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Case Report

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Cerebrospinal fluid cytokine profile in autoimmune encephalitis related to covid-19 vaccination

Abstract

Encephalitis is an inflammatory disease of the central nervous system most usually caused by a viral infection. Autoimmune encephalitis is also common. The mechanism of action of various vaccines aim to elicit immune response. Major neurological complications indicative of vaccination-related autoimmune encephalitis and acute encephalitis after the first dose of mRNA COVID-19 vaccines have been reported. We present a 59-year-old female patient with subtle initiation of cognitive and behavioral deterioration two months after the second dose of SARSCoV-2 vaccine. Diagnostic work-up was suggestive of encephalitis. The findings fulfilled the criteria for possible autoimmune encephalitis related to prior vaccination with detected cytokine elevation.

Keywords: Covid-19, vaccine, autoimmune encephalitis, interleukin, electroencephalography

Volume 8 Issue 3 - 2023

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Received: December 12, 2023 | **Published:** December 27, 2023

Abbreviations: CNS, central nervous system; HSV, herpes simplex virus; AIE, autoimmune encephalitis; EEG, electroencephalography; ADEM, acute disseminated encephalomyelitis; GBS, guillain–barré syndrome; MMSE, mini mental state examination; PCR, polymerase chain reaction; CRP; c-reactive protein; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; CJD, creutzfeldt-jakob disease

Introduction

Encephalitis is an inflammatory disease of the central nervous system (CNS). Viral infection is the most common cause (most often by herpes simplex virus (HSV), Autoimmune encephalitis (AIE) is also common.[1] Encephalitis is a neurological emergency that can cause severe cognitive impairment or death if not treated promptly. The diagnosis is based on at least two of the following criteria: fever, seizures, focal neurological findings by a cause of brain parenchymal damage, electroencephalography (EEG) findings indicative of encephalitis, cerebrospinal fluid pleocytosis (more than four white cells per _L), or neuroimaging findings suggestive of encephalitis.[2] The mechanism of action of various vaccines aim to elicit immune response. The mRNA-based vaccines (PfiZerBioNTech and Moderna) consist of genetically modified viruses RNA or DNA that produces a viral protein.[3] Altered mental status, autoimmune encephalitis (AIE), acute disseminated encephalomyelitis (ADEM), dizziness, myalgia, fatigue, cognitive impairment, gait instability, facial palsy, Guillain–Barré syndrome (GBS), convulsions, strokes, transverse myelitis, chronic fatigue syndrome, and acute encephalopathy are amongst the neurological complications, reported related to Covid-19 vaccination.

Major neurological complications indicative of vaccination-related autoimmune encephalitis and acute encephalitis after the first dose of mRNA COVID-19 vaccines have been reported recently. Abdelhady et al.[1] cite reports on 19,529 neurological adverse events after COVID-19 vaccination, including encephalitis, acute disseminated encephalomyelitis (ADEM) after the viral vector based vaccines or inactivated viral vaccine (AstraZeneca, Sputnik V, Sinopharm), temporal association between ChAdOx1 nCov-19 vaccination (AstraZeneca) and encephalitic symptoms, several cases of mRNA-1273 vaccine-induced encephalitis and status epilepticus.[1] The underlying mechanism is still not clarified; some researchers theorized that SARS-CoV-2 spike protein produced by mRNA-based vaccines may function as a catalyst for the inflammatory processes that ensue, particularly in autoimmune encephalitis[1] Consequent activation of the immune system goes with cytokine secretion. We present a case of autoimmune encephalitis related to prior SARSCoV-2 mRNA vaccination with detected cytokine elevation.

Case presentation

A 59-year-old female patient living alone with hypertension and a history of metal osteosynthesis after femoral fracture presented with steady progressive deterioration of behavior and memory loss two months after the second dose of SARS-CoV-2 mRNA-based vaccine (Pfizer). She was not aware of the problem, trying to explain inappropriate clothing or reaction with daily over exhaustion. Her family noticed certain behavior and memory deterioration a month after the vaccination. The patient's condition progressively worsened. She could not dress herself properly at the time of first visit to the neurologist's office. There was memory impairment, severe loss of attention and concentration (Mini Mental State Examination (MMSE) = 25/30 points), agitation. Two weeks later at the second admission to clinic MMSE graded 23/30 points. The patient was admitted into the neurological department. She was alert and afebrile. Routine blood tests, urine analysis and ECG were within normal limits. Neurological examination revealed no focal neurological signs apart from the cognitive and psychological impairment. Polymerase chain reaction (PCR) and real-time PCR for SARS-CoV-2 were negative. Computer tomography of the brain without contrast showed brain atrophy relevant to the patient's age.

