. 1999;17(2):285–288.
29. World Health Organization. *Coronavirus Disease 2019 (COVID-19): Situation Report*. 2020;72.
30. Zulkifli NA, Sivapatham S, Guan Ng C. Brief psychotic disorder in relation to coronavirus, covid-19 outbreaks: a case report. *Malays J Psychiatry*. 2020;29(1)
31. Stevens J. Brief Psychoses: Do They Contribute to the Good Prognosis and Equal Prevalence of Schizophrenia in Developing Countries? *Br J Psychiatry* . 1987;151:393-396.
32. Crow TJ. Viral causes of psychiatric disease. *Postgrad Med J*. 1978 Nov;54(637):763-7. doi: 10.1136/pgmj.54.637.763.
33. Yolken R. Viruses and schizophrenia: a focus on herpes simplex virus. *Herpes*. 2004 Jun;11 Suppl 2:83A-88A.
34. Dickerson F, Katsafanas E, Origoni A, et al. Exposure to Epstein Barr virus and cognitive functioning in individuals with schizophrenia. *Schizophr Res*. 2021;228:193-197.
35. Torrey EF, Leweke MF, Schwarz MJ, et al. Cytomegalovirus and schizophrenia. *CNS Drugs*. 2006;20(11):879-85.
36. O'Reilly RL. Viruses and schizophrenia. *Aust N Z J Psychiatry*. 1994 Jun;28(2):222-8.
37. Sewell DD. Schizophrenia and HIV. *Schizophr Bull*. 1996;22(3):465-73.
38. Kneeland RE, Fatemi SH. Viral infection, inflammation and schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;42:35-48.
39. Shuid AN, Jayusman PA, Shuid N, et al. Association between Viral Infections and Risk of Autistic Disorder: An Overview. *Int J Environ Res Public Health*. 2021;18(6):2817.
40. Karlsson H, Sjöqvist H, Brynge M, et al. Childhood infections and autism spectrum disorders and/or intellectual disability: a register-based cohort study. *J Neurodev Disord*. 2022;14(1):12.
41. Tanaka T, Matsuda T, Hayes LN, et al. Infection and inflammation in schizophrenia and bipolar disorder. *Neurosci Res*. 2017;115:59-63.
42. Barichello T, Badawy M, Pitcher MR, et al. Exposure to Perinatal Infections and Bipolar Disorder: A Systematic Review. *Curr Mol Med*. 2016;16(2):106-18.
43. Frye MA, Coombes BJ, McElroy SL, et al. Association of Cytomegalovirus and Toxoplasma gondii Antibody Titers With Bipolar Disorder. *JAMA Psychiatry*. 2019;76(12):1285-1293.
44. Yalin N, Conti I, Bagchi S, et al.. Clinical characteristics and impacts of HIV infection in people with bipolar disorders. *J Affect Disord*. 2021;294:794-801.
45. Coughlin SS. Anxiety and Depression: Linkages with Viral Diseases. *Public Health Rev*. 2012;34(2):7.
46. Bornand D, Toovey S, Jick SS, Meier CR. The risk of new onset depression in association with influenza--A population-based observational study. *Brain Behav Immun*. 2016;53:131-137.
47. Vindegaard N, Petersen LV, Lyng-Rasmussen BI, et al. Infectious mononucleosis as a risk factor for depression: A nationwide cohort study. *Brain Behav Immun*. 2021;94:259-265.
48. Ronaldson A, Arias de la Torre J, Sima R, et al. Prospective associations between depression and risk of hospitalisation for infection: Findings from the UK Biobank. *Brain Behav Immun*. 2022;102:292-298.
49. Kulaga SS, Miller CWT. Viral respiratory infections and psychosis: A review of the literature and the implications of COVID-19. *Neurosci Biobehav Rev*. 2021;127:520-530.
50. Khandaker GM, Zimbron J, Dalman C, et al. Childhood infection and adult schizophrenia: a meta-analysis of population-based studies. *Schizophr Res*. 2012;139(1-3):161-8.
51. Baj J, Karakuła-Juchnowicz H; Teresiński G, et al. COVID-19: Specific and Non-Specific Clinical Manifestations and Symptoms: The Current State of Knowledge. *J. Clin. Med*. 2020;9:1753.
52. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. *N. Engl. J. Med*. 2020.
53. Butowt R, Bilinska K. SARS-CoV-2: Olfaction, Brain Infection, and the Urgent Need for Clinical Samples Allowing Earlier Virus Detection. *ACS Chem. Neurosci*. 2020;11:1200–1203.
54. Markiewicz-Gospodarek A, Górska A, Markiewicz, et al. The Relationship between Mental Disorders and the COVID-19 Pandemic—Course, Risk Factors, and Potential Consequences. *Int. J. Environ. Res. Public Health*. 2022;19:9573.
55. Varatharaj A, Thomas N, Ellul MA, et al; CoroNerve Study Group. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psychiatry*. 2020;7(10):875-882.
56. Kozato N, Mishra M, Firdosi M. New-onset psychosis due to COVID-19. *BMJ Case Rep*. 2021;14(4):e242538.
57. Faisal HKP, Taufik FF, Sugihen TTG, et al. Brief psychotic disorder in COVID-19 patient with no history of mental illness. *J Infect Dev Ctries*. 2021;15(6):787-790.
58. Taquet M, Geddes J, Husain M. Six-Month neurological and psychiatric outcomes in 236,379 survivors of COVID-19. *MedRxiv* 2021.
59. Parra A, Juanes A, Losada CP, et al. Psychotic symptoms in COVID-19 patients. A retrospective descriptive study. *Psychiatry Res*. 2020;291:113254.
60. Ferrando SJ, Klepacz L, Lynch S, et al. COVID-19 psychosis: a potential new neuropsychiatric condition triggered by novel coronavirus infection and the inflammatory response? *Psychosomatics*. 2020;61:551–5.
61. Severance EG, Dickerson FB, Viscidi RP, et al. Coronavirus immunoreactivity in individuals with a recent onset of psychotic symptoms. *Schizophr Bull*. 2011;37:101–7.
62. Kazi SE, Hoque S. Acute Psychosis Following Corticosteroid Administration. *Cureus*. 2021 Sep 19;13(9):e18093.

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