Anti-N-methyl-D-aspartate receptor encephalitis after coronavirus disease 2019
A case report and literature review

Hyesun Lee, MD*, Jong Hyun Jeon, MD*, Hojin Choi, MD, PhD*, Seong-Ho Koh, MD, PhD*, Kyu-Yong Lee, MD, PhD*, Young Joo Lee, MD, PhD*, Hyuk Sung Kwon, MD, PhD**

Abstract
Rationale: Coronavirus disease 2019 (COVID-19) has become a global pandemic and COVID-19-associated anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis may occur through an immune-mediated pathomechanism.

Patient concerns: A 21-year-old woman with a history of COVID-19 presented to our hospital with memory decline and psychiatric symptoms.

Diagnosis: The patient was diagnosed with anti-NMDAR encephalitis.

Intervention: Intravenous methylprednisolone (1 g/day over 5 days) followed by immunoglobulin (0.4 g/kg/day over 5 days) were administered. The patient underwent laparoscopic salpingo-oophorectomy to remove an ovarian teratoma.

Outcomes: The patient was discharged with sequelae of short-term memory impairment, without other neuropsychiatric symptoms.

Lessons: Cases of previously reported anti-NMDAR encephalitis with COVID-19 were reviewed and compared with the present case. Clinicians should be aware of the occurrence of anti-NMDAR encephalitis in patients who present with neuropsychiatric complaints during or after exposure to COVID-19. Further studies are required to determine the causal relationship between the 2 diseases and predict the prognosis of anti-NMDAR encephalitis after COVID-19 exposure.

Abbreviations: COVID-19 = coronavirus disease 2019, CSF = cerebrospinal fluid, IL-6 = interleukin-6, NMDAR = N-methyl-D-aspartate receptor, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Keywords: anti-N-methyl-D-aspartate receptor encephalitis, case report, COVID-19, ovarian teratoma

1. Introduction
Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common form of autoimmune encephalitis, occurring more frequently in young women. It is also associated with tumors, especially ovarian teratomas.[1] About 80% of patients with anti-NMDAR encephalitis benefit from adaptive immunotherapy with or without removal of teratomas, and early tumor removal is associated with good prognosis.[1-4]

Coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), occurred in 2019, and various neurological diseases associated with it have been continuously reported. SARS-CoV-2 can invade the central nervous system through systemic circulation via angiotensin-converting enzyme 2 receptors and the cribriform plate.[5]

Until now, only a few cases of anti-NMDAR encephalitis associated with COVID-19 have been reported.[6,7] Structural similarities between NMDAR and a subunit of SARS-CoV-2 may trigger anti-NMDAR encephalitis after COVID-19.[6] We report a case of a patient with anti-NMDAR encephalitis triggered by COVID-19. To the best of our knowledge, this is the first such case reported in East Asia.

2. Case report
A 21-year-old woman visited the emergency department with a complaint of short-term memory loss and abnormal behavior for past 1 week. She repeated the same words and presented an incoherent speech. She had no known underlying diseases and received the third dose of BNT162b2 vaccination against...
SARS-CoV-2 4 months prior to the visit. A polymerase chain reaction test performed on the nasopharyngeal swab collected from her approximately 10 days prior to admission was positive for COVID-19. Her abnormal behavior was noticed 3 days after SARS-CoV-2 infection was detected.

Laboratory tests revealed no abnormalities. Cerebrospinal fluid (CSF) analysis revealed a high opening pressure of 252 mm H$_O$, white blood cell count of 500/mm$^3$ (90% lymphocytes), red blood cell count of 85,700/mm$^3$, protein level of 402.4 mg/dL, glucose level of 57.8 mg/dL (serum glucose level of 104 mg/dL), adenosine deaminase level of 5.9 IU/L, and corrected white blood cell count of 642.92/mm$^3$. Brain fluid-attenuated inversion recovery images showed contrast-enhanced lesions in the cerebellum and hippocampus (Fig. 1A-C). Electroencephalography exhibited diffuse beta wave activity with rare sharp waves in both the temporal lobes. Chest and abdomen-pelvic computed tomography revealed a mass of 5 cm in size in the right ovary, suspected to be a teratoma (Fig. 1D). Brain fluid-attenuated inversion recovery images showed enhancing lesional lesions in both the temporal lobes. Chest and abdomen-pelvic computed tomography revealed a mass of 5 cm in size in the right ovary, suspected to be a teratoma (Fig. 1D). Subsequently, her serum and CSF specimens were found to be positive for anti-NMDAR antibodies. The CSF oligoclonal band was negative; moreover, the serum was negative for paraneoplastic autoantibodies such as anti-Hu, Ri, Yo, amphiphysin, CV2, PNMA2 (Ma2/Ta), Recoverin, SOX1, and Titin.

