Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Case Report

A case of encephalitis following COVID-19 vaccine

Yuya Kobayashi [a,*], Seishu Karasawa [a], Nobuhiko Ohashi [a], Kanji Yamamoto [a]

[a] Department of Neurology, Nagano Municipal Hospital, 1333-1 Tomitake, Nagano, 381-8551, Japan

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ABSTRACT

We describe the first case of encephalitis following coronavirus disease 2019 (COVID-19) vaccination. Our patient was a 46-year-old Japanese woman who presented with acute onset diplopia. Subsequent magnetic resonance imaging revealed brain stem encephalitis that was rapidly responsive to high dosage steroid therapy and completely improved. Although the occurrence of encephalitis after vaccination could have just been a casual temporal association, her symptoms were temporally correlated with two vaccinations. Our case suggests caution and indicates treatment and prognosis, despite no evidence of a causal relationship. Nonetheless, this report emphasizes the enormous benefits of vaccination, which should not be undermined.

1. Introduction

The neurotropism of the coronavirus disease 2019 (COVID-19) has been well known, with reports showing that COVID-19 can cause neurological diseases such as acute transverse myelitis (ATM), neuromyelitis optica (NMO), acute disseminated encephalomyelitis, and acute motor axonal neuropathy [1–3]. However, the mechanism by which it causes these diseases remains unclear. The Centers for Disease Control and Prevention (CDC) Vaccine Adverse Event Reporting System related to COVID-19 vaccines had reported that as of September 9, 2021, 66 cases had developed encephalitis [4] However, the details of such cases have not been revealed. We herein present a case that developed encephalitis after COVID-19 vaccination.

2. Case presentation

Our patient is a 46-year-old Japanese woman with no previous medical history. After receiving her COVID-19 vaccination [BNT162b2 (Lot EY3860, Comirnaty, BioNTech and Pfizer)], she began having trouble focusing her eyes the next day. Two days later, persist diplopia occurred and gradually worsened, for which she visited a general physician, otolaryngologist, and neurosurgeon. However, given that no significant findings were observed, she was followed up without treatment. Although diplopia fluctuated between improvement and worsening, it persisted without completely disappearing. However, a day after receiving her second dose of vaccination [BNT162b2 (Lot FC5947, Comirnaty, BioNTech and Pfizer)], which was administered 3 weeks after the first dose, her diplopia exacerbated. Five days later, the patient was admitted to our section. On admission, her vital signs and physical examination were normal. Bilateral abduction restrictions were present, whereas other neurological findings were unremarkable. Brain MRI revealed a lesion on the dorsal pons across the midline and no gadolinium enhancement (Fig. 1). Old foci, which could indicate multiple sclerosis, were not detected. MR angiography showed no vascular lesions, and whole-spine MRI was unremarkable. On cerebrospinal fluid examination, total protein content was 53 mg/dL; 3 mononuclear cells/mm3 were detected; glucose was 63 mg/dL, IgG index was 0.5; and oligoclonal bands (OCBs) was absent. Blood tests showed no abnormalities, and serum antibodies to acquaporin-4 (AQP4) and myelin-oligodendrocyte (MOG) tested negative in the cell-based assay. No other abnormalities suggestive of infection, collagen disease, and vasculitis were noted. The patient was thereafter treated with three sessions of high dose methylprednisolone (1 g/day over 3 days, with 4 days off). Subsequently, oral medication was administered starting from 1 mg/kg/day and gradually decreasing. The patient's symptoms improved, with MRI showing a reduction in the lesions (Fig. 1). No recurrence has been experienced after discontinuing steroid therapy.

3. Discussion

To date, no report on COVID-19 vaccine-related encephalitis has been published. The patient's symptoms exacerbated associated with the timing of the vaccination and have not recurred since. Although multiple sclerosis and NMO had been strongly suspected based on the brain lesions, examinations showed no OCBs, and serum antibodies against AQP4 were negative. Moreover, the patient had negative results

* Corresponding author.
E-mail address: jururi@shinshu-u.ac.jp (Y. Kobayashi).

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on other examinations to rule out brainstem encephalitis such as MOG antibody, vasculitis, infection, and systemic autoimmunity. COVID-19 vaccine-associated encephalitis was strongly suspected in the current case owing to the close temporal relationship between COVID-19 vaccination and the worsening symptoms.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has higher neuroinvasive potential compared to previous coronaviruses. The high frequency of anosmia during acute infection probably reflects viral invasion of the olfactory bulbs [1]. One common neurological disorder caused by COVID-19 infections is ATM, the incidence rate of which was higher than that generally observed [3] Two onset distributions have been observed for ATM. In most cases (68%), the latency period ranged from 10 days to 6 week, whereas in the remaining cases (32%), the latency period ranged from a few hours to 5 days [3]. The postulated mechanisms causing ATM and various neurological syndromes associated with SARS-CoV-2 include, either individually or in combination, direct viral neuronal injury and the host's secondary hyperinflammation syndrome [2]. Although SARS-CoV-2 virus infections may elicit an immune response, it remains unclear whether COVID-19 vaccines may also induce the same. There has been an ongoing discussion related to neurological impairment after vaccination with COVID-19 [3,5], with three cases of encephalitis having been reported after vaccination [6,7], all of whom developed psychiatric symptoms without MRI findings. The acute onset and excessive production of neuroinflammatory mediators have been speculated to indicate cytokine storm-related brain dysfunction [6]. Historically, this phenomenon has not been limited to COVID-19. In fact, vaccinations have been found to potentially trigger autoimmunity either through a specific mechanism of molecular mimicry, possibly enhanced by an immunological adjuvant [8], or a nonspecific mechanism of bystander activation [9]. In the current case, the short time interval between vaccination and onset of neurological symptoms suggests nonspecific immune activation mechanisms, such as bystander activation.

