






Post COVID-19 Infection Psychosis: Could SARS-CoV-2 Virus Infection Be a Neuropsychiatric Condition That Triggers Psychotic Disorders? – A Case-Based Short Review

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Abstract: Corona virus (COVID-19) is an epidemic of respiratory disease caused by a novel corona virus and it was declared by the World Health Organization (WHO) to be a global health pandemic emergency. Due to the neuropsychiatric manifestation of Covid-19 that have been associated with psychotic disorders, in this paper we choose to present a case from “Elena Doamna” Psychiatric Hospital from Galati, Romania and to correlate it with other cases from literature in a mini review presentation. In our paper, we present the case of a patient of 44-year-old men, with no past psychiatric history whose behavior included psycho-motor agitation, perception and thinking disorders, disorganized behaviour, attempted suicide by stabbing. The last perspectives from the two years of pandemic together with psychiatric disease linked the virus infections with psychosis to the main concern that Covid-19 could determine psychiatric disorders. There were also presented same literature studies of patients with no personal pathological history in the psychiatric field which developed psychiatric disorders after COVID-19 infection. SARS-CoV-2 has a psychological impact on the mental health status of the worldwide and, especially when it is associated with psychotic symptoms and can affect the quality-of-life. In some cases, the virus affected the brain and as a result, the psychosis symptoms could be an emerging phenomenon associated with the corona virus. Based on the DSM V and ICD-10 criteria, the diagnosis was of acute psychiatric disorders with symptoms of schizophrenia (F23.1). The case report and review reliefs that there is a causal link between the SARS CoV-2 infection and mental disorders, which is currently being investigated.

Keywords: COVID-19 pandemic, psychiatric disorders, DSM V and ICD-10 criteria

Introduction

Known as respiratory infections, both SARS (severe acute respiratory syndrome) and MERS (Middle East Respiratory Syndrome) had the ability to infect the nervous system.^{1,2} The most convincing data linking several human coronaviruses

to psychosis are from Severance et al, who found that patients with psychotic symptoms and a diagnosed mood or psychotic disorder are associated with coronaviruses.³ Based on literature, it is suspected that COVID-19, can induce a massive inflammatory response,⁴ and can contribute to future psychotic symptoms.

COVID-19 disease is an infection caused by a virus and was declared a global pandemic in 2020. SARS-CoV-2 is the name of the coronavirus that caused the current pandemic and can be found under the name 2019-nCoV (from “novel coronavirus”) or “new coronavirus”. The name SARS comes from severe acute respiratory syndrome, which is caused by the disease, CoV from coronavirus, and 2 shows that it is the second version of the virus.⁵

The COVID-19 pandemic has been proven to have significant harmful effects on the global health system, having both an economic and medical impact, and the latest research shows that it has also led to consequences for mental health.^{6,7}

Although attempts have been made to implement many solutions to prevent and fight the spread of the virus, such as maintaining social distance, mandatorily wearing a mask,⁸ the virus has managed to profoundly change people’s lifestyles by affecting their daily lives different organs from skin to liver, from vessels to brain,^{9,10} also, affecting their sexual and mental health.^{11,12}

In general, the term psychosis refers to a mental disorder that becomes manifest under the form of symptoms, such as hallucinations, delusions, thought disorders.¹³ There can be various causes of psychosis, related to the consumption of psychostimulants, directly related to a medical condition or due to stressors.

Neuropsychiatric complications of the SARS-CoV-2 infection are thought to be the direct result of a central nervous system infection (COVID-19 encephalopathy) or of cerebrovascular damage (secondary to pro-coagulant status) or the indirect result of hypoxia, of the immune response or of the medication.¹⁴ An important role in the pathogenesis of the psychiatric disorders connected with SARS-CoV-2 may be played by prolonged isolation or emotional stress in response to a potentially unknown pathogen, by the fear not to get infected or to infect the others and, last but not least, by the stigma.¹⁵

A Spanish study on several Covid 19 patients presented the psychosis diagnosis for patients with no previous psychiatric diagnosis. A part of them presented acute delirium, and another part presented thoughts of reference and structured delusional beliefs as in primary psychosis conditions, such as schizophrenia. Because the number of the cases was increased in the period of Covid 19 the authors considered that the specific behaviour of psychosis can be associated with Covid-19 but further clinical studies should be conducted.¹⁶

As Watson et al presented in their mini review, the proofs from historical pandemic periods, they suggested that the infection of viral respiratory pathogens like COVID-19, is a risk factor for schizophrenia-like illnesses in infected patients. It is not yet clear what biomechanisms lead us to neuropsychiatric associations. It is possible that direct neuronal viral infection, or post-infectious neuronal autoimmunity (eg, inflammatory effects of a pervasive severe pathogen).¹⁷

