Case Report

Clinical Manifestation, Management, and Outcomes in Patients with COVID-19 Vaccine-Induced Acute Encephalitis: Two Case Reports and a Literature Review

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Abstract: Introduction: Vaccination is one of the best strategies to control coronavirus disease 2019 (COVID-19), and multiple vaccines have been introduced. A variety of neurological adverse effects have been noted after the implementation of large-scale vaccination programs. Methods: We reported two rare cases of possible mRNA-1273 vaccine-induced acute encephalitis, including clinical manifestations, laboratory characteristics, and management. Results: The clinical manifestations might be related to hyperproduction of systemic and cerebrospinal fluid (CSF) cytokines. mRNA vaccines are comprised of nucleoside-modified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA, which is translated into SARS-CoV-2 spike protein by the host’s ribosomes, activating the adaptive immune response. Exposed mRNA or vaccine components may also be detected as antigens, further resulting in aberrant proinflammatory cytokine cascades and activation of immune signaling pathways. Both patients exhibited significant clinical improvement after a course of steroid therapy. Conclusions: The use of COVID-19 vaccines to prevent and control SARS-CoV-2 infections and complications is the most practicable policy worldwide. However, inaccurate diagnosis or other diagnostic delays in cases of vaccine-induced acute encephalitis may have devastating and potentially life-threatening consequences for patients. Early diagnosis and timely treatment can result in a favorable prognosis.

Keywords: COVID-19 vaccine; mRNA-1273 vaccine; moderate; steroid; encephalitis

1. Introduction

Vaccinating as many individuals as possible against coronavirus disease 2019 (COVID-19) is one of the most effective strategies for controlling the pandemic. In addition to complications like myocarditis and pericarditis, other neurological adverse effects have been reported following vaccination with messenger RNA (mRNA) vaccines, including the
BNT162b2 vaccine (Comirnaty® (New York, NY, USA); Pfizer-BioNTech (Mainz, Germany)) and mRNA-1273 vaccine (SPIKEVAX™; Moderna; Cambridge, MA, USA). We reported two rare cases of possible mRNA vaccine-induced acute encephalitis, both of whom had a favorable prognosis after steroid therapy. We speculate that the excessive innate immune response is due to cytokine storms triggered by vaccination. In certain individuals, vaccine components may be detected as antigens, triggering aberrant proinflammatory cytokine cascades and activation of immune signaling pathways, resulting in inflammatory symptoms, and secondary organ damage [1–7]. While vaccination provides substantial benefits and a means to eventually control the COVID-19 pandemic, clinicians should also be aware of the potential for vaccine-induced severe neurological complications.

2. Case Presentation

2.1. Case 1

A healthy 58-year-old woman was admitted due to acute delirium 7 days after receiving the mRNA-1273 vaccination (SPIKEVAX™). Prior to the recent vaccination, she had also received two doses of the Vaxzevria® (ChAdOx1 nCov-19; AstraZeneca (Cambridge, UK)) vaccine 11 and 27 weeks before, without experiencing significant adverse effects. She had no history of neurological disorders. Physical examination revealed a low-grade fever (38 °C), cognitive deficits, left deviation of the head and eyeballs, and mild weakness of the right upper limb. Laboratory results, including complete blood cell counts, blood sugar levels, electrolyte levels, liver function tests, kidney function tests, and urinalysis, were normal (Table 1). A real-time reverse-transcription polymerase chain reaction (RT–PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was negative. Chest X-ray and brain computed tomography showed no obvious abnormalities.