Doppler sonography of brain vessels found no significant changes. Electroencephalography (EEG) revealed abnormal recordings with generalized slow theta waves (5-7Hz). Permanent theta waves, single polymorphic delta waves and high amplitude triphasic sharp waves were registered in the frontotemporal regions bilaterally, predominantly on the right (Figure 2A). During admission, extensive diagnostic workup was performed, including peripheral blood, kidney and liver function, and thyroid hormone levels, all of which were within normal limits. Erythrocyte sedimentation rate and C-reactive protein (CRP) were elevated (52mm/h and 8.7mg/l respectively) (Table 1). The control test four days later registered sedimentation rate 33mm/h and CRP

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4.9mg/l. Three weeks after an immunosuppressive treatment with methylprednisolone the sedimentation rate was 78.0mm/h and CRP was 16.2mg/l. Vit B12 and folic acid were below the normal limits (159.0pg/ml and 5.61ng/ml) . She was admitted to the department two weeks later because of the progression in behavioral deterioration. Neurological examination revealed no focal neurological signs. Magnetic resonance imaging (MRI) with angiography, performed three months after the initial symptoms, revealed no brain tumor, vascular or inflammatory changes, no hyperintense lesions (Figure 1).

EEG registered theta waves (5-7 Hz) with delta waves. Symmetrical frontotemporal high amplitude triphasic sharp waves and episodic disorganized alfa activity (9 Hz) in the occipital regions. The triphasic sharp waves tend to generalized during hyperventilation. The findings correlated with clinical diagnosis of dementia (Figure 2B). A lumbar puncture was performed. The cerebrospinal fluid (CSF) analysis showed no pleocytosis but elevated CSF protein (0.635mg/l*). CSF immunoelectrophoretic analysis showed absence of oligoclonal bands (Table 1). The rest of the CSF parameters were within normal limits. Serological testing for viral infection registered IgG antibodies indicative for past infections. Posvaccinational SARS-CoV-2 IgG antibodies were detected. The patient was diagnosed with viral encephalitis. She underwent treatment with immunosuppressive therapy with a total of 2.5g methylprednisolone over 5 days. There was no clinical improvement. The following CSF analysis detected slight elevation of CSF protein three weeks later (0.654g/l) and white blood cell count 6.10ˆ6/l. EEG activity was abnormal after the steroid administration (Figure 2C). ProcartaPlex Human Cytokine panel 10-plex was performed. The test detected elevated levels of Interleukin-1beta (IL- β), Interleukin-10 (IL-10), GMCSF, Interferon- gamma (INF- γ), Tumor necrosis factor-alpha (TNF- α), Interleukin-4 (IL-4), and Interleukin-8 (IL8). They are significant for an acute inflammatory immunological reaction. Assuming possible postvaccination autoimmune encephalitis, Immunoglobulin 400mg/kg was administered. The patient presented no improvement at discharge. There was progression in cognitive deterioration (MMSE= 21/30 points). She could not collaborate with any further investigations. The family reported worsening of symptoms over the next months with severe cognitive decline, hallucinations, and behavioral deterioration with apathy, mutism, and aggression. The patient did not survive and passed away eight months later.

Table 1 Study of laboratory profile

Blood and urine investigation	Cell count, hemoglobin, hematocrit, glucose, **Sedimentation rate, CRP**, albumin, total serum protein, urea, creatin, cholesterol, triglycerides, bilirubin, ASAT, ALAT, CPK, LDH, TSH, K, Na, Ca, Cl, UIBC, Ferritin, Procalcitonin, **Folic acid, Vitamin B12**, Urine analysis, hemostasis		
CSF analysis	White blood cell count 3.10ˆ6/l*, Red blood cell count 0.000 10ˆ12/l*, Segmentocytes 0%, Monocytes 0%, Lymphocytes single %, **Total Proteins 0.635mg/l***, Glucose 5.66mmol/l mg/dl, Chloride 122.3mmol/l Immunoelectrophoresis – no oligoclonal bands White blood cell count 6.10ˆ6/l**, Red blood cell count 0.002 10ˆ12/l**, Segmentocytes 40%, Monocytes 0%, Lymphocytes 60 %, **Total Proteins 0.654mg/l****, Glucose 3.66mmol/l mg/dl, Chloride 127.0mmol/l Immunoelectrophoresis – no oligoclonal bands		
CSF virus investigation	Varicella Zoster Virus, Herpes Simplex Virus, Cytomegalovirus, Adenovirus, Entero Virus, Parecho Virus, Epstein-Barr Virus, Human Herpes Virus- type 6, Human Herpes Virus- type7, B-19 Parvovirus, Covid-19-negative		
Serum virus investigation	Varicella Zoster Virus (VZV) IgM negative, **IgG 1591** Herpes Simplex Virus 1/2 (HSV 1/2) IgM negative, **IgG 11.9** Cytomegalovirus (CMV) IgM negative, **IgG 177** Adenovirus IgM, IgG negative Influenza A, B IgM, IgG negative Enterovirus IgM, IgG negative VCA >>750 Human Immunodeficiency Virus (HIV) negative Syphilis RPR negative Lyme disease IgM, IgG negative Covid-19 IgM negative, **IgG 303**		
CSF Cytokines (pg/ml)	IL-1 β	21.37*	0.58**
	IL-10	33.20*	30.92**
	IL-6	21.42*	13.5 **
	GM-CSF	7.07*	0.49 **
	IL-5	-	2.72 **
	INF-γ	113.01*	91.09 **
	TNF- α	90.98*	6.29 **
	IL-2	1.90*	3.98**
	IL-4	14.35*	16.96**
	IL-8	2483.29*	219.07**

