



COVID-19-booster vaccine-induced encephalitis

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In 2020, the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing COVID-19, rapidly resulted in a pandemic. Different neurological diseases secondary to COVID-19 have been described, varying from cerebral vascular disorders to acute inflammatory polyneuropathies [1].

Vaccination against the SARS-CoV-2 virus is the key strategy to manage the pandemic, prevents severe or fatal illness, and started by the end of 2020. Vaccines, like any drug, can cause adverse effects. It is important to share this with peers and public health officers to enhance recognition of adverse effects of COVID-19 vaccines.

We present a case of encephalitis after a booster shot with the Moderna COVID-19 (mRNA-1273) vaccine in a 48-year-old man. The patient was admitted to the emergency department because of behavioral changes. There initially was agitation and even physical aggression, with the condition eventually evolving to mutism. The patient denied headache, but mentioned epigastric pain and anorexia since 3 days.

His medical history only revealed the transition from female to male 2 years ago which still required intramuscular injection of Sustanon[®] every 3 weeks. He did not take daily

medication. Six days before clinical onset, the patient had received his booster shot against COVID-19.

Heteroanamnestic substance abuse and a psychiatric history were denied. His mother was diagnosed with schizophrenia.

On clinical examination, the left arm was paretic (MRC scale: 4–) and atactic. Likewise, discrete neglect for the left side of his body was observed. He was bradyphrenic and confused, and only answered with short sentences; his speech was neither dysarthric nor aphasic. There were no signs of meningeal irritation. Cranial nerve function was normal. His vital parameters were stable with in particular no fever. His COVID-19 PCR test was negative as well as other tests for viral or bacterial pathogens (see Table 1). CT scan of the brain and EEG were normal.

As encephalitis was suspected, a lumbar puncture was performed at the emergency department. Subsequently, empirical treatment with ceftriaxone, amoxicilline, and aciclovir was immediately started. Cerebrospinal fluid (CSF) revealed lymphocytic pleocytosis and an elevated protein level. When all CSF analyses returned negative including cultures and viral PCR testing (see Table 1), empirical treatment was discontinued. Extensive laboratory work-up (see Table 1) did not reveal any abnormalities except of acute renal insufficiency after 1 day of treatment with aciclovir. Dehydration because of the anorexia for 3 days was the most probable cause; aciclovir nephrotoxicity (tubulotoxicity with slight increased proteinuria and glucosuria) with hypovolemia as a predisposing factor was included in the differential diagnosis. Renal function recovered quickly after intravenous fluid substitution.

MRI of the brain only showed a small left internal capsule developmental venous anomaly; SPECT scan revealed normal perfusion.

Because of the improvement of the clinical syndrome of the patient after 3 days, we decided not to administer steroids. The patient was discharged after 1 week of hospitalization after complete remission of the encephalitis signs, except for amnesia for the day of admission. The

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Table 1 Laboratory results of serum and cerebrospinal fluid

	Reference range	Day 1	Day 3
Lumbar puncture			
White-cell count (μL)	0–5	34 (95% lymphocytes)	n.a
Red-cell count (μL)	< 1000	200	n.a
Protein (mg/dL)	< 45	107	n.a
Glucose (mg/dL)	40–70	63	n.a
Lab results			
Red-cell count ($\times 10^9/\text{L}$)	3.8–5.2	5.7	n.a
Hemoglobin (g/dL)	11.8–16	16.4	n.a
White-cell count ($\times 10^9/\text{L}$)	3.5–11	5.1	6.8
Platelet count ($\times 10^9/\text{L}$)	150–400	179	166
C-reactive protein (mg/L)	< 5	3.3	50
Creatinine (mg/dL)	0.57–1.11	0.96	2.30
Ureum (mg/dL)	19–44	44	56
Gfr (mL/min)	60	89	32
Ferritin ($\mu\text{g}/\text{L}$)	10–204	74	
D dimers ($\mu\text{g}/\text{L}$)	0–549	427	
PCR on urine		<i>Legionella pneumophila</i> and <i>Streptococcus pneumonia</i> negative	
PCR on CSF		Enterovirus, Herpes Simplex Virus and <i>Varicella zoster</i> Virus negative	
Culture on CSF		Negative	

Other laboratory results: porphyrins negative, copper and ceruloplasmin within normal range, ganglioside antibodies negative, anti-nuclear factor and ANCA negative, neuronal antibodies negative. CSF IgG and isoelectric focusing n.a

n.a. not available

pharmacovigilance unit of the Belgian Federal Agency for Medicines and Health Products was informed.

Our case meets the Graus criteria for possible autoimmune encephalitis as follows: (1) subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms, (2) CSF pleocytosis, and (3) exclusion of alternative causes [2]. Because of the temporal association with the booster vaccination, the possibility of COVID-19-booster induced encephalitis was considered. In previous cases, symptom onset was 5, 6, 8, and 21 days after vaccination in line with our case [2, 3]. Previously, vaccine-induced encephalitis has already been described in vaccination for influenza, hepatitis B, haemophilus influenza type B, measles-mumps-rubella, tetanus, diphtheria, pertussis, polio, and Japanese encephalitis [2, 3].

Besides post-COVID-19 vaccination encephalitis, acute disseminated encephalomyelitis and aseptic meningitis following SARS-CoV-2 vaccination have been described, as well. In one case on aseptic meningitis, it is hypothesized that additives in these vaccines would be responsible for the post-vaccination autoimmune reaction. The patient in that case developed symptoms after her first

Pfizer-BNT162 vaccine. The BNT162 adjuvant is considered to be a trigger of autoimmune syndrome induced by adjuvants (ASIA-syndrome) [4]. The patients suspected with CNS autoimmune responses after SARS-CoV-2 vaccinations were all successfully treated with steroids. To our knowledge, we report the first case of encephalitis after booster vaccination with the Moderna mRNA-1273 vaccine. It is important to be aware of the possible autoimmune responses secondary to vaccination against the SARS-CoV-2 virus. Zuhorn and colleagues estimated the incidence of encephalitis after vaccination with the ChAdOX1 nCov-19 and Pfizer-Biontech mRNA vaccine to be, respectively, 8 per 10 million and 2 per 10 million vaccination doses [2]. This is far less than the incidence of 0.215% as a complication of COVID-19 [5]. In addition to the rarity of this adverse event, our case confirms the good outcome of post-COVID-19 vaccination encephalitis, comparable to previous cases. Obviously, the potential risks of COVID-19 vaccination do not outweigh its benefits. Adverse event reporting increases awareness and thus improves both diagnosis and treatment.

Declarations

Conflict of interest All the authors report no disclosure nor conflict of interest relevant to the manuscript. All authors report no financial disclosure.

Ethical approval This manuscript does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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