

FIRST EPISODE OF PSYCHOSIS FOLLOWING THE COVID-19 VACCINATION - A CASE SERIES

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INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has a major impact on the mental health of the population (Reinfeld et al. 2021). Various types of vaccines have been developed as an essential tool to end the COVID-19 pandemic and decrease neuropsychiatric complications (Borovina et al. 2021, Reinfeld et al. 2021, Sultana et al. 2022). Evidence gathered to date has confirmed the efficacy and safety of COVID-19 vaccines (Sultana et al. 2022), but as with all pharmaceuticals, side effects associated with vaccines are possible. There are still limited data on the psychiatric side effects of the vaccine against COVID-19. Recent reports have documented acute psychotic symptoms following the administration of the COVID-19 vaccine (Grover et al. 2022).

In view of this, in this article we present a series of three patients who had no past or family history of mental illness and developed psychotic disorders following COVID-19 vaccination.

CASE SERIES

Case 1

This case involves a 45-year-old male patient. The patient was reluctant to be vaccinated for COVID-19. He showed little trust in health and government officials. He said that he got vaccinated mainly because he was pressured at his workplace to get vaccinated. The patient's unusual behaviour began within five days of being vaccinated with Ad26.COV2.S adenoviral vector vaccine. He became anxious, suspicious, paranoid, disorganised and complained of headaches. Accordingly, the patient was examined twice by the neurologist. The examination and diagnostic tests (including computed tomography (CT) of the brain) revealed no neurological deficits. Finally, two weeks after the COVID-19 vaccination, persecutory delusions and delusions of reference led the patient to suicide attempt by stabbing himself in the abdomen. After abdominal surgery, the patient was admitted to the Clinic of Psychiatry. In addition to paranoid delusions, the psychiatric evaluation revealed intrapsychic tension and low affect modulation. Drug and alcohol abuse were

denied. Physical examination did not reveal any acute findings. Blood work showed elevated leukocytes ($13.4 \times 10^9/L$ ref: 3.4-9.7), an elevated level of C-reactive protein (158.8 mg/L ref: < 5.0) and elevated liver enzymes (AST 62 U/L ref: 11-38; ALT 112 U/L ref: 12-48; GGT 127 U/L ref: 11-55). The chest X-ray showed pneumonia, which was treated with an antibiotic. The stab wound healed without complications.

The patient was offered reassurance and support from our psychiatric team. He was treated with haloperidol 10 mg/day and alprazolam 2 g/day. After two weeks of treatment, the patient's condition improved enough to allow a psychological evaluation. It revealed mild depressive symptoms with suspected paranoid experiences. After 23 days of treatment in our Clinic, he was discharged without psychotic symptoms.

Case 2

This case involves a 41-year-old male patient. During the COVID-19 pandemic, he developed symptoms of anxiety for which he did not seek psychiatric help, so we cannot say whether his symptoms were clinically significant.

Five days after the second dose of the BNT162b2 mRNA vaccine, he began to experience frontal headaches, pain in the left intercostal space, paresthesias on the left side of his body, as well as paranoid delusions and severe anxiety. The patient was examined several times by a neurologist. No neurological deficits were found on examination and diagnostic tests (including magnetic resonance imaging (MRI) of the brain). Finally, he was admitted to the Clinic of Psychiatry due to psychotic symptoms and psychomotor agitation.

In addition to the above symptoms, the psychiatric examination revealed a depressed, irritable mood and olfactory hallucinations. Drug and alcohol abuse were denied. The physical examination revealed no acute findings. His blood examination showed no pathological findings. Psychopharmacological treatment included risperidone 4 mg/day and diazepam 15 mg/day, with regular psychotherapeutic support. He was discharged on request after four days with reduced but still present psychotic symptoms. After 6 days, he was again admitted to our Clinic as his condition continued to

deteriorate. This time his therapy was gradually changed to quetiapine 600 mg/d, olanzapine 30 mg/d, fluphenazine 5 mg/d, clonazepam 6 mg/d. After 10 days, the patient was discharged with complete remission of his psychotic symptoms.