The parameters with abnormal ranges are in boldface. CRP- C-reactive protein, CSF- cerebrospinal fluid, *- before steroid administration, **- after steroid administration

Citation: Petrova VG, Prinova KG. Cerebrospinal fluid cytokine profile in autoimmune encephalitis related to covid-19 vaccination. *Int Phys Med Rehab J.* 2023;8(3):223–227. DOI: 10.15406/ipmrj.2023.08.00364

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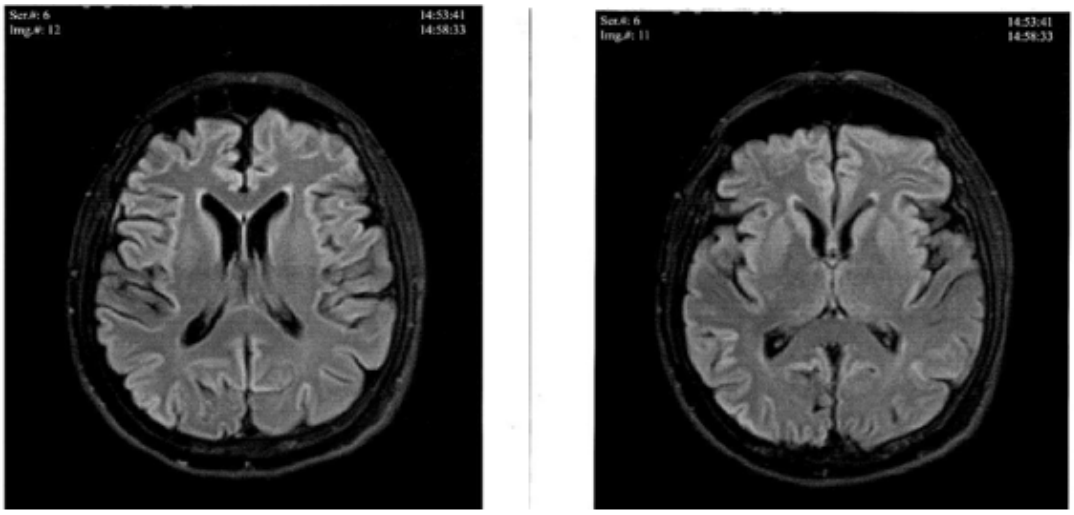
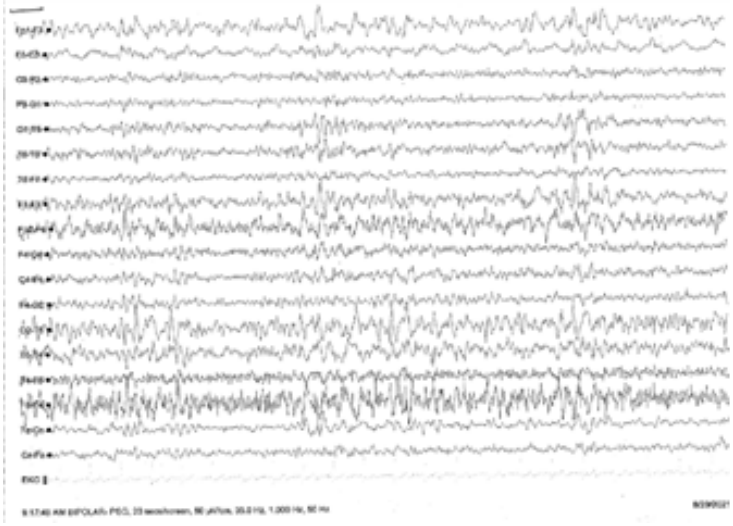
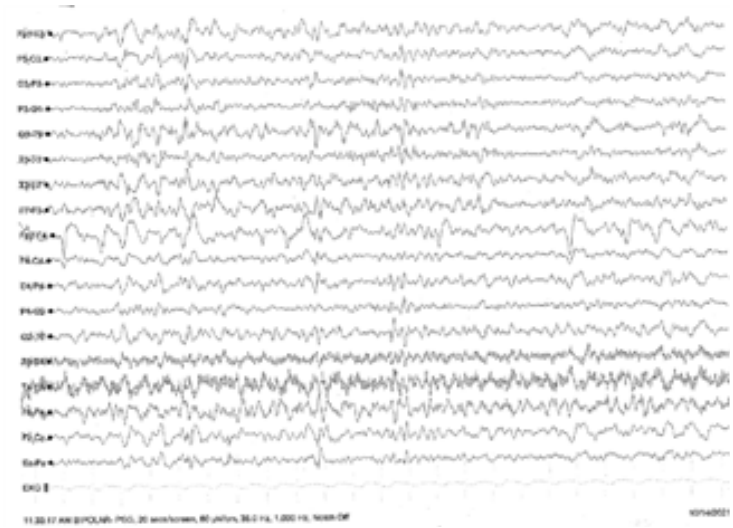


