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A Case Report of Acute Schizophreniform Psychosis and following Encephalitis Associated with COVID-19 as a Rare Post Infectious Complication: What is known until Now?

Yoanna Marinova[1*] and Milena Stoyanova[2]

[1]Clinic "Psychiatry and Military Psychology", Military Medical Academy, Sofia, Bulgaria

[2]Clinic "Psychiatry and Military Psychology", Military Medical Academy, Sofia, Bulgaria

[*]**Corresponding author**: Yoanna Plamenova Marinova, Clinic "Psychiatry and Military Psychology", Military Medical Academy, Sofia, Bulgaria, Tel: + 359888056350; Email: joanna.marinova@icloud.com

Abstract

COVID-19 has been proven to cause multiple neuropsychiatric conditions such as encephalitis, encephalopathy, stroke, cerebral venous thrombosis, delirium, psychotic, mood and sleep disorders and others. We present a case of a 25-year-old male patient with rare neuropsychiatric complication 25 days after the first symptoms of acute COVID-19 respiratory infection (with no previous psychiatric history or substance use disorder). Primarily, the patient appears with symptoms of acute schizophreniform psychosis and 4 days upon admission he develops symptoms of encephalitis. SARS-CoV-2-specific IgG and IgM antibodies were detected in the blood serum. CSF showed elevated total protein and decreased glucose levels. Significantly elevated inflammatory markers – CRP, IL-6 – were present as well. He was treated with corticosteroids, antiviral agents and antibiotics and he recovered physically. Nonetheless, the psychotic features and a state of disorientation and psychomotor agitation persisted. Psychotic symptoms in the absence of delirium continued for 26 more days. After treatment with up to 6 mg Risperidone daily, 1500 mg Valproate and Biperiden SR 4 mg/daily the psychotic symptoms relieved. Although there are currently described cases of psychosis and cases of encephalitis, associated with Covid-19, ours is unique and complex for that it combines both which might be a form of autoimmune neuroinfection. Psychotic symptoms are effectively treated by an atypical antipsychotic with a predominant D2 receptor antagonist profile. Clinicians must always suspect encephalitis with the occurrence of altered mental status, depressed consciousness and high inflammatory markers. Timely and adequate antiviral and corticosteroid therapy, invariably accompanied by symptomatic treatment measures, leads to a favourable outcome of these conditions.

Keywords: Neuroinfection; Post-covid-19; Delirium; Autoimmune; Cytokines; Risperidone

