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¹Yuryeva L. M., ¹Shornikov A. V., ¹Kokashynskiy V. O., ²Brydun O. Y., ²Rachynska T. V.**COVID-ASSOCIATED PSYCHOTIC DISORDERS WITH COGNITIVE IMPAIRMENT: A CASE SERIES**¹Dnipro State Medical University (Dnipro, Ukraine)²Dnipro Multidisciplinary Clinical Hospital for Psychiatric Care (Dnipro, Ukraine)

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The COVID-19 pandemic has significantly changed the health care system in the world, and also leads to a significant number of COVID-associated mental disorders. Usually psychiatrists diagnose non-psychotic (neurotic) mental disorders associated with SARS-CoV-2 virus, including asthenic, anxiety, and depressive disorders, but COVID-19-associated psychotic disorders are considered to a much lesser extent. Goal was to investigate the effect of coronavirus infection on the mental state of the elderly. Identify risk factors for the development of psychotic symptoms. Clinical and psychopathological research and psychodiagnostic research was conducted according to the following methods:

- Generalized Anxiety Disorder-7 (GAD-7)
- Patient Health Questionnaire-9 (PHQ-9)
- Montreal Cognitive Assessment (MoCA)
- Asthenic State by L.D. Malkova (SAS)
- Brief Psychiatric Rating Scale (BPRS)

Conclusions:

1. *Patients with short-term reactive psychotic states have a high risk of suicide, as well as the likelihood of recurrence of psychosis, which indicates the need for thorough care in the acute phase of the disease and follow-up.*
2. *Older patients need more attention because of the risk of complications, including psychotic disorders.*
3. *Elderly patients with anosmia may have a higher risk of cognitive impairment, which is important for the development of preventive measures for the condition.*
4. *The considered series of cases testifies the need for an integrated approach to the management of patients with COVID-19 and the need for close cooperation with the psychiatric service during counseling, observation and management of this group of patients.*
5. *Treatment of psychotic states with antipsychotics is effective, but the focus should be on the effective treatment and prevention of COVID-19 complications.*

Key words: psychosis, cognitive impairment, anxiety, depression, anosmia.

Relationship between the publication and planned research work. The paper has been written within the scientific research work «Development of a system of diagnostic, psycho-corrective, treatment-rehabilitation and preventive measures for patients with non-psychotic mental disorders and their family members», state registration № 0118U 001281.

Introduction. The Coronavirus Disease-2019 (COVID-19) pandemic, which was declared by the World Health Organization on March 11, 2020, has significantly changed the health care system in the world, and also leads to a significant number of COVID-associated mental disorders. Researchers have focused on non-psychotic mental disorders associated with Severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2), including asthenic, anxiety, and depressive disorders. COVID-19-associated psychotic disorders are considered to a much lesser extent. Currently, the study of the mechanisms of coronavirus on the central nervous system (CNS) continues, the main mechanisms of the flow are psychological influences (social isolation, unemployment, lack of housing, relationship breakdown, domestic violence and deterioration of physical health), «cytokine storm» followed by acute or sub-acute CNS damage due to exposure to Angiotensin-converting enzyme-2 (ACE-2)

receptors, medication (glucocorticoids, antiviral and antimalarial drugs, etc.), being on artificial lung ventilation [1, 2]. The impact of low levels of saturation on the risks of psychotic disorders remains debatable [3].

Goal. Investigate the effect of coronavirus infection on the mental state of the elderly. Identify risk factors for the development of psychotic symptoms.

Object and methods of research. We offer a review of a series of four cases of COVID-associated psychosis among men over the age of 50 without previous mental and drug addiction disorders. Psychopathological and psychometric examination of all patients was performed 2–3 weeks after hospitalization, after the disappearance of acute psychotic symptoms and behavior. In accordance with the Declaration of Helsinki, written informed consents to undergo a psychiatric examination were received from all participants. Prior to hospitalization in the psychiatric hospital, none of the patients had cognitive or psychopathological symptoms. Clinical and psychopathological research and psychodiagnostic research was conducted according to the following methods:

- Generalized Anxiety Disorder-7 (GAD-7)
- Patient Health Questionnaire-9 (PHQ-9)
- Montreal Cognitive Assessment (MoCA)

- Asthenic State by L.D. Malkova (SAS)
- Brief Psychiatric Rating Scale (BPRS)

The results of the research.