| Parameter       | Result | Unit        | Normal Range          |
|-----------------|--------|-------------|-----------------------|
| BUN             | 15.2   | mg/dL       | 7–25                  |
| Creatinine      | 0.68   | mg/dL       | F: 0.44–1.03; M: 0.64–1.27 |
| eGFR            | 94.5   | ml/min/1.732 m² | 136–146         |
| Sodium          | 140.8  | mmol/L      | 136–146                |
| Potassium       | 4.1    | mmol/L      | 3.5–5.1                |
| Calcium         | 8.6    | mg/dL       | 8.6–10.3               |
| Chloride        | 105.9  | mmol/L      | 101–109                |
| GOT             | 17     | mmol/L      | Adult: ≤34             |
| GPT             | 21     | mmol/L      | Adult: ≤36             |
| Total bilirubin | 0.87   | mmol/L      | 0.3–1.2 (5 days-60 y) |
| Glucose         | 102.9  | mg/dL       | AC: 74–100 (≥18 y)PC: <140 (≥18 y) |
| White blood cell count | 8.01 | 10⁹/µL | M: 3.9–10.6; F: 3.5–11 |
| Red blood cell count | 4.5 | 10⁹/µL | M: 4.5–5.9; F: 4.0–5.2 |
| Hemoglobin      | 14.1   | g/dL        | M: 13.5–17.5; F: 12–16 |
| Hematocrit      | 44.4   | %           | M: 41–53; F:36–46     |
| MCV             | 98.7   | fl          | 80–100                 |
| MCH             | 31.3   | pg          | 26–34                  |
| MCHC            | 31.8   | g/dL        | 31–37                  |

BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; GOT: glutamyl oxaloacetic transaminase; GPT: glutamyl pyruvate transaminase; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; and MCHC: mean corpuscular hemoglobin concentration.
A lumbar puncture was performed, and cerebrospinal fluid (CSF) in Case 1 was analyzed. Laboratory tests revealed lymphocyte-predominant pleocytosis (white blood cell (WBC) count: 40/µL, 59% lymphocytes), an elevated protein level of 82.9 (reference range: 15–45) mg/dL, an elevated CSF/serum albumin ratio of 19.7 (reference range: 5–8) × 10⁻³, a normal glucose level of 61.72 (reference range: 40–70) mg/dL, and a normal immunoglobulin G (IgG) index of 0.32 (reference range: 0.0–0.7). The patient was initially diagnosed with encephalitis based on the following clinical symptoms: (1) altered mental status lasting ≥24 h with no alternative cause, (2) documented fever within 72 h, (3) new onset of focal neurological findings, and (4) laboratory results (WBC count ≥ 5/µL) [8]. Intravenous empiric antibiotics and antiviral drugs, including ceftriaxone, vancomycin, and acyclovir, were initiated to treat acute encephalitis with an unknown cause. After 2 days of treatment, the patient’s symptoms persisted, without any improvement. CSF microbiological tests were negative for herpes simplex virus-1 (HSV-1), HSV-2, tuberculosis (TB), and bacterial culture; the venereal disease research laboratory (VDRL) test was also negative. Additionally, the patient’s influenza A and B viral nasal swab PCR tests, CSF cytological examination, and autoimmune encephalitis panel were negative (Table 2). Moreover, the patient’s blood tests for common pathogens and auto-antibodies (blood culture, virus serology, rheumatoid factor, antinuclear antibody (ANA), antithyroid peroxidase antibody, antimitochondrial, etc.) were all negative (Table 3). Brain magnetic resonance imaging (MRI) with contrast showed unremarkable findings. Finally, a diagnosis of COVID-19 vaccine-induced acute encephalitis was made. Dexamethasone (40 mg per day) was added on the 3rd day, and the patient exhibited a dramatic improvement on the next day. She regained normal cognitive function and displayed no further neurological impairment. We maintained treatment with intravenous steroids and gradually halved the dosage every 3 days. The patient was uneventfully discharged on the 13th day.

Table 2. Results of the cerebrospinal fluid (CSF) examination (Case 1).

| Parameter                        | Result | Unit       | Normal Range |
|----------------------------------|--------|------------|--------------|
| White blood cells                | 40     | count/µL   | 0–5          |
| Neutrophils                      | 0      | %          |              |
| Eosinophils                      | 0      | %          |              |
| Monocytes                        | 41     | %          |              |
| Lymphocytes                      | 59     | %          |              |
| Red blood cells                  | 26     | count/µL   | 0–5          |
| pH                               | 7.28   |            | 7.35–7.4     |
| Total protein                    | 82.9   | mg/dL      | 15–45        |
| LDH                              | 16.1   | U/L        | <40          |
| Chloride                         | 126.5  | mmol/L     | 118–132      |
| Glucose                          | 61.7   | mg/dL      | 40–70        |
| Albumin                          | 55.1   | mg/dL      | 10–30        |
| CSF/serum albumin ratio (× 10⁻³) | 19.7   |            | 5–8          |
| IgG index                        | 0.32   |            | 0–0.7        |
| HSV 1 PCR                        | Not detected |         |              |
| HSV 2 PCR                        | Not detected |         |              |
| VDRL test                        | Negative |          |              |
| CSF bacterial culture            | No growth |         |              |
| Gram stain                       | Negative |          |              |
| Indian Ink                       | Not found |          |              |
| Parameter                  | Result   | Unit    | Normal Range       |
|----------------------------|----------|---------|--------------------|
| TB PCR DNA                 | Negative |         |                    |
| Acid-Fast Stain            | Not found|         |                    |
| TB culture                 | Negative |         |                    |
| Anti-NMDR                  | Negative |         |                    |
| Anti-AMPAR1                | Negative |         |                    |
| Anti-AMPAR2                | Negative |         |                    |
| Anti-GABABR                | Negative |         |                    |
| Anti-LGI1                  | Negative |         |                    |
| Anti-CASPR2                | Negative |         |                    |

