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Anti-NMDAR Encephalitis and Myasthenia Gravis Post-COVID-19 Vaccination: Cases of Possible COVID-19 Vaccination-Associated Autoimmunity

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Abstract

BACKGROUND: Coronavirus disease 2019 (COVID-19) continues to be a global issue. While immunizations comprise an important line of defense, adverse effects may occur. We report two cases of autoimmune conditions affecting the nervous system, anti-N-Methyl-D-Aspartate-receptor (NMDAR) encephalitis and myasthenia gravis (MG), that developed in close association with COVID-19 vaccination.

CASE REPORT: In our first case, a 29-year-old woman presents with recurrent seizures, auditory hallucinations, psychiatric symptoms, and autonomic abnormalities, with an onset of 1 day after receiving the second dose of inactivated SARS-CoV-2 whole virus vaccine. CSF analysis and electroencephalogram (EEG) were consistent with anti-NMDAR encephalitis. In our second case, a 23-year-old woman presents with ocular ptosis, diplopia, hoarseness, and fatigability, which first appeared 1-day after her first dose of inactivated SARS-CoV-2 whole virus vaccine. Electromyography (EMG) results established a definite diagnosis of MG.

CONCLUSION: To the best of our knowledge, this is the first report of anti-NMDAR encephalitis and MG associated with inactivated SARS-CoV-2 whole virus vaccine. In both cases, COVID-19 vaccination appears to be the only remarkable feature of history. The authors postulate that COVID-19 vaccination may trigger underlying defects or induce failure of positive and negative selection, which may lead to autoreactivity and subsequent autoimmunity. However, further studies are required to confirm this possibility.

Introduction

Two years have lapsed since the World Health Organization (WHO) has declared coronavirus disease 2019 (COVID-19) a global pandemic on March of 2020. At the time of writing, there have been more than 5.2 million deaths, and 262 million infections reported worldwide [1]. Immunizations comprise an important line of defense against the global pandemic, with hopes of suppressing transmission as well as disease-related morbidity and mortality. A variety of vaccines against COVID-19, each with different mechanisms of inducing immunity, are widely available in circulation, and millions of individuals across the globe have received immunizations and its benefits [1], [2]. However as with all drugs, adverse effects are bound to occur. Several side effects have been reported following COVID-19 vaccination ranging from mild (e.g., fatigue and myalgia) to severe (e.g., myocarditis and thromboembolic events). Rarely, there have also been reports of COVID-19 vaccine-induced autoimmunity [3]. We report the case of two autoimmune conditions affecting the nervous system, anti-N-Methyl-D-Aspartate-receptor (NMDAR) encephalitis and myasthenia gravis, that developed in close association following COVID-19 vaccination. To the best of our knowledge, this is the first report of anti-NMDAR encephalitis and myasthenia gravis thought to be associated with the inactivated SARS-CoV-2 whole virus vaccine.

Anti-NMDAR encephalitis is a rare form of autoimmune or paraneoplastic encephalitis commonly found in late adolescence, with a strong female preponderance (80% of cases). The appearance of anti-NMDAR encephalitis is closely associated with previous viral infections (such as herpes simplex virus, Japanese encephalitis virus, and recently SARS-CoV-2) [4], [5], [6], [7] or tumors (namely, ovarian teratoma, which is present in 45% of female cases) [8], although 37%–50% of cases are of unknown etiology [4], [8], [9]. The clinical manifestations of anti-NMDAR encephalitis can typically be divided into two stages. The early stage consists of psychiatric symptoms, cognitive impairment, and/or seizures, while the advanced stage is characterized by altered consciousness, movement disorders, and autonomic dysfunction. Within the 1st month, nearly 90% of patients will experience symptoms such as behavioral or cognitive

problems, memory deficits, speech dysfunction, seizures, movement disorders, loss of consciousness, autonomic symptoms, and hypoventilation [9].

Myasthenia gravis (MG) is an autoimmune condition involving the neuromuscular junction and is caused by the presence of autoantibodies against the nicotinic acetylcholine receptors (AChRs). The predominant manifestation of MG consists of fluctuating muscle weakness that typically worsens with repeated activity. Extraocular muscles are frequently affected, but patients can develop a more generalized form of MG with proximal muscles weakness of the extremities and trunk. In its more severe form, MG could affect the respiratory muscles, leading to a life-threatening condition known as myasthenic crisis [10]. There have been previous reports of SARS-CoV-2 infection-associated MG [11].