Introduction

The COVID-19 pandemic emerged to be one of the most severe infectious diseases of present times. The humanity faced tremendous challenges with the appearance of the novel SARS-Cov-2 in the end of 2019 **[1].** Scientific communities from all over the world gather together diligent efforts and dedication in order to spread the knowledge about diagnosis and therapeutic approaches to handle the consequences from the disease. There is much more clarity nowadays about the majority of pathophysiological mechanisms by which COVID-19 affects tissues, organs and systems in the human organism but less is known about the pathophysiology of the so called "long" or "post-covid" syndrome **[2-5].** The multifaceted medical manifestations after surviving the acute COVID-19 infection continue to challenge the clinicians to this day. For the first time the idea for "long COVID" appeared in May 2020, after an infectious case with persistent symptoms was reported 7 weeks after SARS-CoV-2 infection **[6].** The growing number of articles published since then highlighted that post-COVID symptoms may persist or new symptoms may appear lasting many months after acute infection **[7].** At present, various nomenclatures and time ranges (3–12 weeks) are used to define the syndrome and a poor understanding of its etiology and potential treatment remains **[8].** "Long COVID" or "post-COVID syndrome" was defined by Tenforde et al. **[9]** by collecting demographic and subjective symptoms data 14–21 days after a positive RT-PCR for SARS- CoV-2. They observed that acute infection may be followed by prolonged illness not only in severe cases but also in milder outpatient illness. Acute neurologic complications or long-term sequelae of COVID-19 have been called "neuro-COVID" **[10,11].** Patients admitted to the hospital with COVID-19 experience multiple neurologic complications, including cognitive complaints, seizures, encephalopathy, hypoxic brain injuries, altered mental status, psychiatric symptoms, cerebrovascular events, autoimmune/post or para-infectious encephalitis, and debilitating symptoms described as "brain frog" **[12].** Neurological complications have been observed in up to 36% of hospitalized COVID-19 patients, according to research made in Wuhan in 2019 **[13].** Encephalitis is a rare complication of SARS-CoV-2 with incidence of approximately 2% - 18% and has been reported mostly as a para-infectious manifestation occurring within several days to 3 weeks of the initial infection **[14].** Psychotic symptoms have been related to other coronavirus infections in the past. A retrospective cohort study investigating neurological and psychiatric sequelae among 236,379 patients with COVID-19 over a 6-month follow-up reported an estimated incidence of 0.42% for a first diagnosis of psychotic disorder as well as a significantly increased Hazard Risk (HR) of presenting psychotic symptoms compared to patients with influenza (HR 2.27) or other respiratory tract infections (HR 1.49) in the same period **[15].** Up to present there is no systematic review that summarizes the development of acute psychosis in the post infectious period of COVID-19. The incidence of psychotic complications after COVID-19 infection is still unclear although a popular study published in 2020 investigating the neurological and neuropsychiatric complications of COVID-19 in 153 patients in UK concludes that 10 (6,5%) of those showed symptoms of new-onset psychosis. Structured delusions mixed with confusional features were the most frequent clinical presentations **[16].** A descriptive study from Spain described 10 patients with no previous psychiatric history who presented to emergency and psychiatric departments at least 2 weeks after experiencing the somatic symptoms of COVID-19. The most frequent presentation was delusions **[17].** Supporting this, a systematic review of case reports including 48 patients with COVID-19 associated psychosis concluded that delusions were the most common psychiatric sign (92%) and psychosis lasted between 2 and 90 days **[18].** 8 case reports of post-COVID-19 psychosis (approximately a month after the acute phase) are mentioned in a short review describing the possible

connection between the COVID-19 infection and the psychotic symptoms. The patients (5 men and 3 women between age 30-46 years) showed bizarre behaviour, auditory or/and visual hallucinations, suicidal ideations, sleep disturbances upon admission [19].

Pathophysiological Mechanisms of Neuropsychiatric Complications, Associated with COVID-19

The main pathological and immunological mechanisms of SARS-CoV-2 are widely known provided the numerous investigations of its predecessors SARS-Cov and MERS-Cov [20-22]. SARS-CoV-2 binds to the Angiotensin-Converting Enzyme 2 (ACE-2) receptor to access human cells, analogically to SARS-CoV and MERS-CoV [23,24]. Cells that express ACE-2 are therefore vulnerable targets to SARS-CoV-2 infection. Such cells in the Central Nervous System (CNS) are the neurons and glial cells, the endothelial and arterial smooth muscle cells [25-27]. Currently two main pathways are known for those viruses to enter the CNS (central nervous system): hematogenous and neuronal retrograde dissemination [28,29]. In the first way, the virus particles infect endothelial cells of the Blood Brain Barrier (BBB), binding to ACE-2 in the capillary endothelium cells. Another mechanism is to infect leukocytes, monocytes and macrophages and migrate into the CNS [28,29]. One additional hypothesis is that SARS-CoV infects endothelial cells of the BBB causing viremia which allows direct transport through the BBB into the CNS [30].

In the second way, the viruses enter the brain through the olfactory bulb by transneuronal (axonal) retrograde transport. ACE-2 is widely expressed on the epithelial cells of the oral and nasal mucosa [31,32]. Olfactory neurons project their dendrites into the nasal cavity and extend axons through the cribriform plate into the olfactory bulb of the brain [33]. In support to this is the discovery that SARS-CoV-2 enters the brain mainly through the olfactory bulb and rapidly spreads transneuronally to other related zones of the brain. One study with hACE2 mice explicitly shows the importance of this pathway as it appears to be the major cause of encephalitis and therefore of death in investigated mice population [34]. This evidence could be a part of the explanation of the mechanism of developing CNS symptoms associated with COVID-19 (SARS-Cov-2). In the before mentioned pathways there is direct contact of SARS-CoV-2 particles with the different cells and parts of the CNS.