LDH: lactate dehydrogenase; HSV: herpes simplex virus; VDRL: venereal disease research laboratory; TB PCR: tuberculosis polymerase chain reaction; Anti-NMDR: anti-N-methyl-d-aspartate receptor; Anti-AMPAR: anti-α-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid receptor; Anti-GABABR: anti-γ-gamma-aminobutyric acid receptor; Anti-LGI1: anti-leucine-rich glioma inactivated-1; and Anti-CASPR2: anti-contactin-associated protein-like 2.

**Table 3.** Results of encephalitis-related blood tests (Case 1).

| Parameter                  | Result   | Unit    | Normal Range          |
|----------------------------|----------|---------|-----------------------|
| HSV-1 IgG                  | Negative |         |                       |
| HSV-1 IgM                  | Negative |         |                       |
| HSV-2 IgG                  | Negative |         |                       |
| HSV-2 IgM                  | Negative |         |                       |
| CMV IgM                    | Negative |         |                       |
| EB-VCA IgM                 | Negative |         |                       |
| HBsAg                      | Nonreactive|        |                       |
| Anti-HCV                   | Nonreactive|        |                       |
| RSV screening test         | Not detected|      |                       |
| Adenovirus Ag              | Not detected|      |                       |
| Rotavirus Ag               | Not detected|      |                       |
| PRP                        | Nonreactive|        |                       |
| TPPA                       | Nonreactive|        |                       |
| Cryptococcus Ag            | Not detected|      |                       |
| Blood culture (2 sets)     | No growth|         |                       |
| ANA                        | 1:80     |         | 1:40–1:1280          |
| Anti-dsDNA                 | 1.4      | U/mL    | < 2.0               |
| TSH                        | 0.262    | µL/U/mL | 0.45–4.94          |
| T3                         | 0.66     | ng/mL   | 0.64–1.52           |
| Free T4                    | 1.7      | ng/mL   | 0.89–1.79          |
| Anti-TPO Ab                | <5       | IU/mL   | <5                  |
| Anti-thyroglobulin Ab      | <15      | IU/mL   | <115                |
| Anti-mitochondrial Ab      | Negative |         |                      |

HSV: herpes simplex virus; Ig: immunoglobulin; CMV: cytomegalovirus; EB-VCA: Epstein–Barr virus viral-capsid antigen; HBsAg: hepatitis B surface antigen; Anti-HCV: anti-hepatitis C virus; RSV: respiratory syncytial virus; PRP: rapid plasma reagin; TPPA: treponema pallidum particle agglutination assay; ANA: antinuclear antibodies; Anti-dsDNA: anti-double-stranded deoxyribonucleic acid; TSH: thyroid stimulating hormone; and Anti-TPO Ab: Anti-thyroid peroxidase antibody.
2.2. Case 2