Another important review article conducted by Smith et al presents a study of adult patients with a history of COVID-19 infection with incident psychosis after or concurrent with COVID-19 infection. The selection of cases from this review suggests that clinical presentations and case descriptions are missing clinically relevant details, including how or if delirium was excluded in patients with COVID-19-associated psychosis. However, psychosis is a complex condition of disease and an increasing number of case reports have described psychosis in patients with COVID-19 infection.¹⁸

Regarding previous reports of SARS-CoV-2 infection, a few psychiatric complications have been identified following respiratory virus infections, such as anxiety, depression, suicidal ideation, and manic-depressive disorders.¹⁹

Another hypothesis is that long-term and significant use of corticosteroids may be a trigger for psychosis.²⁰

Case Presentation

Based on these international data, we present here the case of a patient hospitalized in the “Elisabeta Doamna” Psychiatric Hospital from Galați, who had a personal history of pathological infection with the SARS CoV-2 virus and who developed a psychiatric disease.

At the beginning of September 2021, the patient that first was presented at the Clinical Hospital of Infectious Diseases “Sf. Cuvioasa Parascheva” Galati, Romania, was diagnosed with Covid-19, and was treated as an outpatient. At that time, the patient did not present any psychiatric history. The patient was an outpatient treated until the healing

of COVID-19, to the disappearance of Sars-cov 2 symptomatology and PCR test was negative. The psychiatric disorders have increased after the negative COVID-19 test and the patient felt very bad “Thinking that all his family will die” After the COVID-19 treatment the patient arrived at “Elena Doamna” Clinical Hospital of Psychiatry, where he was diagnosed on the base of symptomatology that emerged from the anamnesis, paraclinical examination, laboratory examination and imagistic investigation. At the beginning of December 2021, he was hospitalized. The onset of psychiatric symptomatology was insidious during SARS-cov-2 the patient presented generalized anxiety, mild cognitive impairment which did not require psychiatric hospitalization at that moment. The patient was hospitalized 20 days and the clinician diagnosed him based on the DSM V and ICD-10 criteria. The specific symptomatology drew attention to this case. The Covid 19 and the psychosis of the patient can highlight a link between the viral infection and psychiatric disease. There is no direct impact on the brain, at least not demonstrated yet, but we cannot exclude the link between the Covid-19 infection and psychotic disorder. In the literature, there are presented evidence that viruses alter the dopamine metabolism^{21,22} and affect glutamate transmission,^{23,24} leading to changes to the psychiatric system. In the imagistic investigation, we did not observe macroscopic modification of brain substances, but there is a possibility that the psychotic behaviour could be induced by the microscopic modification of the dopaminergic mediator level of dopaminergic neurons from the mesolimbic pathways.²⁵

The male patient, aged 44, an IT engineer, from the urban environment, having his own business in industrial robots with a very good financial situation, married to no problem in his relation comes to the emergency room by ambulance and escorted by a police crew for psychomotor agitation, auditory and visual hallucinations (“I am hearing and seeing the devil”), delusional ideas “If I die, my family will not get sick”, bizarre behaviour (“Rubbing alcohol inhalations will cure me of COVID”), verbal incoherence, verbal stereotypes (the patient repeats “20 ... 20 ... 20”) and suicide attempt by stabbing (puncture wound in the left parasternal window).

The patient has no psychiatrically significant heredo-collateral history, among the personal pathological antecedents that may be mentioned, only the SARS CoV-2 infection stands out, at the beginning of September 2021.

Regarding the psychosocial factors the living and working conditions are very good, the patient is married, he comes from an urban environment, he is an IT engineer with a doctorate, he is a non-smoker, and consumes alcohol only occasionally, in small quantities.

From the data obtained from the family, we find out that the patient was infected with the SARS CoV-2 virus in September 2021, he was isolated at home for 14 days, later showing behavioural (the patient donated 20,000 lei to a hospital in Galați, despite the family’s opposition, began inhaling rubbing alcohol in order to treat minor post-COVID lung sequelae) and mental disorders. In the hospitalization period, the wife and the brother of patient described that in the time of outpatient period from Clinical Hospital of Infectious Diseases, he started to have same “fears” with different intensity which was varying from a general anxiety to a psychotic anxiety and these ideas had dominated him like obsession. More than this he donates an amount of money to the hospital contrar to the wish of the family “Thinking that only God can help him”.