Intravenous acyclovir (10 mg/kg per 8 hours for 8 days) and corticosteroids (methylprednisolone 1 g/day for 5 days) were initiated. Laparoscopic right salpingo-oophorectomy was performed. The psychosis, anxiety, and memory loss persisted even after treatment with corticosteroids. Therefore, intravenous immunoglobulin (0.4 g/kg/day over 5 days) was administered. She was discharged with improvement in psychosis. However, recovery of her memory impairment was incomplete, which would require continuous monitoring.

3. Discussion

Anti-NMDAR encephalitis occurs when antibodies against NMDAR are produced, and is triggered by herpes simplex type 1 encephalitis and tumors, including ovarian teratomas.[1] However, infection with diverse viruses including the Japanese encephalitis virus could also elicit anti-NMDAR encephalitis.[1-4] Furthermore, H1N1, polio, diphtheria, and pertussis vaccination is also related to the manifestation of anti-NMDAR encephalitis.[3]

Recently with the occurrence of the COVID-19 pandemic, some research regarding the relationship between COVID-19 and anti-NMDAR encephalitis has emerged. The subunits of NMDAR and non-structural proteins 8 and 9 in SARS-CoV-2 are structurally similar, and this mimicry may affect the cross-reactivity between them.[3] Furthermore, COVID-19 increases the release of inflammatory markers from the alveolar epithelium and macrophages. This leads to increased vascular permeability, and disruption of the blood-brain barrier.[11] Blood-brain barrier breakdown raises the risk of NMDAR antibodies invading the central nervous system.[6,10]

Among more than 50 micro-ribonucleic acid biomarkers of COVID-19, 7 are known to be related to anti-NMDAR

Figure 1. Brain magnetic resonance images (A–C) and enhanced abdominopelvic computed tomography (CT) image of the patient (D). Enhanced fluid-attenuated inversion recovery (FLAIR) images show enhancing lesions in bilateral cerebellum (A, B) and hippocampus (C). CT shows right ovarian mass with calcification suggestive of teratoma (D, arrow).
Table 1