A 21-year-old male was admitted to the Emergency Department due to coma approximately one week after receiving the mRNA-1273 (SPIKEVAX™) vaccination. The patient had no history of seizures, and the family history was unremarkable. RT–PCR results for SARS-CoV-2 were negative. Complete blood counts and electrolytes were normal (Table 4). Chest X-ray, brain computed tomography, and electrocardiography showed no obvious abnormalities. He experienced an episode of status epilepticus in the emergency department and was transferred to the intensive care unit (ICU) for further management. A lumbar puncture was performed. CSF analysis revealed no pleocytosis, an elevated protein level of 65.5 (normal range: 15–45) mg/dL, and an elevated microalbumin level of 37 (normal range: <6.5) pg/dL (Table 5). Although brain MRI with contrast was unremarkable, electroencephalography (Supplementary Figure S1) revealed a continuous diffuse slowing in the theta and delta ranges, indicating moderate diffuse cerebral dysfunction (3rd hospital day). The cerebral perfusion scan with single-photon emission computed tomography (SPECT) indicated hypoperfusion in the right temporal region (Supplementary Figure S2), which was compatible with the probable seizure origin. The patient was also diagnosed with encephalitis based on the following clinical symptoms: (1) altered mental status lasting ≥24 h with no alternative cause, (2) generalized seizures not fully attributable to a pre-existing seizure disorder, (3) abnormal electroencephalography results, and (4) abnormal neuroimaging of the brain parenchyma [8]. The test results for HSV, VDRL, TB, and other bacterial and fungal cultures of the CSF were all negative (Table 5). Similar to Case 1, the results of Case 2’s blood tests for common pathogens and auto-antibodies were also negative (Table 6). The autoimmune antibody tests for limbic encephalitis (anti-NMDR, anti-AMPAR1, anti-AMPAR2, anti-GABABR, anti-LGI1, anti-CASPR2) were also negative. A final diagnosis of COVID-19 vaccine-induced encephalitis complicated by seizures was made.

Table 4. Results of biochemistry tests and complete blood counts (Case 2—upon admission).

| Parameter       | Result | Unit       | Normal Range                  |
|-----------------|--------|------------|-------------------------------|
| BUN             | 12.8   | mg/dL      | 7–25                          |
| Creatinine      | 0.92   | mg/dL      | F: 0.44–1.03; M: 0.64–1.27    |
| eGFR            | 109.3  | ml/min/1.732 m² |                      |
| Sodium          | 136.2  | mmol/L     | 136–146                       |
| Potassium       | 4.2    | mmol/L     | 3.5–5.1                       |
| GOT             | 20.9   | mmol/L     | Adult: ≤34                    |
| GPT             | 33.5   | mmol/L     | Adult: ≤36                    |
| CRP             | 2.68   | ng/mL      | <5                            |
| Glucose         | 103.0  | mg/dL      | AC: 74–100 (≥18 y); PC: <140 (≥18 y) |
| White blood cells | 5.23  | 10^3/μL    | M: 3.9–10.6; F: 3.5–11        |
| Red blood cells | 5.38   | 10^6/μL    | M: 4.5–5.9; F: 4.0–5.2        |
| Hemoglobin      | 15.1   | g/dL       | M: 13.5–17.5; F: 12–16        |
| Hematocrit      | 45.8   | %          | M: 41–53; F: 36–46            |
| MCV             | 85.1   | fl         | 80–100                        |
| MCH             | 28.1   | pg         | 26–34                         |
| MCHC            | 33.0   | g/dL       | 31–37                         |
| Platelet count  | 241    | 10^3/mm   | 150–400                       |

BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; GOT: glutamyl oxaloacetic transaminase; GPT: glutamyl pyruvate transaminase; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; and MCHC: mean corpuscular hemoglobin concentration.
Table 5. Results of cerebrospinal fluid (CSF) examinations (Case 2).

| Parameter                          | Result   | Unit   | Normal Range |
|-----------------------------------|----------|--------|--------------|
| White blood cells                 | <5       | count/µL | 0–5          |
| Red blood cells                   | 15       | count/µL | 0–5          |
| pH                                | 7.33     |        | 7.35–7.4     |
| Total protein                     | 65.5     | mg/dL  | 15–45        |
| LDH                               | 16.0     | U/L    | <40          |
| Chloride                          | 125.7    | mmol/L | 118–132      |
| Glucose                           | 76.7     | mg/dL  | 40–70        |
| Albumin                           | 37.0     | mg/dL  | 10–30        |
| CSF/serum albumin ratio (× 10⁻³)  | 8        |        | 5–8          |
| IgG index                         | 0.60     |        | 0–0.7        |
| HSV 1 PCR                         | Not detected |
| HSV 2 PCR                         | Not detected |
| Influenza A                       | Not detected |
| Influenza B                       | Not detected |
| VDRL test                         | Negative |
| CSF bacterial culture             | No growth |
| Gram stain                        | Negative |
| Indian Ink                        | Not found |
| TB PCR DNA                        | Negative |
| Acid-Fast Stain                   | Not found |
| TB culture                        | Negative |
| Anti-NMDR                         | Negative |
| Anti-AMPAR1                       | Negative |
| Anti-AMPAR2                       | Negative |
| Anti-GABABR                       | Negative |
| Anti-LGI1                         | Negative |
| Anti-CASPR2                       | Negative |