The patient was hospitalized in December 2021 for further investigations and specialized treatment.

At the objective clinical examination of the body, the only changes are the traumatic marks on the anterior surface of the forearms, caused by a sharp object, and a self-inflicted left submammary lesion, also with a sharp object.

The patient’s mental examination shows a relatively neat outfit, proper body hygiene, and anxious facies. The mimicry and hypermobile gestures are in accordance with the mood. The patient has a suspicious attitude and tense posture, he establishes and maintains psychovisual contact with difficulty. He is spatio-temporally and allopsychically disoriented and, due to psycho-motor agitation, the praxic and mnesic functions cannot be evaluated. At the time of examination, no data could be obtained on perceptual disturbances, but a hallucinatory-delusional behaviour was confirmed by the anamnesis in the following days. At admission, the patient is partially cooperative, he displays thought disorder symptoms and disorganized speech, he presents verbal stereotypes “20 ... 20 ... 20”, incoherent speech, bradylalia and bradypsychia. There is a marked slowdown in logical associations, social withdrawal, anhedonia, low productivity, decreased eating instinct, mixed hypnic disorders.

Based on the DSM V and ICD-10 criteria, the diagnosis was of acute psychiatric disorders with symptoms of schizophrenia (F23.1). Following the diagnosis, the following treatment was decided upon:

- An antipsychotic drug – Olanzapine 15 mg – 1 tablet/day administered in the evening, in a single dose.
- A hypnoinductive anxiolytic–Diazepam 20 mg – 1 tablet/day administered in 3 doses (5 mg in the morning, 5 mg at noon and 10 mg in the evening), which was gradually decreased to a dose of 10 mg tablet/day administered in a single dose, in the evening.
- A mood stabiliser – Valproic acid 1000 mg – 1 mini tablet/day administered in a single dose, in the evening.
- Vitamin therapy – vitamin B1 – 1 vial/day, vitamin B6 – 1 vial/day both vials injected intravenously, in the morning, Neuromultivit 2 capsules/day administered in the morning and at noon
- A hepato-protective drug – Lagosa – 2 capsules/day administered in the morning and in the evening, Arginine 1 bottle/day, infusion solution administered in the morning, together with the vitamins B1 and B6.

Under specialized treatment, the patient presents a favourable evolution. The patient becomes cooperative, spatio-temporally and allopsychically oriented 5 days after starting treatment. Perception and thought disorder symptoms diminish, visual and auditory hallucinations becoming less frequent and subsiding completely 10 days after starting treatment. At the same time, the suicidal ideation disappears, the patient becomes aware of his own symptoms and the abnormality of his previous activities. As appetite improves, hypnic disorders disappear. At discharge, the psychiatric symptoms are completely resolved.

The patient is discharged after 20 days, in good general condition, without any mental or respiratory manifestations, with the recommendation to continue the treatment at home with:

- An antipsychotic drug – Olanzapine 10 mg – 1 tablet/day administered in the evening, in a single dose.
- A mood stabiliser – Valproic acid 500 mg – 1 mg tablet/day administered in a single dose, in the evening.
- A hypnoinductive anxiolytic – Bromazepam 3 mg – 1 tablet/day administered in a single dose, in the evening.
- Vitamin Therapy – Neuromultivit 2 tablets/day administered in the morning and at noon.
- A hepato-protective drug – Lagosa – 2 capsules/day administered in the morning and in the evening.

After 20 days of hospitalization the patient went home in stable condition. His psychological state got better from month to month. From the end of 2021 and until the beginning of 2022, the patient followed the treatment and is still stable.

Materials and Methods for Literature Review

Search Strategy and Data Extraction

For this research study, articles published in the last two years on PubMed Central and Google Scholar were used, the search taking place between February 2022-March 2022. The keywords for the search were as follows: COVID 19, SARS CoV-2, PSYCHOSIS, ACUTE PSYCHOTIC EPISODE, ACUTE PSYCHOTIC DISORDER. Current research showing the main mental symptoms associated with the SARS CoV-2 infection has been studied, as well as clinical cases that have been reported worldwide as associating specific manifestations of psychosis with COVID-19 infection. Among the selected clinical cases, those referring to other mental disorders, such as depression, were excluded.

Results

Domain-Specific Literature Studies

Regarding the post-COVID-19 infection psychosis we analysed about 54 articles related to our case presentation.