The CDC had reported a total of 66 cases of encephalitis associated with COVID-19 vaccines [4]. However, the submitted reports did not indicate that the vaccine caused or contributed to the adverse events. It is difficult to confirm whether the vaccine induced acute encephalitis. Encephalitis and other nervous system diseases can occur with a certain frequency during the vaccination period. The current report is anecdotal and does not prove a cause-and-effect relationship between SARS-CoV-2 mRNA vaccines and encephalitis. One important finding this report highlights is that the patient exhibited clinical improvement after a short course of steroids. We are experiencing the biggest vaccination opportunity in human history. Vaccination certainly has enormous benefits and provides hope toward eventually mitigating the COVID-19 pandemic. Therefore, the current report does not undermine vaccination but suggests caution and indicates treatment and prognosis while awaiting further confirmation from larger epidemiological studies and meta-analyses to understand the causality. Presently, it would seem that the benefits of COVID-19 vaccination outweigh any potential risks.

COI statement

The authors declare that they have no competing interests.

Consent

Written informed consent was obtained from the patient for publication of this case report.

ICMJE statement

Yuya Kobayashi: data acquisition, data analysis, and writing of the manuscript. Kanji Seishu Karasawa and Nobuhiko Ohashi: data acquisition and revision of the manuscript. Yamamoto: critical revision of the manuscript.

Ethical approval

Informed consent was obtained from the patient regarding the

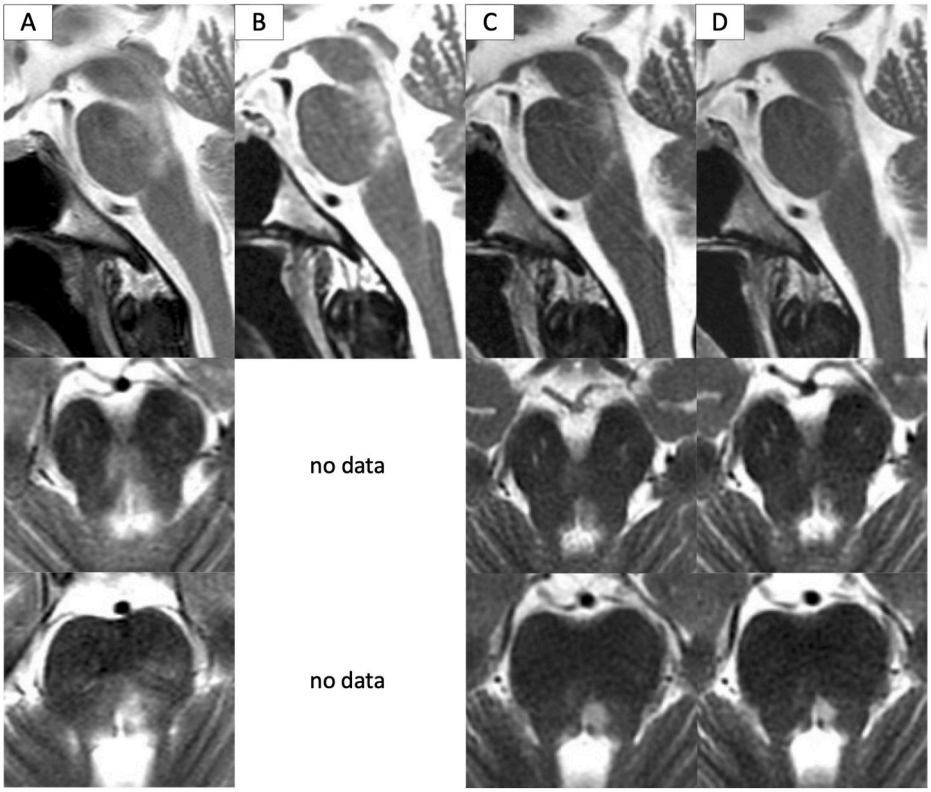

Fig. 1. T2-wighted magnetic resonance imaging revealing brain stem encephalitis. Panels A, B, C, and D indicate 0, 5, 17, and 31 days after methylprednisolone medication, respectively. The lesion was located in the dorsal portion of the pons, which based on which could explain the eye-movement disorder of the patient could be explained. The border of the lesion was unclear and crossed the midline. The possibility of cerebrovascular diseases, such as cerebral infarction, was ruled out because the lesion did not correspond to the vascular dominant region. The lesions showed improved in course.

publication of the case report.

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