Case 3

This case involves a 35-year-old male patient. Although he was neither diagnosed nor treated psychiatrically, according to the heteroanamnesis he developed mild depressive symptoms during the COVID-19 pandemic.

Three days after receiving the first dose of the BNT162b2 mRNA vaccine, the patient began to complain of headaches and paraesthesia in his legs. He also had syncope and was examined by a neurologist, who found no deficit. Two weeks later, he visited the psychiatric emergency room twice because of persecutory delusions and delusions of reference. He was commenced on olanzapine 10 mg/day and diazepam 30 mg/day. Due to the ongoing worsening of his psychotic symptoms, the patient was hospitalised in our Clinic a few days later. During the psychiatric evaluation, he was agitated, dysphoric, and paranoid. He denied auditory or other sensory hallucinations. He denied drug or alcohol abuse. No acute findings were noted on physical examination. The patient's blood work showed no pathologic findings. CT brain scans, electroencephalogram (EEG), Doppler ultrasound of the carotid and vertebral arteries also showed no abnormalities.

The patient was offered reassurance and support from our psychiatric team. He was treated with the following, gradually increased, therapy: olanzapine 20 mg/day, haloperidol 15 mg/day, promazine 300 mg/day, valproic acid 1500 mg/day, and diazepam 30 mg/day. After one month of hospitalisation, the patient was discharged with partial remission of his psychotic symptoms.

DISCUSSION

SARS-CoV-2, a coronavirus that causes a highly infectious respiratory disease named COVID-19, has rapidly become a global pandemic (Jakovljević et al. 2020). As an essential tool for the control of the SARS-CoV-2 pandemic, different types of vaccines have been developed (Sultana et al. 2022). Today, five COVID-19 vaccines are authorized or approved for use in the EU (see European Commission 2021). The evidence gathered so far has confirmed the short- and medium-term efficacy and safety of the COVID-19 vaccines (Sultana et al. 2022), but as with all pharmaceutical agents, side effects are possible with vaccines. There are several case reports in the literature of the development of psychotic disorder following vaccine administration (against influenza, rabies, yellow fever, etc.). In particular, few case reports have documented the association between administration of the COVID-19 vaccine and a psychotic disorder (Grover et al. 2022).

In view of the limited data available, here we present a case series of three patients who developed a psychotic disorder after the administration of the COVID-19 vaccine. Two patients had been vaccinated with the BNT162b2 mRNA vaccine. Similarly, Flannery et al. reported acute psychosis due to encephalitis following BNT162b2 mRNA vaccination (Flannery et al. 2021). One of our patients had been vaccinated with Ad26.COV2.S adenoviral vector vaccine. To our knowledge, this is the first report of a psychotic disorder following this specific vaccine, although there are reports of psychotic symptoms after another adenoviral vector vaccine (ChAdOx1 nCoV-19 vaccine) (Grover et al. 2022, Takata et al. 2021).

All our cases of psychotic disorders described in these reports involved individuals with no personal or family history of mental illness. The psychotic symptoms began within 2 weeks after administration of the COVID-19 vaccine. We observed that all the patients had paranoid delusions and one of them also had hallucinations.

The pathogenesis of psychosis, in general, is still not fully understood, although there is growing evidence of a link between inflammation, immunological dysfunction and psychosis (Suvisaari & Mantere 2013). Several different studies examining peripheral inflammatory markers in first-episode psychosis have consistently reported the presence of elevated levels of IL-6, TNF- α and IL-1 β . Inflammatory cytokines are thought to play a role in the development of psychotic disorders by interacting with several pathways such as neurotransmitter metabolism, synaptic plasticity and neuroendocrine function (Zajkowska & Mondelli 2014). Interestingly, some cases of psychotic disorders have been associated with a COVID-19 induced hyperinflammatory state (Reinfeld et al. 2021). mRNA vaccines also elicit a robust immune response inducing both B and T cells responses with the production of IFN- γ , IL-2, and TNF- α (Guerrera et al. 2021). Similarly, Alter et al. in their study found a T-cell response and production of the aforementioned cytokines after administration of a vector vaccine against COVID 19 (Alter et al. 2021). Therefore, the vaccine may mimic a mild version of the infection, so its potential role in psychotic disorders must be considered (Reinfeld et al. 2021).