Case Report

First case

A 29-year-old woman presented with recurrent episodes of focal and generalized seizures and auditory hallucinations a day after receiving the second dose of inactivated SARS-CoV-2 whole virus vaccine. Focal seizures manifested as ocular movements, upward right head movements, and facial twitches with transient hemiparesis of the right extremities in the post-ictal state (i.e., Todd's paralysis). Two weeks following onset, psychiatric symptoms emerged with manifestations such as fear/paranoia, sleep disturbances, and chattering, accompanied by abnormal movements such as dyskinesia, dystonia, opisthotonus, and other bizarre behaviors. A medical history was non-significant except for a previous history of febrile seizure at the age of 11 months. The patient also demonstrated autonomic abnormalities manifesting as tachycardia and hypersalivation, but the general and neurological physical examinations were otherwise normal. A head MRI was conducted, for which results returned normal. CSF analysis revealed lymphocytic pleocytosis (43 cells/mm3) and was positive for anti-NMDAR antibodies, while PCR studies for HSV and cytomegalovirus (CMV) were negative. An electroencephalogram (EEG) examination revealed "delta brush" epileptiform waves of the right frontal lobe, confirming the diagnosis of anti-NMDAR encephalitis [7]. The patient has also undergone several tests to uncover possible underlying causes of anti-NMDAR encephalitis. An abdominal CT and Ca-125 tumor marker was ordered to exclude the presence of ovarian teratoma, for which results were inconclusive, excluding a paraneoplastic etiology. A COVID-19 PCR nasopharyngeal swab test was also ordered and returned negative. The patient received intravenous methylprednisolone (1 g daily), and a 5-day course of intravenous immunoglobulins (IVIg), followed by two cycles of rituximab (1 g) 2 weeks apart, antiepileptics, and antipsychotics. Six weeks following treatment, the seizures subsided. At follow-up evaluation conducted 3 months after, there was resolution of residual psychotic symptoms, thus antipsychotics were stopped and doses of antiepileptic drugs were tapered.

Second case

A 23-year-old woman presented with fluctuating right ocular ptosis and concomitant diplopia, which first appeared 1 day after her first dose of inactivated SARS-CoV-2 whole virus vaccine. The patient also experienced fluctuating hoarseness and dyspnea on exertion 1 week after vaccination. The neurological examination was significant for fluctuating right third cranial nerve palsy and diminished motoric strength and dulled physiological reflexes of the extremities. A routine blood panel, head CT, and chest X-ray (to exclude thymic abnormalities) were ordered and demonstrated no abnormalities. Her medical and familial history was non-significant. On electromyography (EMG) with repetitive nerve stimulation (RNS), the patient exhibited a positive decremental result, establishing a definitive diagnosis of MG [10]. The patient was started on oral pyridostigmine (3 × 60 mg) and IV methylprednisolone (1 g for 5 days), and showed clinical improvements in ptosis, hoarseness, and dyspnea. The patient was then discharged with oral pyridostigmine (3 × 60 mg) and methylprednisolone (64 mg/day, tapered weekly). On the 2nd month of follow-up, she regained complete motor strength and demonstrated improvement of physiologic reflexes. The patient continues to take oral pyridostigmine, for which doses have been successfully tapered down.

Discussion

Both cases presented above described the emergence of autoimmune disorders acutely following administration of the inactivated SARS-CoV-2 whole virus vaccine. In both patients, other possible underlying causes and/or triggers have been ruled out, and COVID-19 vaccination appears to be the only remarkable feature of history, given their symptoms appeared very shortly following vaccination. While there have been reports regarding the emergence of autoimmune conditions following the BNT162b2 mRNA vaccine and COVID-19 infection, none have been reported regarding the inactivated SARS-CoV-2 whole virus vaccine. A report by Flannery details a case of anti-NMDAR encephalitis following COVID-19 vaccination with the BNT162b2 mRNA vaccine in a female patient in her twenties with chief complaint of urinary incontinence 1 week following her first dose

Table 1: Differences between cases of anti-N-Methyl-D-Aspartate-receptor encephalitis following COVID-19 vaccination reported by the authors and Flannery *et al*.