Case 1. A 55-year-old man without previous history of mental and physical disorders, accompanied by relatives, was transferred to a psychiatric hospital from the infectious diseases department of a multidisciplinary hospital with complaints of anxiety, fear of death, suspiciousness, and sleep disturbances. The condition of patient changed during inpatient treatment for COVID-19, during which formal thinking disorders, delusions of staging, persecution and poisoning, and disorganized behavior emerged. Saturation was reduced to 70 %. Patient received oxygen therapy, treatment of COVID-19 in accordance with current protocols. In the clinical picture prevailed anosmia. When using psychometric scales, the following results were set: Generalised Anxiety Disorder-7 (GAD-7) – 2 points (minimum anxiety), Patient Health Questionnaire-9 (PHQ-9) – 11 points (moderate depression), Montreal Cognitive Assessment (MoCA) – 21 points (mild / moderate cognitive impairment), Scale of Asthenic State by L.D. Malkova (SAS) – 68 points (mild asthenia), Brief Psychiatric Rating Scale (BPRS) (after 3 weeks of treatment) – 29 points.

Case 2. A 53-year-old man with no previous history of mental disorders on the background of inpatient treatment of COVID-19 with a minimum saturation of 98 % and anosmia began to state that «coronavirus got into his brain and ate it» and other complaints that belong to Cotard syndrome. The patient left the infectious disease hospital arbitrarily, his behavior at home was disorganized, he committed suicidal attempt with the elements of demonstration (strangling himself with a belt) because he believed that he was now a burden to surrounding people, and spread COVID-19 around the world. In a psychiatric hospital, these symptoms persisted for about two weeks during antipsychotics treatment. Additional research methods revealed GAD-7–5 points (moderate anxiety), PHQ-9–6 points (mild depression), MoCA – 20 points (mild / moderate cognitive impairment), SAS – 46 points (no asthenia), BPRS after 3 weeks of treatment) – 23 points.

Case 3. A 51-year-old man after receiving inpatient treatment for COVID-19 was hospitalized in a psychiatric hospital two and a half months after discharge. It is known from the anamnesis that his mental state changed for the first time immediately after discharge: he began to express delusional ideas of greatness, wealth, unmotivated high mood. He shows hyperactivity, hypersexuality, restlessness at hospitalization, his speech and thinking were accelerated. He expressed the megalomaniacal delusion of wealth and the persecution idea. Additional research methods revealed GAD-7–2 points (minimum anxiety), PHQ-9–14 points (moderate depression), MoCA – 21 points (mild / moderate cognitive impairment), SAS – 55 points (mild asthenia), BPRS after 3 weeks of treatment) – 40 points.

Case 4. A 59-year-old patient in hospital with pneumonia due to COVID-19, with a minimum saturation of 90 %, received standard therapy according to clinical guidelines, which included corticosteroids (dexamethasone). Anosmia was observed in the clinical picture. There is no history of mental disorders and addictions. The mental state changed for the first time 4 days after discharge from the hospital, when the patient began to make strange judgments, suddenly there were periods of psychomotor arousal during which the patient fell to the floor, punched, shouted, and did not react to other people. Within 3 days before hospitalization in a psychiatric hospital, this condition occurred 5 times, each new episode the duration of seizures increased, arousal changed to a state of stupor, after the seizures the patient reported that he was a god and a genius. After hospitalization for 2 weeks there was a condition with speech impediment, disorientation, and behavior revealed misconceptions. After recovery, amnesia was observed for this period of time. The examination was performed on 15th day of treatment in a psychiatric hospital after recovery from a state of impaired consciousness. Additional research methods revealed GAD-7–6 points (moderate anxiety), PHQ-9–11 points (moderate depression), MoCA – 21 points (mild / moderate cognitive impairment), SAS – 71 points (mild asthenia), BPRS – 40 points.

Half of the patients underwent a brain CT scan, which revealed signs of organic damages.

In all cases, a differential diagnosis was made, in particular with mood disorders, severe psychotic symptoms and endogenous psychotic states. All patients were older than the typical age expected for the first episode of schizophrenia.