LDH: lactate dehydrogenase; HSV: herpes simplex virus; VDRL: venereal disease research laboratory; and TB PCR: tuberculosis polymerase chain reaction. Anti-NMDR: anti-N-methyl-d-aspartate receptor; Anti-AMPAR: anti-α-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid receptor; Anti-GABABR: anti-γ gamma-aminobutyric acid receptor; Anti-LGI1: anti-leucine-rich glioma inactivated-1; and Anti-CASPR2: anti-contactin-associated protein-like 2.

To prevent oxidative stress and maintain cellular homeostasis, controlling status epilepticus, intravenous levetiracetam and valproate sodium were administered. His seizures persisted in the ICU, and pulse corticosteroid therapy was administered on the 6th day of hospitalization with 1000 mg of intravenous methylprednisolone. We gradually halved the dosage every 3 days during the total 21-day hospital stay (14-day ICU stay). The patient’s clinical condition improved significantly after steroid administration. He was seizure-free during the rest of the hospital stay as well as at a 3-month outpatient department (OPD) follow-up.
Table 6. Results of encephalitis-related blood tests (Case 2).

| Parameter                | Result  | Unit         | Normal Range |
|--------------------------|---------|--------------|--------------|
| HSV-1 IgG                | Negative|              |              |
| HSV-1 IgM                | Negative|              |              |
| HSV-2 IgG                | Negative|              |              |
| HSV-2 IgM                | Negative|              |              |
| CMV IgM                  | Negative|              |              |
| EB-VCA IgM               | Negative|              |              |
| Varicella zoster IgG     | Negative|              |              |
| Blood culture (2 sets)   | Negative|              |              |
| ANA                      | 1:40 (negative) | |              |
| Anti-dsDNA               | 0.5     | U/mL         | <92.6        |
| TSH                      | 0.113   | µl/U/mL      | 0.35–4.94    |
| Free T4                  | 1.43    | ng/mL        | 0.89–1.79    |
| Anti-Thyroglobulin Ab    | 15      | IU/mL        | <115         |

HSV: herpes simplex virus; Ig: immunoglobulin; CMV: cytomegalovirus; EB-VCA: Epstein–Barr virus viral-capsid antigen; ANA: antinuclear antibodies; Anti-dsDNA: anti-double-stranded deoxyribonucleic acid; TSH: thyroid stimulating hormone; and Anti-TPO Ab: Anti-thyroid peroxidase antibody.

3. Discussion

Given the absence of evidence of infection and the dramatic improvement after receiving corticosteroid treatments in both cases, we assumed that an immune-mediated mechanism was responsible for the presentation of acute encephalitis in both patients. In addition, both patients failed to meet the clinical diagnostic criteria for paraneoplastic or autoimmune encephalitis [9]. Therefore, we believe that the COVID-19 vaccine is the only possible cause of acute encephalitis in our patients, given the temporal proximity of receiving the COVID-19 vaccine and the lack of other risk factors for encephalitis.