A study conducted by Oxford University on a sample of 62,000 people, hospitalized patients with moderate or severe forms of Sars-CoV2 infection between January 20, 2020, and January 20, 2021, showed that 18.1% of the patients received a psychiatric diagnosis within 14 to 90 days of diagnosis confirmation and a quarter of the patients were experiencing psychiatric symptoms for the first time. On the same sample, it was observed that the most common psychiatric disorder was anxiety-depressive disorder that required specialized treatment, but also psychotherapy, and in

patients over 65 years of age, it was observed that 1.2% had an increased risk of developing vascular dementia, this being attributed to the risk of the virus spreading to the brain.²⁶

A study conducted in China on a sample of 2400 people, hospitalized patients with moderate forms of SARS-CoV-2 infection, showed that, during hospitalization, patients showed a wide range of psychiatric symptoms such as:

- Insomnia – 42%;
- Attention disorders – 38%;
- Anxiety – 36%;
- Memory impairments – 34%;
- Depressive disorders – 33%;
- Confusion – 28%²⁷

The latest studies show concrete cases of patients without a personal pathological history in the psychiatric field, who developed psychiatric disorders after COVID-19 infection. One example is a 30-year-old male patient who was immediately hospitalized for bizarre behaviour, suicidal ideation, auditory hallucinations, and delusional ideas (“I see people who follow me and want to hurt me”), hypnic disorders. The patient had no psychiatric history but was infected approximately a month before with the SARS CoV-2 virus, having a mild form that did not require hospitalization, and psychiatric symptoms began in the following two weeks after the infection. No pathological changes were observed at the clinical examination and laboratory examinations, the pulmonary X-ray and the native cranial CT being within normal parameters.

The patient was hospitalized for 4 days, treated with antipsychotics (Quetiapine), during which time the psychiatric symptoms subsided. The patient was discharged in good general condition.²⁸

In a study conducted in Spain, between January 1, 2020 and December 30, 2020, 4 patients, 2 women and 2 men aged between 35 and 45 years, were observed; they were active people, without a personal psychiatric pathological history. The 4 patients were diagnosed with transient acute psychotic disorder with a favourable evolution under specialized treatment.^{29,30}

Another reported case highlights a 46-year-old man who came to the emergency room with suicidal ideation, bizarre behaviour, auditory and visual hallucinations. The man jumped from the 1st floor after “God told me to do this because nothing would happen to me.” The patient was allopsychic and partially spatio-temporally oriented and with no personal psychiatric or heredo-collateral pathological personal history. From the patient’s history we found out that a month before he was hospitalized for the SARS CoV-2 infection, having a moderate form that required hospitalization for two weeks. After discharge and recovery from the COVID 19 virus, the patient began to develop behavioural and mental disorders.

The patient was hospitalized with a diagnosis of acute psychotic disorder and received treatment with Olanzapine 5 mg/day for 2 weeks, during which time the psychiatric symptoms diminished until they subsided. The patient was discharged in good general condition and with the recommendation to take the medication and come to a follow-up check-up in two weeks. At the check-up, both the patient and the relatives noticed a favourable evolution, with the disappearance of the bizarre behaviour and of the perception disorders.³¹

Another case is that of a 33-year-old patient, without a mental history, who in the context of a SARS CoV-2 infection, of isolation for 3 weeks associated with the risk of losing his job, developed symptoms such as visual hallucinations (he saw strangers coming to hurt him), suicidal ideation. The patient was treated with Olanzapine 10 mg/day, and after 48 hours, the symptoms subsided.⁶

In the same context, the literature also presents other cases of patients, without a psychiatric history and without associated comorbidities, such as that of a 43-year-old woman who, following the SARS CoV-2 infection, developed symptoms such as delusional and suicidal ideas, marked, and suddenly developed irritability. After specialised treatment with Aripiprazole 30 mg/day, in combination with Clonazepam 4 mg/day, the patient’s symptoms subsided completely.³²

Discussion

In the case presented in this article, it stands out that we are talking about a young patient, with no personal pathological or psychic heredo-collateral history, who immediately developed serious post-COVID-19 psychiatric symptoms. Under

specialized treatment, both in the case presented, and in the previously reported cases, we are talking about a favourable evolution, the psychiatric manifestations subsiding completely.

It seems that the ethnology of psychosis and the way it becomes manifest remain an enigma, despite the fact that it has been at the core of psychiatric practice for centuries.