Feature	Our case	Flannery *et al*. [12]
Gender	Female	Female
Age	29	20's
Chief complaint	Seizure	Urinary incontinence
Other symptoms	Focal seizure, generalized seizure, facial twitches, dystonia, bizarre behavior, tantrums, stiffness, auditory hallucination	Anxiety, decreased mental acuity, insomnia, hypochondriac delusions, motor dysfunction, aphasia, somatization, psychosis, catatonia, auditory hallucination
Onset following vaccination	1 day after second dose	1 week after first dose
COVID-19 vaccine type	Inactivated SARS-COV-2 whole virus vaccine	BNT162b2 mRNA vaccine
SARS-CoV-2 PCR swab test	Negative	Negative
Head MRI and/or CT-scan	Normal	Normal
CSF analysis	Mild lymphocytic pleocytosis 43 cells/mm^3	Mild lymphocytic pleocytosis 12–14 cells/mm^3
CSF anti-NMDA titers	Positive	1:20
EEG	"Delta brush" epileptiform waves of the right frontal lobe	Normal
Abdomen CT-scan and/or USG	Normal	Normal
Ca-125 tumor marker	Negative	No information

PCR: Polymerase chain reaction, NMDA: N-Methyl-D-Aspartate, EEG: Electroencephalogram, SARS COV-2: Severe acute respiratory syndrome coronavirus 2, CT: Computed tomography, CSF: Cerebrospinal fluid, USG: Ultrasonography, MRI: Magnetic resonance imaging

of vaccine [12]. Additional information detailing the differences between these two cases are detailed in the following table (Table 1) [12].

Furthermore, a case of an 82-year-old man with newly diagnosed myasthenia gravis following a second dose of BNT162b2 COVID-19 vaccine has also been reported [13]. Other details of the case are presented in the following table (Table 2) [13]. Both patients were treated with pyridostigmine and showed clinical improvements.

Table 2: Differences between cases of myasthenia gravis following COVID-19 reported by the authors and Chavez *et al*.

Feature	Our case	Chavez *et al*. [13]
Gender	Female	Male
Age	23	82
Chief complaint	Fluctuating right eye ptosis	Intermittent slurred speech
Other symptoms	Fluctuating hoarseness and dyspnea	Hoarse voice, difficulty chewing, trouble spitting Symptoms appeared mostly at night
Onset after vaccine	1 week after first dose	2 days after second dose
COVID-19 vaccine type	Inactivated SARS-COV-2 whole virus vaccine	BNT162b2 mRNA vaccine
SARS-CoV-2 PCR swab test	Negative	Negative
Brain MRI and/or CT scan	Normal	Age related white matter changes and no evidence of acute intracranial abnormality
Acetylcholine receptor antibodies	Not done	Markedly elevated Ach receptor binding Ab 11.4 (normal < 002) Ach receptor modulating Ab 93% (normal 0%–20%) Striational Ab titer 1:245760 (normal < 1:120)
Electromyography	Normal	Decrement repeated nerve stimulation
Evaluation for thymoma	Negative	Negative

PCR: Polymerase chain reaction, SARS COV-2: Severe acute respiratory syndrome coronavirus 2, CT: Computed tomography, MRI: Magnetic resonance imaging

To understand the possible mechanisms by which inactivated SARS-CoV-2 whole virus vaccine could lead to autoimmunity, we must first review the immunological mechanisms underlying COVID-19 vaccination, anti-NMDAR encephalitis, and MG. The inactivated SARS-CoV-2 whole virus vaccine and BNT162b2 mRNA confer immunity in different ways. Whole virus vaccines rely on various chemical and physical methods, such as formaldehyde, β-propiolactone and UV, to inactivate coronaviruses. The subunits of these inactivated viruses are then used to produce antibodies (primarily protective IgG1 and IgG3 subclasses), while adjuvants are added to achieve an effective and robust humoral immune response through RBD-specific binding antibody and NAb production, without a cellular immune response [2], [14]. Previous clinical trials have demonstrated that inactivated vaccines appear to be safe and well tolerated, with only minor side effects such as pain at the injection site. No serious adverse events have been reported [15]. In contrast, mRNA vaccines such as the BNT162b2 vaccine represent a novel vaccine approach. Once administered, the RNA is translated into the target protein (i.e., a full-length spike protein) and elicits an immune response. BNT162b2 mRNA vaccine triggers protein S1-binding antibody production after the first and second dose of vaccination with NAb production after the second dose. This vaccine also triggers the enhancement of antigen-specific CD4+ and CD8+ T cells secreting INFγ2 and IL-23 after the second dose [15]. Notably, the immune responses generated by the mRNA vaccine would target only the spike protein, while the response by SARS-CoV-2-inactivated vaccines would also target other components of the virus [16], [17]. However, both injections of vaccines will be recognized as a pathogenic agent that triggers a strong expression of pro-inflammatory cytokines and T-cell responses.