Figure 1 T1w images of MRI performed three months after the initial symptoms. There is no supra- and infratentorial evidence of acute disseminated encephalomyelitis, vasculitis, or neoplasms.

A)



B)



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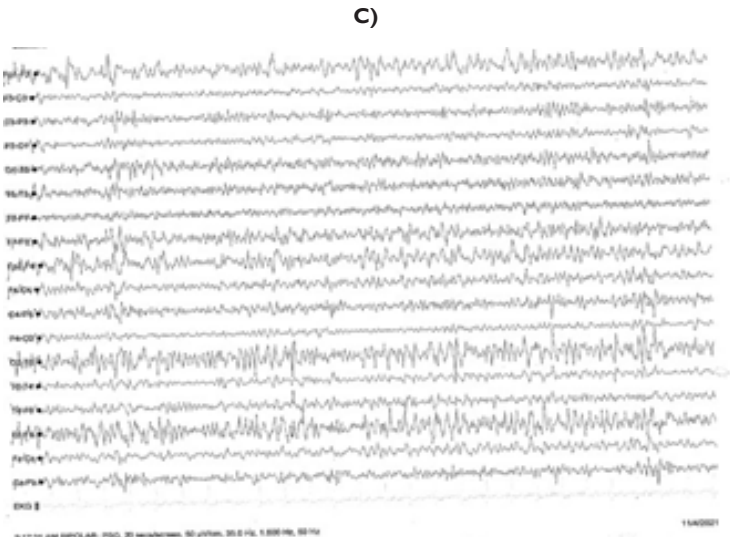

Figure 2 A) EEG on the day of first admittance to hospital; B) EEG two weeks later before the immunosuppressive treatment with methylprednisolone; C) EEG three weeks later before the immunoglobulin treatment.

Discussion

We present a case of post- vaccinal possible autoimmune encephalitis with temporal correlation to SARS-CoV-2 vaccine. The patient presented with subacute progression of cognitive decline and behavioral deterioration two months after a second dose of COVID-19 mRNA vaccine. The condition progressed with the patient becoming demented and experiencing troubles in daily activities. She became dependent on relatives for toilet, feeding and dressing three months later. There was no history of concomitant diseases. It is possible to misdiagnose autoimmune encephalitis due to subacute onset and temporal difference between the first subtle symptoms and the diagnosis. It usually takes weeks to three months to reach the diagnosis.[4] Clinical judgment is essential for AIE recognition. A constellation of neuropsychiatric symptoms, lab studies, neuroimaging, and EEG is in help to answer the diagnostic criteria. A consensus identifies AIE as possible and definite.[5]