However, SARS-CoV-2 may affect CNS indirectly as well [35]. It is known that COVID-19 infection potentially predisposes the development of inflammatory cytokine storm, elevated D-dimer levels, thrombosis or thrombocytopenia [36,37]. One study investigating the neurotropic characteristics and mechanisms of the virus cites that intracranial cytokine storms could result in the breakdown of the BBB without direct viral invasion and this might be the cause for the development of acute necrotizing encephalopathy or Guillain–Barré syndrome [38-40]. Coagulopathy observed in COVID-19, together with a cytokine storm, could predispose patients to a higher risk of thrombotic and hemorrhagic cerebrovascular events [41]. To summarize, the neuropsychiatric complications in the course of post “COVID-19” acute infection emerge through multiple mechanisms such as ACE-2 mediated neurotropism, inflammatory (cytokine storm) and autoimmune mechanisms as well as coagulopathies. Taking into consideration all the data provided, we can conclude that SARS-Cov-2 is a potentially dangerous neurotropic pathogen and therefore COVID-19 infection increases the risk of developing neurological and neuropsychiatric complications.

Material and Methods

We present the demographic, clinical, laboratory and neuroradiological characteristics of a patient with proven mild COVID-19 infection which initially improved completely. 25 days after the first symptoms of the viral infection, he developed symptoms of acute schizophreniform psychosis followed by symptoms of encephalitis - altered mental status, disorientation and depression of consciousness. After 5 days in Intensive Care Unit (ICU), the patient had psychotic symptoms in the course of delirium for 4 days. Paranoid delusions sleep disturbances and agitation in the absence of delirium continued for 26 more days. The hospitalization lasted 37 days in total.

Results

A 25-year-old white man was admitted urgently in the psychiatric department because of disorganized and aggressive behaviour towards his relatives. 2 days prior hospitalization he reported hearing voices telling him "to cut his throat", "the voice of the Devil", and "other demons", who "messed up with his actions and thoughts". He threatened his relatives with a knife and he declared that he wanted to kill himself too. The patient complained from "white spots" in the memory. Objectively upon admission he was highly agitated and angry, with rapid and tangential thought process, delusions of control and active auditory hallucinations accompanied by hyperbolic activity. In the emergency department he was consulted with toxicologist and was tested for psychoactive substances as well as alcohol. All of the results were negative. The patient had no history of mental illness or any recent stressful events and there was no family history of neurological or psychiatric conditions or substance abuse disorder. 25 days prior hospitalization – he had cough, myalgia, and loss of sense of smell and taste and temperature up to 38 C. He was tested positive for COVID-19 (RT-PCR) and he recovered completely. 10 days prior admission in the psychiatric department the duration of sleep shortened drastically and his appetite decreased. Upon admission he was tested with Rapid Antigen test for COVID-19 which resulted negative. Treatment with Zuclopenthixol 100 mg and Promethazine 50 mg i.m/per day, Valproate 1000 mg/i.v./daily was initiated. On the 3rd day of the psychiatric hospitalization – the patient appeared with fever up to 38 C, hypertonia and tachycardia (160/100, 120 bpm), saturation was 93% on room air. RT-PCR for COVID-19 was negative, however serum probe for COVID-19 associated IgM and IgG antibodies was positive. X-ray of the lungs and heart showed increased pulmonary density in the right perihilar-upper pole and in the left paracardial side. Laboratory findings showed leukocytosis, lymphopenia and eosinopenia at this time. Toxicological analyses of the blood showed positive for the used medications in therapeutic range. On the 4th day the patient became disoriented, quantitative changes of consciousness were observed - from somnolence to sopor. Hyporeflexia was detected without meningeal irritation or pathological reflexed. Treatment with antipsychotics was discontinued. The patient was transferred to ICU with suspicion for COVID-19 associated encephalitis. MRI of the head did not show any abnormalities. Treatment with Dexamethasone 8 mg/d, Acyclovir 400mg/d and i.v Ceftriaxone 2 g/d was initiated.