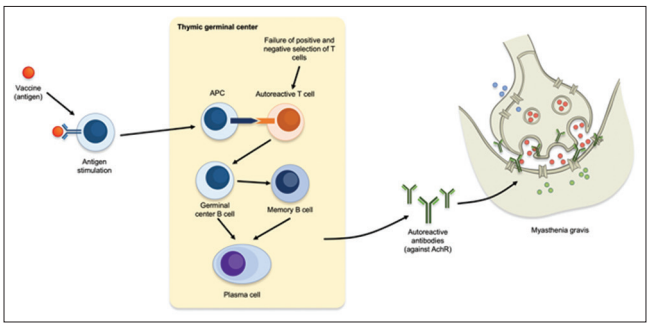

Figure 1: Proposed pathomechanism behind the generation of pathogenic IgG1 and IgG3 autoantibodies in inactivated SARS-COV-2 whole virus vaccine-associated myasthenia gravis [20], [22], [23]

While targeting different anatomical components, anti-NMDAR encephalitis and MG are similar in that both are IgG1 and IgG3 autoantibody-mediated autoimmune disorders of the nervous system. In anti-NMDAR encephalitis, generation of IgG1 and IgG3 antibodies binding to the GluN1 subunit of NMDA-R results in a significant decrease in NMDAR clusters, resulting in disruption of hippocampal pathways, overexcitation of NMDARs

(leading to neurotoxicity), and sustained hypofunction of the NMDAR [18], [19]. These changes are thought to be the dominant pathomechanisms behind the typical symptoms of persistent amnesia, epilepsy, and psychosis observed in anti-NMDAR encephalitis [20]. In MG, IgG1 and IgG3 autoantibodies against acetylcholine receptors (AChR), muscle-specific kinase (MuSK), or other AChR-related protein in the postsynaptic muscle membrane lead to ACh receptor blockade, receptor internalization/degradation, as well as complement activation and subsequent degradation of the neuromuscular junction [21]. In addition, while both autoimmune conditions possess paraneoplastic ties (50% of female anti-NMDAR encephalitis patients have ovarian teratomas and 10% of all MG patients have thymomas) thought to drive antibody production [10], [21], [22], the exact etiology of antibody production, regardless of origin, remains unknown. We propose that the immune response induced by COVID-19 vaccination may trigger underlying defects or induce failure of positive and negative selection of T cells in the thymus, or dysregulation of clonal deletion, receptor selection, and anergy of B-cells in the bone marrow (primarily with those with pre-existing predispositions), which may lead to the development of autoreactive B and T cells and the generation of pathogenic IgG1 and IgG3 autoantibodies against the AchR (myasthenia gravis) (Figure 1) and GluN1 subunit (anti-NMDAR encephalitis) (Figure 2) [5], [18], [19], [23]. However, further studies are required to confirm this possibility.

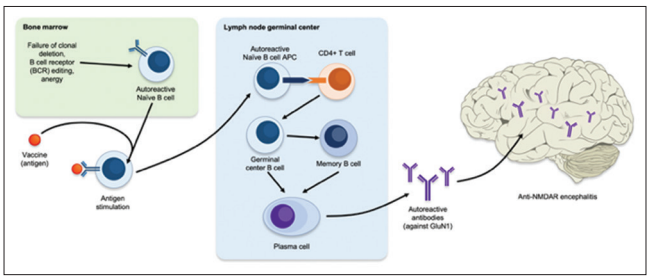

Figure 2: Proposed pathomechanism behind the generation of pathogenic IgG1 and IgG3 autoantibodies in inactivated SARS-COV-2 whole virus vaccine-associated anti-NMDAR encephalitis [17], [18], [22]

Our report does not attribute definitive causation to COVID-19 vaccination toward the emergence of autoimmunity, but rather that vaccination may uncover/trigger pre-existing immunological defects or predispositions. Various autoimmune conditions have been reported in relation with COVID-19 infection, sequelae, and recently COVID-19 vaccination. Therefore, awareness of risk factors such as history of autoimmunity in the family or in the medical history should always be considered in managing patients with COVID-19. Close monitoring is also required following COVID-19 vaccination, particularly in patients with known risk factors for autoimmune disease.

Conclusion

We report the possible emergence autoimmunity shortly following administration of the inactivated SARS-CoV-2 whole virus vaccine. To the best of our knowledge, this is the first report of anti-NMDAR encephalitis and myasthenia gravis associated with inactivated SARS-CoV-2 whole virus vaccine. In both cases, other possible causes and/or triggers have been ruled out, and COVID-19 vaccination appears to be the only remarkable feature of history. The authors postulate that COVID-19 vaccination may trigger underlying defects or induce failure of positive and negative selection, which may lead to autoreactivity and subsequent autoimmunity. However, further studies are required to confirm this possibility.

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