The discussion of the research results. Given that the activation of microglia, anti-inflammatory cytokines, antineuronal autoantibodies and blood-brain barrier disorders may be associated not only with neurodegenerative but also mental disorders [4]. Psychotic disorders in the proposed series of cases can be explained this mechanism. Also, COVID-19 is associated with a large number of cases of ageusia and hypo / anosmia. This is due to the penetration of COVID-19 virus through the nasal epithelium and may be a manifestation of the retrograde neuronal pathway of penetration of the virus into the CNS [5]. Direct viral infiltration can cause a neuroinflammatory reaction that leads to the activation of microglia [6], that triggers demyelinating processes, which is one of the main causes of encephalopathy. In patients with COVID-19, psychosis is often regarded as encephalopathy, the symptoms of which include delirium, the absence of focal neurological symptoms, and signs of CNS inflammation [7].

The effect of COVID-19 on cognitive processes is shown in a prospective study of residents of Atualpa (Ecuador), which found that the average score of MoCA after a pandemic was significantly lower among seropositive people (21.7±4 vs. 19.6±4.2; p=0.010) [8].

According to a study of patients without a history of cognitive dysfunction hospitalized for functional rehabilitation after the subacute phase of COVID-19 at the IRCCS Clinic in San Raffaele (Italy), 89.6 % of patients that received oxygen support through a mask and 77.8 % of patients who did not receive oxygen support were found to be deficient on the MoCA scale [9]. There were no significant differences in cognitive functions depending on the presence of anosmia in the acute period of the disease. However, the authors do not indicate the presence of psychotic disorders in the clinical picture of patients.

Such cognitive impairment, only without a combination of symptoms of psychosis, can be observed after acute respiratory distress syndrome [10], but patients presented in this series had no history of intubation.

The onset of maniac-like psychotic disorder in COVID-19 may be associated with an ongoing infection influence effect while the reverse transcriptase-polymerase chain reaction on ribonucleic acid for the SARS-CoV-2 was negative [11]. Further studies are needed to the relationship between the titer of antibodies to SARS-CoV-2 virus and the appearance of psychotic symptoms.

In a clinical case report from Kamal and colleagues, a patient with altered mental status, severe agitation, and fluctuations in consciousness due to COVID-19 infection was diagnosed with encephalitis based on tomography data indicating multiple hypodense lesions of the islet cortex and deep periventricular lesions of the white matter of the frontal lobes bilaterally [12]. Established lesions in the future may lead to cognitive impairments.

On the other hand, Cotard syndrome, which was found in one of our patients, may be associated with multifocal brain atrophy and lesions of the medial part of the frontal lobe [13], possibly of viral or indirect genesis.

Another possible explanation for cognitive decline in patients with COVID-associated psychosis is the appearance of false-positive test results, among which are [14]:

- low educational level and social status of the patient, prolonged isolation from society;

- situational inattention, high situational anxiety at the time of neuropsychological research;
- state of intoxication at the time of the study or the day before,
- severe fatigue / asthenia at the time of the study;
- indifferent or negative attitude to testing, due to lack of understanding of the purpose and significance of neuropsychological research;
- conscious or unconscious opposition to the assessment of the state of cognitive functions due to internal negative attitudes.

Conclusions. 1. Patients with short-term reactive psychotic states have a high risk of suicide, as well as the likelihood of recurrence of psychosis, which indicates the need for thorough care in the acute phase of the disease and follow-up.

2. Older patients need more attention because of the risk of complications, including psychotic disorders.

3. Elderly patients with anosmia may have a higher risk of cognitive impairment, which is important for the development of preventive measures for the condition.

4. The considered series of cases testifies the need for an integrated approach to the management of patients with COVID-19 and the need for close cooperation with the psychiatric service during counseling, observation and management of this group of patients.

5. Treatment of psychotic states with antipsychotics is effective, but the focus should be on the effective treatment and prevention of COVID-19 complications.

Prospects for further research. The appearance of psychotic disorders with additional cognitive impairment in patients after COVID-19 with a history of anosmia forms a new problem in the treatment of patients with COVID-associated mental disorders. These disorders can be explained both by the direct manifestation of neurological lesions through the main mechanisms of the virus on the nervous system, or the influence of the virus as a trigger in the emergence of endomorphic mental disorders. Such mental disorders require thorough attention of clinicians and further study.