The patient spent 5 days in ICU where he was consulted by psychiatrist every per day. On the 6th day he was still subfebrile (37, 4 C), saturation was 94% with 3l O2/min intermittently, RR 135/80, 120 bpm. On the 7th day he appeared with delirium symptoms - acute psychomotor agitation, aggressive behaviour, confusion, auditory and visual hallucinations and paranoid delusions towards the personnel. He was medicated with Haloperidol up to 10mg/day and Promethazine up to 100mg/day i.m. Through the following days his level of agitation and confusion fluctuated, but there were no signs of depression of consciousness. The patient remained

disoriented for time and place but had relative periods of lucidity and his physical condition was stable. Lumbar puncture was performed and CSF laboratory examination showed increase in the total protein levels 0,87 g/l (0,15-0,45 g/l) and a slight decrease in the glucose levels 1,8 mmol/l (2,2 – 3,9 mmol/l). White Blood Cells (WBC) were in the normal range, no Red Blood Cells (RBC) was detected. SARS-Cov-2 (RT-PCR) was not detected in CSF. On the 10th day the patient was stabilized and was transferred to the psychiatric department because of persistent agitation, paranoid delusions, intermittent voice hallucinations and fluctuating state of confusion. The treatment with corticoids and antiviral agent continued for 5 more days. Treatment with the atypical antipsychotic Risperidone was initiated and was titrated up to 6mg/day given together with Biperiden 4 mg/day and Valproate up to 1500 mg/day.

Laboratory investigations (summarised in **Tables 1 and 2**) demonstratetypical haematological changes for COVID-19 infection, including pro-coagulopathic states and a transient lymphopenia, eosinopenia. Earlyinvestigation results included a positive Ig M, Ig G for COVID- 19, raised CRP and IL-6, ferritin, lactate dehydrogenase, D-dimer, characteristic of acute inflammatory states. Imaging examinations demonstrated radiological changes consistent with COVID-19 on chest X-ray, however no abnormality on Magnetic Resonance Imaging (MRI) of the head was detected.

Table 1: Blood parameters during hospital admission.

	17.06.21	18.06.21	19.06.21	21.06.21	23.06.21	27.06.21
Blood cells count						
White cell count 3.5-10.5x10^9L	12,5	14,97		8,59	10,9	12,4
Haemoglobin 130-180 g/L	147	144		133	144	146
Erythrocytes 4,6-6.2 x10^9L	5.02	4,76		4,69	5,05	4,88
Mean Corpuscular Volume 82-92fL	84.9	88		85,1	8,46	88,05
Platelet count 150-400 x10^9L	217	221		231	267	327
Neutrophils 1,56-6,13 x10^9L	11,02	12,6		5,86	7,51	6,82
Lymphocytes 1,18-3,74 x10^9L	0,71	0,87		1,69	2,07	3,87
Monocytes 0,24-0,82 x10^9L	0,77	1,34		0,9	1,12	1,28
Basophils 0-0,08 x10^9L	0,03	0,05		0,03	0,04	0,06
Eosinophiles 0,04-0,54 x10^9L	0,01	0,11		0,11	0,16	0,21
Serum						
Glucose 3,8-6 mmol/l	7,5	5,13		5,73	4,89	
Sodium 136-150 mmol/l	143	147	148	142		149
Potassium 3,5-5,5 mmol/l	4	5	4,3	3,5		4,3
Chlorides 98-110 mmol/l		105,6	105,3		103,8	
Calcium 2,2-2,7 mmol/l	2,44	2,12	2,24		2,21	2,26
Ionized calcium 1,1-1,3 mmol/l			1,05			
Magnesium 0,7-1.1 mmol/l		0,93	0,85		0,75	
Phosphate 0,8-1,6 mmol/l			1,25			
Ferrum 10-30 µg/l		2,4	2,1			
Urea 2,8-8,3 mmol/l		3,2	3,1		3,1	
Creatinine 75-130 µmol/l	84	90	82		77	
Uric Acid 154-428 µmol/l	279	170	145			
Ammonium 18-72		40,3				