A variety of postvaccination neurological complications have been reported since the introduction of the COVID-19 vaccines, but the underlying pathological mechanism remains unclear [1–4,10–23]. In addition to vaccines for COVID-19, postvaccination encephalitis has also been reported in association with several other vaccines, including those for measles, yellow fever, and smallpox [24]. mRNA vaccines consist of nucleoside-modified SARS-CoV-2 mRNA, which is translated into the SARS-CoV-2 spike protein by the host’s ribosomes, thus activating the adaptive immune response. However, exposed mRNA or vaccine components may be detected as antigens in certain individuals, triggering aberrant proinflammatory cytokine cascades and activation of immune signaling pathways [1–6]. These responses may result in elevated levels of circulating cytokines, inflammatory symptoms, and secondary organ damage. The underlying pathophysiology of cytokine-related neurotoxicity may resemble immune effector cell-associated neurotoxicity syndrome [25]. Furthermore, the spike protein alone can disrupt the blood–brain barrier (BBB), resulting in an increased BBB permeability, which may allow the overproduced inflammatory substances to enter the central nervous system. The elevation of the CSF/serum albumin ratio in both patients indicated impairment of the BBB, possibly due to disruption of cerebrovascular endothelial cells by the spike protein [26–28]. This brief report does not challenge the benefits of vaccination, but it does suggest caution and can guide management and provide prognosis for such patients. Larger epidemiological studies or meta-analyses are needed to understand the underlying mechanisms of postvaccination encephalitis. Presently, the benefits of COVID-19 vaccination outweigh any potential risks. The innate immune response of these two may explain this phenomenon, but further studies are needed to clarify the pathophysiology. We also reviewed the literature and
compared clinical manifestations, management, and outcomes in patients with COVID-19 mRNA vaccine-induced acute encephalopathies (Table 7).

Table 7. Literature review of COVID-19 mRNA vaccine-induced acute encephalopathies.

| Ref. | Diagnosis/ Clinical Feature | Vaccine/ Age and Sex/ Duration after Vaccination | Relevant Laboratory Data | Examinations/Images | Treatment |
|------|----------------------------|-----------------------------------------------|-------------------------|---------------------|-----------|
| [2]  | Aseptic meningitis         | 1st Comirnaty® BNT162b2 (BioNTech and Pfizer) | CSF exam:              | EEG: (-)            | Acyclovir and methylprednisolone 500 mg/day (3rd day) |
|      | - headache - fever (38 °C) | 42 F/7 days                                  | - protein level: normal | CT: (-)             | Improved after steroid treatment; discharge on 5th day |
|      |                            |                                              | - pleocytosis: 528/3 mm³ | MRI: (-)            |           |
|      |                            |                                              | - glucose level: (+)    |                     |           |
|      |                            |                                              | - IgG index: normal     |                     |           |
| [3]  | Acute disseminated encephalomyelitis | 1st Comirnaty® BNT162b2 (BioNTech and Pfizer) | CSF exam:              | EEG: normal         | Prednisone: 75 mg/day |
|      | - unsteady gait - clumsiness of left arm | 56 F/14 days                                | - protein level: normal | MRI (FLAIR):        | Improvement 50 days after onset |
|      |                            |                                              | - no pleocytosis        | hyperintensity      |           |
|      |                            |                                              | - glucose level: normal | involving the left cerebellar peduncle and supratentorial areas |           |
|      |                            |                                              | Cytokine level          |                     |           |
|      |                            |                                              | - IL-10 CSF/serum ratio: 1.47 |                     |           |
|      |                            |                                              | - IFN-gamma CSF/serum ratio: 3.66 |                     |           |
|      |                            |                                              | - IL-6 CSF/serum ratio: 6.64 |                     |           |
|      |                            |                                              | Microbiological studies: negative AE antibodies: negative Demyelinating disorder-related antigens: negative | | |
|      |                            |                                              | EEG: (-)                | CT: (-)             | Quetiapine: 12.5 mg HS |
|      |                            |                                              | MRI: (-)                |                     | Gradual improvement over the next 48 h |
| [10] | Delirium                  | 1st Comirnaty® BNT162b2 (BioNTech and Pfizer) | CSF exam: (-)          | EEG: (-)            | Ibuprofen |
|      | - confusion - fluctuating attention - inversion of the sleep-wake cycle | 89 M/1 day               | Microbiological studies: (-) | CT: (-)             | Ceased spontaneously |
|      |                            |                                              | EEG: (-)                | MRI: (-)            |           |
| [11] | Movement disorder         | 2nd Comirnaty® BNT162b2 (BioNTech and Pfizer) | CSF exam: (-)          | EEG: (-)            | Ceftriaxone, acyclovir and methylprednisolone 1 g/day (6th day) |
|      | - restless movement - fever | 36 F/12 h                                   | Microbiological studies: (-) | CT: (-)             | Dramatic improvement after steroid treatment |
|      |                            |                                              | EEG: (-)                | MRI: (-)            |           |
|      |                            |                                              | - protein level: elevated 0.76 gm/L |                     |           |
|      |                            |                                              | - no pleocytosis        |                     |           |
|      |                            |                                              | - glucose level: normal |                     |           |
| [4]  | Encephalopathy            | 1st SPIKEVAX™ mRNA-1273 (Moderna) 32 M/2 days | CSF exam:              | EEG: slowed         | Ceftriaxone, lorazepam (2nd day) and fosphenytoin (2nd day) |
|      | - disoriented - amnesic   |                                              | - background activity  | background activity | Significant improvement after anticonvulsant treatment |
|      |                            |                                              | CT: (-)                | CT: normal          |           |
|      |                            |                                              | MRI: normal            | MRI: normal         |           |
| [12] | Encephalopathy            | 1st SPIKEVAX™ mRNA-1273 (Moderna) 86 F/7 days | CSF exam: (-)          | EEG: nonconvulsive | Ceftriaxone, lorazepam (2nd day) and fosphenytoin (2nd day) |
|      | - acute confusion - visual hallucination |                                              | Microbiological studies: negative | focal status epilepticus | Significant improvement after anticonvulsant treatment |
|      |                            |                                              | EEG: nonconvulsive focal status epilepticus | CT: normal          |           |
|      |                            |                                              | Microbiological studies: negative | MRI: normal         |           |
Table 7. Cont.