All of our patients complained of headaches within five days of vaccination with the COVID-19 vaccine, considering that two of the patients who had received the mRNA vaccine also had paraesthesia and one of them also had syncope. In two cases (mRNA and vector vaccine) the neurological and psychotic symptoms started simultaneously, and in one case (mRNA vaccine) the neurological symptoms preceded the psychotic symptoms. In all cases, neurological examination, MRI/CT of the brain revealed no abnormalities. Headache, dizziness, myalgias and paraesthesias are among the most common neurological symptoms expected to occur as effects of vaccination (Goss et al. 2021). The underlying mechanism is still unclear, but some suggest that, for

example, the headaches may be the result of a pro-inflammatory state, similar to COVID-19 related headaches (Ekizoglu et al. 2021).

We need to be mindful that the patient described in the first case expressed vaccine hesitancy before he received a vaccine. His disbelief in health care and government policy has already been documented as a factor associated with refusal and delay in receiving the COVID-19 vaccine (Dhama et al. 2021). The negative anticipation of the vaccination, i.e. the psychosocial factors of this patient, might play a role in the dynamics of the psychotic onset (Reininghaus et al. 2016). Furthermore, the clinical presentation of this case culminated in a suicide attempt. Acute stress, as vaccination could be for this patient, has been significantly associated with an increased risk of suicide in individuals with brief psychotic disorders (Valdés-Florido et al. 2020). The literature reports a woman who developed depression and attempted suicide following inactivated SARS-CoV-2 vaccine (Gencan et al. 2021). In addition, two other presented cases developed either anxiety or depressive symptoms during the COVID-19 pandemic. We can assume that psychosocial factors and heightened stress associated with the pandemic had a significant impact on these patients, as they developed the previously mentioned symptoms (Necho et al. 2021). Moreover, psychotic disorders may develop due to the psychosocial distress derived from the COVID-19 pandemic as has already been documented (Valdés-Florido et al. 2020). However, it is significant that here reported patients, who had no past or family history of mental illness, developed neurological and psychiatric symptoms shortly after vaccination. We can think in these cases of susceptibility to stress, with the COVID-19 vaccine triggering psychosis through an increased immune response (Alter et al. 2021, Guerrero et al. 2021).

CONCLUSION

We report the case series of three patients who developed psychotic symptoms after the COVID-19 vaccination. Considering the evidence in the literature of an association between altered immune function and psychosis, the negative family and personal psychiatric history of our patients, the clinical presentation, and the close temporal relationship between the COVID-19 vaccination and the presenting symptoms, we hypothesise that the COVID-19 vaccine may play a role in the aetiology of their symptoms. Since the COVID-19 vaccine has been shown to be safe and effective (Sultana et al. 2022), and the development of psychosis after vaccination is very rare (Reinfeld et al. 2021), we firmly believe that this case series should not discourage the use of the COVID-19 vaccine. Rather, future systematic studies should be conducted with adequate control of confounding variables to establish coincidence, association or causality between reported psychotic symptoms and the COVID-19 vaccine.

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Contribution of individual authors:

Tonka Borovina & Jelena Popović: were involved with conception and design, data collection, manuscript preparation, writing the paper. Shared first authorship.

Tonći Mastelić: was involved with conception and design, data collection, manuscript preparation and approval of the final version.

Mirjana Sučević Ercegovac, Lea Kustura & Boran Uglešić: were involved with patient's care, data collection, reviewed draft manuscript.

Trpimir Glavina: was involved with patient's care, data collection, study design, reviewed draft manuscript, manuscript preparation.

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