µmol/l						
Total Protein 63-95 g/l	66,6	63	62,6		63,9	
Albumin 35-52 g/l		37,1	37,8		38,6	
Aspartate Aminotransferase 5-40 U/l	104,8	132,2	96,5		96,5	134,2
Alanine Aminotransferase 5-40 U/l	34,5	43,6	43,6		50,8	114,6
Gama-glutamiltranspeptidase 10-55 U/l	20,2	14,8			16,8	
Total Bilirubin 5-21 µg/l	15	20,4	11,4		7,9	
Creatine Phosphokinase 15-180 U/l	3060	3959	2702			
Creatine Phosphokinase MB-fraction 1-24 UI/l		103	29			
C-reactive protein 0-5 mg/l	4,4	43	64,6	76	6,7	3,6
Prothrombin time % 70-130		62		94,0	88	
Prothrombin time 10-14 sec		18,4		13,9	16,1	
International Normalized Ratio 0,7-1,3		1,4		1.04	1,09	
Activated partial thromboplastin time 28-40 sec		30,2		30,1	29,4	
D-dimer 0-0,5 mg/l		0,84		0,8	2,32	0,6
Fibrinogen 2-4,5 g/l		5,09		5,66	5,28	4,9
Lactate Dehydrogenase 208-378 UI/l		407	440	888	423	
Ferritin 20-250 µg/l		275	310	322	313	
IL-6 5,30-7,50 pg/ml		47,4		83,6		7,3
High-sensitive Troponin 0,0-0,0198 ng/ml		0,011	0,0077			
Cholesterol 1-5,2 mmol/l	2,45	2,49	2,32			
High Density Lipoprotein Cholesterol		1,12				

1-3 mmol/l						
Low Density Lipoprotein Cholesterol 1,9-3,6 mmol/l		1,12	1,23			
Myoglobin 2-70 ng/ml			215,4			

Table 2: Other laboratory parameters.

Blood		
	Result	Normal Range
Covid-19 IgM	Positive	
Covid-19 IgG	Positive	
HIV 1+2	Negative	
Syphilis	Negative	
Varicella Zoster Virus IgM	Negative	
Varicella Zoster Virus IgG	Positive	
Enterovirus IgM	Negative	
Tick-Borne Encephalitis IgM	Negative	
Hantavirus IgM	Negative	
Rickettsia conorii IgM	Negative	
Rickettsia conorii IgG	Negative	
West Nile Virus IgM	Negative	
West Nile Virus IgG	Negative	
Herpes Simplex Virus 1,2 IgM	Negative	
Herpes Simplex Virus 1,2 IgG	Positive	
Influenza A IgM	Negative	
Influenza B IgM	Negative	
Cytomegalovirus IgM	Negative	
Cytomegalovirus IgG	Negative	
Adenovirus IgM	Negative	
Malaria Antigen (immunochromatographic test)	Negative	
Cerebrospinal Fluid		
	Result	Normal range
CSF WCC	1	5
CSF RBC	0,001	0
CSF Protein	0,87	0,15-0,45 g/l
CSF Glucose	1,8	2,2-3,9 mmol/l
CSF Chlorides	125	112-130 mmol/l
CSF Microscopy	-	
CSF Culture	No growth	

CSF SARS-Cov-2	Negative	
Other		
Urine Culture	No growth	
Blood culture	No growth	
Nasopharyngeal Swab Culture	No growth	
RT-PCR Covid-19	Negative (2 times)	