Possible AIE is evaluated if three of the following criteria are met: a) subacute onset (usually within a few weeks but less than three months) with change in the level of consciousness or personality; limbic system involvement including working memory deficits, lethargy, or psychiatric manifestations; b) At least one of the following: new focal clinical CNS findings, seizures not explained by a previously diagnosed seizure disorder, CSF pleocytosis (>5 WBC per mm3), MRI brain findings suggestive of encephalitis; c) reasonable exclusion of possible alternative causes: infectious meningoencephalitis, septic encephalopathy, metabolic encephalopathy, toxins, cerebrovascular disease, neoplasms, Creutzfeldt-Jakob disease (CJD), epileptic disorders, Hashimoto encephalopathy, autoimmune disorders, mitochondrial/metabolic storage disorders.[4] We excluded infectious encephalitis as a differential before considering AIE. Serum investigation registered past infections with VZV, HSV, CMV. There was no data for acute viral or bacterial infection. There were normal levels of glucose and Chloride. CJD did not meet the criteria.[6] The patient developed subtle progressive CNS symptoms. The repeated CSF analysis proved pleocytosis. We found elevated CSF protein together with significant elevation of cytokines. Although immunoelectrophoretic analysis showed no oligoclonal bands, the cytokine evaluation revealed acute inflammatory immune activation. We registered elevation of certain cytokines. A concise review of their functions supports the inflammatory activation assumption.

Tumor necrosis factor alpha (TNF-α) causes the necrosis of tumors. It is a pathological component of autoimmune diseases. Tumor necrosis factor alpha binds to two different receptors, which initiate signal transduction pathways. These pathways lead to various cellular responses, including cell survival, differentiation, and proliferation. The inappropriate or excessive activation of TNF-α signaling is associated with chronic inflammation and can eventually lead to the development of pathological complications such as autoimmune diseases. In addition to its proinflammatory potential, TNF- α applies pleiotropic effects on various cell models. It is a significant factor in the pathogenesis of autoimmune diseases.[7] Tumor necrosis factor- α level before methylprednisolone administration was more than ten times higher (90.98pg/ml*) than after the immunosuppressive treatment (6.29pg/ml **). This is indicative for intense immune activation. Interleukin-4 is important in the development of certain immune disorders, particularly allergies and some autoimmune diseases.[8] The Th2 cytokine IL-4 is significant in cognition.[9] Interleukin-4 receptor subunit alpha (IL-4Rα) expression at the presynapse and the connection to presynaptic molecules indicate the involvement of IL-4Rα signaling in synaptic transmission.[10] Interleukin-6 is expressed and produced in CNS during viral meningitis, in encephalitis mouse models, and in CSF of patients with acute viral infections.[11] It modulates the expression of many genes involved in inflammation, apoptosis, and oxidative stress.[12] Interleukin-8 is a chemoattractant, which recruits neutrophils, T cells, and basophils into the brain in response to inflammation and/or injury. It is secreted by neurons, microglia, and astrocytes.[13]

The production of the antiinflammatory cytokine interleukin IL-10 is an essential mechanism of immune cells to counteract damage driven by excessive inflammation. Microglia as a part of the CNS innate immune system operates through IL-10. The cytokine is elevated in the injured adult brain in several neurodegenerative diseases and animal models of disease, such as excitotoxic shock, multiple sclerosis, EAE, middle cerebral artery occlusion, traumatic brain injury, Alzheimer's disease, and Parkinson's disease.[14] Interleukin-1β (IL-1β) is an important mediator of the inflammatory response, produced by the innate immune system cells. Apart from the host-response and resistance to pathogens, it also exacerbates damage

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during chronic disease and acute tissue injury.[15] Interferon gamma (IFN-γ), or type II interferon, is a cytokine that is critical for innate and adaptive against viral, some bacterial and protozoan infections.

It is an important activator of macrophages and inducer of major histocompatibility complex class II molecule expression. Aberrant IFN-γ expression is associated with a number of autoinflammatory and autoimmune diseases. The importance of IFN-γ comprises immunostimulatory and immunomodulatory effects.[16] Our report does not prove cause-and-result between SARS-CoV-2 mRNA vaccines and active CNS encephalitis. However, the temporal relation and the CSF cytokine profile justify reasonable assumption of causal relationship. We did not perform further analysis to determine the antibody type of the disease. Both treatment administrations failed to suppress the process of CNS deterioration.

Conclusion

At the present time, the number of people who received mRNA vaccination exceeds many times over the number of reported individuals, experiencing CNS inflammatory diseases after vaccination. We should acknowledge the impact on public health and should not ignore that the benefits of COVID-19 vaccination outweigh any potential risks of CNS complications. Further investigations on CNS immune response would be beneficial for developing safe and effective vaccines.

Informed consent

The relatives of the patient signed an Informed consent for publication. A copy of the informed consent is available for review by the Editor.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of interests

The authors declare that there is no conflict of interests.

Financial support

The authors received no financial support for the authorship and publication of this article.

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