



# Neuroleptic malignant syndrome associated with COVID-19 vaccination

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Dear editor,

Neuroleptic malignant syndrome is a fulminant and life-threatening disorder that occurs in patients treated with antipsychotic medication. Although the pathophysiology of neuroleptic malignant syndrome is not fully understood, it involves a central hypodopaminergic state and an acute phase reaction as an immune response [1]. We report a case of this syndrome after COVID-19 vaccination. Written consent was obtained from the patient.

A 61-year-old Japanese woman was brought to the emergency room with high fever and disorientation. She had developed schizophrenia 35 years ago and had recently been treated with risperidone 6 mg/day. The day before admission, she received an intramuscular injection of 0.3 mL of Comirnaty<sup>®</sup>, a mRNA vaccine against SARS-CoV-2. However, 20 h after the vaccination, she was unable to walk due to muscle pains all over her body and called an ambulance. On arrival, she was confused with a high fever of 40 °C, tremors in her upper limbs, and muscle stiffness all over her body. She was sweating, had tachycardia of 134/min and elevated blood pressure of 168/102 mmHg. A quick blood test in the emergency room revealed a creatine kinase > 5000 IU/L, and complete blood count was remarkable for an elevated white blood cell > 10,000/mm<sup>3</sup>. COVID-19 antigen test was negative. Chest X-ray, urine analysis, and blood culture showed no abnormalities. Her symptoms and blood tests clearly met the diagnostic criteria for neuroleptic malignant syndrome [2]. Risperidone was discontinued, and

she was admitted to the high care unit for systemic management with massive infusion of fluids. Lead-pipe rigidity improved one week after admission. On the 10th day of hospitalization, her creatine kinase level decreased to 2932 IU/L and she was able to walk.

COVID-19 infection increases the risk of developing neuroleptic malignant syndrome [3], but there are few reports of neuroleptic malignant syndrome associated with COVID-19 vaccination [4]. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptors and enters the body. There are many ACE2 receptors in the brain, and it has been speculated that the mechanism by which COVID-19 infection causes neuroleptic malignant syndrome may be via ACE2 receptors [5]. Although the mRNA vaccine promotes the synthesis of viral spike proteins, they do not activate ACE2 receptors, and thus vaccine-induced neuroleptic malignant syndrome is a different mechanism than neuroleptic malignant syndrome caused by COVID-19 infection. After vaccination, immune-transducing cells called dendritic cells begin to work, and synthesizing proinflammatory cytokines [6]. Elevated levels of proinflammatory interleukins such as IL-6 and TNF- $\alpha$  have been reported in neuroleptic malignant syndrome [7]. Thus, the immunostimulatory effect of the vaccine may cause the pathogenesis of neuroleptic malignant syndrome.

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## Declarations

**Conflict of interest** The author has no conflicts of interest relevant to the content of this article.

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