Regarding the link between the SARS CoV-2 virus infection and psychosis, we are still only talking about hypotheses that deserve to be studied on the widest possible scale. Apparently, there are several mechanisms by means of which psychiatric manifestations specific to psychoses would be triggered.³³

There are many already known infectious agents that cause psychiatric manifestations such as: HIV, *Toxoplasma Gondii*, *Treponema Pallidum*, *Brucella*. SARS CoV-2 is thought to be equally neurotropic and can be directly toxic to the nervous system if it infiltrates.³⁴

A second hypothesis states that COVID-19 infection would indirectly cause psychosis due to an abnormal immune response to this new and unknown pathogen. The immune system does not know how to react to a cascade of events, including the unjustified release of excitatory amino acids. Such events have the potential to affect the neural circuits that can lead to psychosis.³⁵

Other studies show that long-term use of antibiotics such as Ceftriaxone and Azithromycin may be responsible for psychosis, manifestations which can be seen in 0.3–3.8% of the population.³⁶

In addition to biological mechanisms, there is the hypothesis of social distancing and lack of communication that can lead to stress and psychiatric impairments. There is evidence in the preclinical literature that social isolation could trigger psychotic manifestations.³⁷

In another study conducted in 2021, British researchers found that within 6 months of the SARS CoV-2 infection, 0.42% of patients developed a first psychotic episode. This research considered that the cause of the psychotic episode was the inflammation of the central nervous system. One possibility of the virus entering the CNS is the direct invasion through nerve endings, and another option would be the immune mechanisms, called cytokine storms.³⁸

We must also pay close attention to patients with a history of psychiatric disorders, who have been diagnosed with an increased risk of exacerbation of these disorders, especially in the case of psychosis or schizophrenia.³⁹ Thus, with regard to the pandemic, respiratory manifestations are on a downward trend, whereas one may notice an increase in the prevalence of mental disorders among the general population.⁴⁰

It should be noted that, both in the case of the patient from the “Elisabeta Doamna” Psychiatric Hospital, Galați, and in other observational studies, most patients who manifested psychiatric symptoms were aged between 35 and 45 years.⁴¹

Another aspect to keep in mind is that, although none of the cases mentioned above showed relapses, the tendency for a patient who had a psychosis onset with hallucinations, delusional ideas, disorganized behaviour is towards chronicity, especially if the patient does not take the prescribed treatment.⁴²

The risk for these patients, who are part of the active population, who have a job and an active social life, is to abruptly interrupt the treatment, to neglect the regular visits to the specialist and, thus, to have a relapse, which could turn the mental disorder into a chronic one.^{43–45}

In this context, the relationship with the relatives is extremely important. Moreover, in order to ensure a long-term therapeutic success, it is imperative for the patients to be aware of the risks they are assuming if they interrupt the treatment.⁴⁶

Therefore, we cannot yet state the obvious cause of COVID 19 post-infection psychosis, but it is important that we continue to investigate the psychiatric implications that this respiratory virus might have. Another noteworthy fact is that, in most of the studies and reported cases, we are talking about patients who do not show any significant cerebral changes from a paraclinical point of view.^{47,48}

At the same time, both in the case presented and in the cases from the specialized studies, there is a complete and fairly rapid remission of symptoms under antipsychotic treatment, which indicates a transient disorder whose cause deserves further investigation, but another pertinent question is what would happen to these patients if they did not receive specialized treatment immediately.

Finally, an interesting aspect is observed in most of the clinical cases that have been studied, namely the presence of the risk of suicide. Whether it is just a suicidal ideation or even a suicide attempt, in most of the reported cases, the

patients presented this type of manifestations. The cause and connection have not yet been sufficiently studied, but they may be associated with psychotic anxiety and acute stress disorder.^{31,49,50}

Conclusion

In conclusion, the case presented, of the 44-year-old man with no personal history of psychiatric pathology supports and strengthens the evidence that there is a causal link between the SARS CoV-2 infection and mental disorders, which is currently being investigated. It is not yet clear whether the psychiatric symptoms were triggered by the subtle neuro-inflammation related to COVID 19 infection, the iatrogenic effect of drugs used in the treatment of the respiratory infection or the psychological effects of the pandemic, but we can consider that. Even the neurological manifestation of COVID-19 generated speculation regarding the neuropsychiatric sequelae, its inflammatory effect is more relevant to later development of schizophrenia.⁵¹

The Covid-19 provides a unique opportunity regarding the research of the pathogenesis of psychotic disorders. To identify the population at risk, identifying specific inflammatory biomarkers that could lead us to new therapies for schizophrenia⁵² could be studied for prophylactic use in vulnerable cohorts affected by COVID-19.

Abbreviation

WHO, World Health Organization.

Consent

The patient gave informed consent for the publication of their case details and any accompanying images. We have the institutional approval to publish the case details.

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