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COVID-АСОЦІЙОВАНІ ПСИХОТИЧНІ РОЗЛАДИ З КОГНІТИВНИМИ ПОРУШЕННЯМИ: СЕРІЯ ВИПАДКІВ

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Резюме. Пандемія COVID-19 суттєво змінила систему охорони здоров'я у світі, а також спричинила значну кількість психічних розладів, пов'язаних із COVID-19. Зазвичай психіатри діагностують непсихотичні (невротичні) психічні розлади, пов'язані з вірусом SARS-CoV-2, включаючи астеничні, тривожні та депресивні розлади, але психотичні розлади, пов'язані з COVID-19, вважаються менш поширеними та значно менше дослідженими. Основними механізмами психічних розладів, пов'язаних з COVID-19, є психологічний вплив (включаючи соціальну ізоляцію, безробіття, розрив стосунків, домашнє насильство), «цитокіновий шторм» (пошкодження ЦНС через вплив рецепторів АПФ-2), лікарські засоби (особливо глюкокортикоїди), перебування на штучній вентиляції легень.

Метою нашої роботи було огляд серії з чотирьох випадків психотичних розладів, асоційованих з COVID-19, серед чоловіків віком старше 50 років без попередніх психічних та наркологічних розладів та з аносмією у клінічній картині. Усі наші пацієнти під час психозу демонстрували легкі/помірні когнітивні порушення, що не є поширеним синдромом під час COVID-19. Крім цього, жоден з наших пацієнтів не мав вираженої астенії, тривоги чи депресії. Таким чином, поява психотичних розладів з додатковими когнітивними порушеннями у пацієнтів після COVID-19 з аносмією в анамнезі формує нову проблему в діагностиці та лікуванні пацієнтів з психічними розладами, пов'язаними з COVID-19. Розглянута серія випадків свідчить про необхідність комплексного підходу до ведення пацієнтів з COVID-19 та необхідність тісної співпраці з психіатричною службою під час консультування, спостереження та ведення цієї групи пацієнтів. Крім того, пацієнти з психотичними розладами мають високий ризик суїциду, що свідчить про необхідність ретельного догляду у гострій фазі захворювання та подальшого спостереження.

Ключові слова: психоз, психотичні розлади, когнітивні порушення, тривога, депресія, аносмія, COVID-19.

COVID-ASSOCIATED PSYCHOTIC DISORDERS WITH COGNITIVE IMPAIRMENT: A CASE SERIES

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Abstract. The COVID-19 pandemic has significantly changed the health care system in the world, and also leads to a significant number of COVID-associated mental disorders. Usually psychiatrists diagnose non-psychotic (neurotic) mental disorders associated with SARS-CoV-2 virus, including asthenic, anxiety, and depressive disorders, but COVID-19-associated psychotic disorders are considered to a much lesser extent. The main mechanisms of the covid-associated mental disorders are psychological influences (including social isolation, unemployment, relationship breakdown, domestic violence), «cytokine storm» (CNS damage due to exposure to ACE-2 receptors), medication (especially glucocorticoids), being on artificial lung ventilation.

The aim of our work was to review of a series of four cases of COVID-associated psychotic disorders among men over the age of 50 without previous mental and drug addiction disorders and with anosmia in the clinical picture. All our patients during the psychosis showed mild/moderate cognitive impairment, that is not a common and frequent syndrome during COVID-19. Except this no one of our patients has severe asthenia, anxiety or depression. Thus, the appearance of psychotic disorders with additional cognitive impairment in patients after COVID-19 with a history of anosmia forms a new problem in the diagnostic process and treatment of patients with COVID-associated mental disorders. The considered series of cases testifies the need for an integrated approach to the management of patients with COVID-19 and the need for close cooperation with the psychiatric service during counseling, observation and management of this group of patients. In addition, patients with psychotic disorders have a high suicidal risk, which indicates the need for thorough care in the acute phase of the disease and follow-up.

Key words: psychosis, psychotic disorders, cognitive impairment, anxiety, depression, anosmia, COVID-19.

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Conflict of interest:

The authors declare no conflict of interest.

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