Caso Clínico

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Refractory psychosis after mRNA COVID-19 vaccine

Psicose refratária após vacina de mRNA COVID-19

Psicosis refractaria después de la vacuna mRNA COVID-19

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ABSTRACT:
Introduction: The vaccination against SARS-CoV-2 has shown efficacy in decreasing morbidity and mortality. There are several systemic side effects and some neuropsychiatric manifestations described. **Case report:** A 38-year-old woman was admitted to the Psychiatry of the Conjunto Hospitalar de Sorocaba presenting disorganized behavior and aggressiveness. Six months ago, she received the first dose of the mRNA vaccine for COVID-19 and, around 24 hours later, had systemic adverse effects followed by aggressiveness and delusional thinking of persecutory nature. She had no past clinical or psychiatric reports. Previously, she was perfectly functional. We performed an extensive clinical-laboratorial investigation, and all tests were negatives. Several pharmacological therapies with antipsychotics and mood stabilizers were used, but after more than four months of hospitalization, the improvements observed were just in orientation and behavior, remaining with symptoms of psychosis. **Discussion:** This is the first report of refractory psychosis after COVID-19 immunization with no improvement of symptoms; there have been related psychoses after COVID-19 immunization. It is suggested that the psychosis occurs by the intense cytokine storm, leading to a high pro-inflammatory status. It is hypothesized that vaccination causes a strong immune response against

the SARS-CoV-19; therefore, similarly mechanisms could underlie the psychosis after COVID-19 immunization.

Keywords: SARS-CoV-2, psychosis, vaccination, refractory psychosis, COVID-19.

RESUMO:
Introdução: A vacinação contra SARS-CoV-2 tem demonstrado eficácia na diminuição da morbimortalidade. Existem vários efeitos colaterais sistêmicos e algumas manifestações neuropsiquiátricas descritas. **Relato de caso:** Mulher de 38 anos foi admitida na Psiquiatria do Conjunto Hospitalar de Sorocaba apresentando comportamento desorganizado e agressividade. Há seis meses, recebeu a primeira dose da vacina de mRNA para COVID-19 e, cerca de 24 horas depois, apresentou efeitos adversos sistêmicos seguidos de agressividade e pensamento delirante de natureza persecutória. Ela não tinha relatórios clínicos ou psiquiátricos anteriores. Anteriormente, ela era perfeitamente funcional. Realizamos extensa investigação clínico-laboratorial e todos os exames foram negativos. Diversas terapias farmacológicas com antipsicóticos e estabilizadores de humor foram utilizadas, mas após mais de quatro meses de internação, as melhoras observadas foram apenas na orientação e comportamento, permanecendo com sintomas de psicose. **Discussão:** Este é o primeiro relato de psicose refratária após imunização para COVID-19 sem melhora dos sintomas; houve psicoses relacionadas após a imunização COVID-19. Sugere-se que a psicose ocorra pela intensa tempestade de citocinas, levando a um alto status pró-inflamatório. Supõe-se que a vacinação cause uma forte resposta imune contra o SARS-CoV-19; portanto, mecanismos semelhantes podem estar subjacentes à psicose após a imunização com COVID-19.

Palavras-chave: SARS-CoV-2, psicose, vacinação, psicose refratária, COVID-19.

RESUMEN:
Introducción: La vacunación contra el SARS-CoV-2 ha demostrado eficacia en la disminución de la morbimortalidad. Hay varios efectos secundarios sistémicos y algunas manifestaciones neuropsiquiátricas descritas. **Caso clínico:** Mujer de 38 años ingresó al Psiquiatría del Conjunto Hospitalar de Sorocaba presentando conducta desorganizada y agresividad. Hace seis meses, recibió la primera dosis de la vacuna de ARNm para COVID-19 y, alrededor de 24 horas después, presentó efectos

adversos sistémicos seguidos de agresividad y pensamientos delirantes de carácter persecutorio. No tenía antecedentes clínicos ni psiquiátricos. Anteriormente, ella era perfectamente funcional. Se realizó una extensa investigación clínico-laboratorial, y todas las pruebas fueron negativas. Se utilizaron varias terapias farmacológicas con antipsicóticos y estabilizadores del ánimo, pero después de más de cuatro meses de hospitalización, las mejoras observadas fueron solo en la orientación y el comportamiento, permaneciendo con síntomas de psicosis. **Discusión:** Este es el primer informe de psicosis refractaria después de la inmunización COVID-19 sin mejoría de los síntomas; ha habido psicosis relacionadas después de la inmunización COVID-19. Se sugiere que la psicosis ocurre por la intensa tormenta de citoquinas, lo que conduce a un alto estado proinflamatorio. Se plantea la hipótesis de que la vacunación provoca una fuerte respuesta inmunitaria contra el SARS-CoV-19; por lo tanto, mecanismos similares podrían ser la base de la psicosis después de la inmunización con COVID-19.

Palabras clave: SARS-CoV-2, psicosis, vacunación, psicosis refractaria, COVID-19.