| Ref. | Diagnosis/ Clinical Feature | Vaccine/ Age and Sex/ Duration after Vaccination | Relevant Laboratory Data | Examinations/Images | Treatment |
|------|-----------------------------|-----------------------------------------------|-------------------------|---------------------|-----------|
| ![image](https://www.mdpi.com/article/10.3390/vaccines10081230/s1) | Encephalopathy - restlessness - cognitive deficits | 1st SPIKEVAX™ mRNA-1273 (Moderna) 73 M/7 days | CSF exam: (-) Microbiological studies: negative | EEG: nonconvulsive status epilepticus CT: normal MRI: normal | Ceftriaxone, lorazepam, and levetiracetam ○ Significant improvement after anticonvulsant treatment |
| ![image](https://www.mdpi.com/article/10.3390/vaccines10081230/s1) | Encephalitis Sweet's syndrome - confusion - orofacial movements - myoclonus - fever - generalized rash | 1st SPIKEVAX™ mRNA-1273 (Moderna) 77 M/1 day | CSF exam: - protein level: elevated (124 m/dL) - pleocytosis (120 × 10⁶/L) - glucose level: normal | EEG: generalized slow background in the theta range, with state changes and reactivity but no sleep features CT: normal MRI: normal | Vancomycin, ampicillin cefepime, ceftriaxone doxycycline, acyclovir and methylprednisolone 1 g/day ○ Returned to baseline before the 4th dose of methylprednisolone |

(-): Laboratory data or examinations not mentioned in the references; CSF: cerebrospinal fluid; EEG: electroencephalogram; CT: computed tomography; MRI: magnetic resonance imaging; FLAIR: fluid attenuated inversion recovery; IL: interleukin; IFN: interferon; AE: autoimmune encephalitis; and HS: hora somni (taken at bedtime).

In summary, COVID-19 vaccinations generate antigens that may be recognized as potential pathogens by pattern-recognition receptors on resident stromal cells and circulating immune cells. Induction and transcription of specific genes may ensue, triggering the synthesis and release of pyrogenic cytokines, including interleukin [IL]-1, IL-6, tumor necrosis factor-alpha [TNF-α], and prostaglandin-E2, into the bloodstream, mimicking the response to natural infection. The cytokine-mediated inflammatory process is proposed to be the key pathophysiological mechanism underlying COVID-19 vaccine-related encephalitis [1–7].

4. Conclusions

COVID-19 vaccine-induced acute encephalitis is rare but may occur in clinical practice. This condition is characterized by activation of the immune response, triggering cytokine storm-mediated inflammation; misdiagnosis or delayed diagnosis may lead to fatal complications. Appropriate corticosteroid administration may be an effective treatment method in these patients [1–4,13–17].

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/vaccines10081230/s1; Supplementary Figure S1. Electroencephalogram demonstrated a continuous diffuse slowing in the theta and delta ranges (Case 2). Supplementary Figure S2. The cerebral perfusion scan with single-photon emission computed tomography (SPECT) that indicated hypoperfusion in the right temporal region (Case 2).

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