On the 12th day the patient was oriented for date, month, year, day and place. Nevertheless, he was constantly agitated, with sleep disturbances, he demonstrated impulsive and aggressive behaviour, provoked by paranoid delusions (that the personnel were trying to poison him, that he was being watched). Suicidal thoughts and hallucinatory production were not declared at this time. On the 29th day the patient's normal sleep cycle recovered, agitation began to improve after this point, but he still reported unstructured paranoid delusions ("feeling of being watched"). His thought process was well structured and logical. Moreover, he demonstrated formal insight towards the psychotic condition with the aid of several psychotherapy sessions. On day 37 the patient completely recovered, no psychotic symptoms were declared by this time and he was discharged on maintenance antipsychotic therapy of Risperidone 6 mg/day and Biperiden 4mg/day and Valproate 1500 mg/d. He had been followed-up by our team once per month in the next year (July 2021-July 2022). During the follow-up process he showed satisfying social functioning, he continued studying in university and performed high results. His antipsychotic therapy was decreased gradually after 6 months to Risperidone 4 mg/day and after 3 more months was decreased to 1 mg/day. On the 10th month the antipsychotic was discontinued without any relapse of the psychotic symptoms. Valproate was discontinued gradually as well during the course of treatment.

Discussion

Although yet no systematic reviews exist describing psychotic symptoms in the post infectious period of COVID-19, enough studies with viral diseases reported a link between elevated inflammatory markers (cytokines) and a psychotic schizophrenic state **[18,42,43].** Elevated levels of interleukins are also associated with delirium-like states, as we observed in our patient **[18].** Numerous infectious pathogens associated with the occurrence of encephalitis were investigated and excluded from the pathogenesis in our case **(Table 2)**. However, a disadvantage is the lack of examination on autoimmune antibodies in the serum, therefore it is impossible to prove an autoimmune genesis of the encephalitis-associated symptoms. A systematic review on COVID-19 encephalitis concludes that in the post-infectious period negative PCR for SARS-CoV-2 virus in CSF, makes the diagnosis of encephalitis caused by the SARS-CoV-2 virus less evident, pointing to a possible autoimmune neuropathogenesis **[14].** Autoimmune encephalitis is the cause of "symptomatic" forms of psychosis too. The discovery of Autoantibody (Ab)-associated Autoimmune Encephalitis (AEs), such as anti-NMDA-R encephalitis, can at least initially mimic variants of primary psychosis. These newly described secondary, immune-mediated schizophreniform psychoses typically present with the acute onset of polymorphic psychotic symptoms **[44].** Typical clinical signs for AEs are the acute onset of paranoid hallucinatory symptoms, atypical polymorphic presentation, psychotic episodes and medical symptoms such as autonomic instability, seizures, motor disturbances and others. Predominant psychotic courses of AEs have also been

described. The term autoimmune psychosis was recently suggested for these patients and the most common symptoms they presented were delusions of prejudice, persecutory and referential beliefs **[44,45].** All the above-mentioned data as well as the successful treatment with corticoids and antiviral agents corresponds to the case presented by us. We chose the atypical antipsychotic Risperidone for long term treatment of the psychotic symptoms as a preferred and effective drug of choice, guided by other published cases **[46,47].** Risperidone has predominant D2-receptor blocking profile **[48].** Although there is still insufficient data for a concrete therapeutic approach in postinfectious COVID-19 psychoses, following the general principle of the dopamine hypothesis in the genesis of schizophrenic psychotic symptoms, better efficacy should be achieved with D-2 blockade.

Conclusion

Cases like ours, although rare, are important for the practice, as they imply meaningful points in the early diagnosis and treatment of post infectious psychosis and encephalitis, when a history COVID-19 infection is presented. Our experience shows that psychotic symptoms are effectively treated by an atypical antipsychotic with a predominant D2 receptor antagonist profile. Clinicians must always suspect encephalitis with the occurrence of altered mental status, depressed consciousness and high inflammatory markers after COVID-19 infection. Timely and adequate antiviral and corticosteroid therapy, invariably accompanied by symptomatic treatment measures, leads to a favourable outcome of these conditions. More specific and scientifically approved therapeutic approaches for treating these medical manifestations are needed in order to improve the clinical outcome.

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