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Introdução

The vaccination against the SARS-CoV-2 has shown efficacy in decreasing morbidity and mortality. According to *Our World In Data* [1], so far, around 64.1% of population across the world received at least one dose of vaccine. The more frequent side effects are pain at the shot site, fever, tiredness, myalgia, and headache [2]. Other reactions such as cardiac alterations and allergic reactions have also been described. Recently, Kadali [3] observed neuropsychiatric manifestations post BNT162b2 mRNA COVID-19

vaccination, among them were sleep reduction and mental confusion. However, manic symptoms and disorganized behavior occurred around 0.3% and 0,1%, respectively. We report a case of a woman with a suddenly onset psychosis after the first shot of an mRNA-COVID-19 vaccine, without response to medications.

Case report

A 38 year-old woman, married, six siblings, without past psychiatric record, was admitted to psychiatric service on 2021 December, 3th presenting aggressiveness, and bizarre behavior. According to her husband, 24 hours later the first dose of BNT162b2 mRNA vaccine, she had high fever, shivering, and myalgia. As soon as these symptoms subsided, within a week, she became agitated, and did not recognize their relatives. She believed that she had born from a bowl, her behavior was disorganized, and the aggressiveness increased. She presented herself disheveled, with poor hygiene, unfriendly face, lacking self-orientation and refusing to talk to staff; also, she was uncooperative with the doctors.

Her thought was delusional; she believed the staff was persecuting her, and that several city mayors were her parents. Her mood was dysphoric and enraged. She had no past clinical or psychiatric reports (including substance use disorders), as well as her parents. Previously, she was perfectly functionally as a housewife. We performed an extensive clinical-laboratorial investigation (blood chemistry, erythrocyte sedimentation rate, urine urinalysis, liver and renal functions, rheumatologic tests, cranial, and chest computerized tomography with-and-without-contrast, cranial magnetic resonance imaging, and lumbar puncture) and all the results were negatives, therefore we excluded diagnosis of delirium. So, given the temporal association with the COVID-19 vaccination, we considered the hypotheses of psychosis by vaccination.

She was started on haloperidol (15 mg/d) plus valproate (1.0 g/d) without response. The medication was changed to olanzapine (30mg/d), also without response. After a month, we tapered olanzapine and started clozapine, increasing doses until 800 mg/d. She was maintained on clozapine for 30 days, without minimum alterations in her mental state. Based on reports of improvement in similar anti-COVID-19 vaccination reactions [4, 5], we replaced the clozapine for risperidone and increased the doses until 12 mg/d, and we observed no improvement. Given the several manic manifestations, lithium carbonate was added, and her restlessness, tachylalia, and orientation were slight ameliorated, but the

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delusions and bizarre behavior were unchanged. So we replaced the medication, and put her on aripiprazole (20mg/d). So far, after almost six months of hospitalization, she was partially self-orientated and less restlessness, she demonstrated more interactivity and she was less delusional and less disorganized. She remained hostile, persecutory, and refusing to talk to staff, so her psychosis was defined as refractory, according to IPAP criterion [6].

Discussion

As far as we know, this is the first report of refractory psychosis after the very first COVID-19 immunization. Even though rare, there have been related psychoses after rabies vaccination [7], yellow fever vaccination [8], and recently after COVID-19 immunization [4, 9, 10]. A number of neuropsychiatric symptoms such as insomnia, anxiety, psychosis and mood disorders have been referred to as manifestations of COVID-19 infection[11]. Psychosis caused by SARS-Cov-2 infection has been described and it is suggested to be secondary an intense cytokine storm, leading to a high pro-inflammatory status, that alters monoamines levels resulting in psychosis.

Yesilkaya & Tasdemir [9], and Grover et al. [10] hypothesized that vaccination causes a strong immune response against the SARS-CoV-19; therefore similarly mechanisms could underlie the psychosis after COVID-19 immunization. Indeed, this patient presented a strong vaccine response before the psychoses onset. Curiously, most of all psychiatric cases occurred in patients with no past of psychiatric reports, like our patient. However, her psychosis was longer and non-responsive to treatment then those already described.

We cannot exclude the psychosocial suffering resulted from the COVID-19 pandemic as a risk factor for the development of psychotic disorders [12]. As well as, we can preclude that had been only a coincidence between vaccination and onset of psychosis. Nonetheless, our report is similar to others described [9, 11, 13, 14] in the sense of there were no past or family history of mental disorders and there were a close temporal relationship between onset of symptoms with vaccination. Reinforcing the hypothesis of the COVID-19 vaccine can cause extremely immune response predisposing to a psychotic condition in very small number of people.

There were some limitations to consider; only the hospital staff ensured adherence, because antipsychotic plasma levels were not available, and we assessed mental state by clinical judgment without standardized rating scales.

Vaccination is safe, necessary, and it is proving its benefit. We strongly recommend the massive immunization. But, knowing the factors associated to psychiatric outcomes (being women, young-to-midlife, within 15 days of taking a shot) [12] can help health professionals to monitor closely particularly this vulnerable people.

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