| No | Article | Age/sex/past history | Neuropsychiatric symptoms | Results (CSF/brain imaging/EEG/sample day for the positive COVID-19, before or after the admission) | Immunotherapy/teratoma removal Surgery | Outcome |
|----|---------|----------------------|---------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------|---------|
| 1  | Bravo et al 2020[11] | 30/F/ none | 3 days prior and admission day: Psychomotor agitation, paranoid ideation, dystharisia with dysprosody, and visual hallucinations | CSF: Lymphocytic pleocytosis, elevated protein levels, SARS-CoV-2 PCR (-) Brain MRI: Hyperintensity in Left hippocampus | IVMP , IVIG, Rituximab | Improvement but cognitive sequelae |
|    |         |          | During HD: Buccalolingual dyskinesia, chorea-dystonic movements, blepharoclonus, and focal and generalized seizures | EEG: Epileptic discharges in the left frontotemporal region. Delta brush pattern with spike and wave discharges in anterior regions | | |
|    |         |          | | COVID-19 Sample: After 3 days (Nasopharyngeal swab) | | |
| 2  | Panariello et al 2020[12] | 23/M/Drug abuse | 3 days prior and admission day: Psychomotor agitation, anxiety, thought disorganization, persecutory delusions, and auditory hallucinations | CSF: Did not reveal any evidence of central nervous system infection. Increased interleukin-6, SARS-CoV-2 PCR (-) | IVMP , IVIG | Improvement |
|    |         |          | | Brain CT: Unremarkable | Not mentioned | Clinical conditions are ameliorating to date |
|    |         |          | During HD: Non-verbal, non-responsive to commands, dyskinesia, and autonomic failure | EEG: Theta activity at 6 Hz | | |
|    |         |          | | COVID-19 Sample: Admission day | | |
| 3  | Monti et al 2020[13] | 50/M/Mild hypertension | Admission day: Psychiatric symptoms including confabulations, and delirious ideas | CSF: Pleocytosis, mildly elevated protein level, Increased interleukin-6, SARS-CoV-2 PCR (-) | IVMP , IVIG, Plasma exchange | Improvement |
|    |         |          | | Brain MRI: Unremarkable | No teratoma | |
|    |         |          | During HD: Focal motor seizures, orofacial dyskinesia, and refractory status epilepticus | EEG: Delta brush pattern. Anterior sub-continuous periodic theta activity | | |
|    |         |          | | COVID-19 Sample: After approximately 8 days (throat swab) | | |
| 4  | McHattie et al 2021[14] | 53/F/Ductal breast carcinoma under remission, depression | 3 weeks prior: Confusion, palilalia | CSF: Lymphocytic pleocytosis, mildly elevated protein, SARS-CoV-2 PCR (-) | IVMP , IVIG, tocilizumab | Improvement, but sequelae of left hemiparesis |
|    |         |          | | Admission day: Alert | No teratoma | |
|    |         |          | | During HD: Severe echolalia, palilalia, high-pitched voice, echopraxia, behavioral disinhibition, mildly left sided weakness, focal seizures, prominent dysautonomia, and no hyperkinetic movement disorder | Brain CT: Unremarkable | |
|    |         |          | | Brain MRI: Hyperintensity in Lt. amygdala, and anterior putamen & subtle signal change in Rt. Amygdala | | |
|    |         |          | | EEG: Slow activity but no epileptiform discharges | | |
|    |         |          | | COVID-19 Sample: After approximately 14 days (Nasopharyngeal swab) | | |
| 5  | Allahyari et al 2021[15] | 18/F/none | 3 weeks prior: Mood change, anhedonia, lack of concentration | CSF: Lymphocytic pleocytosis, elevated protein, SARS-CoV-2 PCR (+) | IVMP , IVIG | Complete recovery |
|    |         |          | | Admission day: Generalized tonic-clonic seizures | Brain CT: generalized brain edema | |
|    |         |          | | During HD: Deteriorated level of consciousness, and confused state | Brain MRI: Unremarkable | |
|    |         |          | | EEG: Not mentioned | Not mentioned | |
|    |         |          | | COVID-19 Sample: Not clearly mentioned, after 1 week immunoglobulinM(+) | | |

Anti-NMDAR = anti-N-methyl-D-aspartate receptor, COVID-19 = coronavirus disease 2019, CSF = cerebrospinal fluid, EEG = electroencephalogram, HD = hospital day, IL = interleukin, IVIG = intravenous immunoglobulin, IVMP = intravenous methylprednisolone, PCR = polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
encephalitis. These common biomarkers are miR-107, miR-29b, let-7a, let-7i, miR-26b, miR-21, and miR-153; they do not contain the main biomarker for anti-NMDAR encephalitis (let-7b), yielding a ratio of <0.2. This may explain the low risk of anti-NMDAR encephalitis occurrence after COVID-19 infection. However, theses common micro-ribonucleic acid biomarkers may explain the causal relationship between COVID-19 and anti-NMDAR encephalitis. COVID-19 might trigger anti-NMDAR encephalitis using these common biomarkers, but the risk of occurrence may be low.[4]

We reviewed published case reports of anti-NMDAR encephalitis related to COVID-19 in adults (aged ≥18 years or more) and found a total of 5 adult patients with anti-NMDAR encephalitis associated with COVID-19 (Table 1).[11-13] All these patients had psychiatric or behavioral symptoms and received immunotherapies such as steroids and intravenous immunoglobulin. However, unlike the previous 5 cases, our case had some distinct features.

In the current study, COVID-19 confirmation preceded the appearance of anti-NMDAR encephalitis symptoms. In previous cases, patients were confirmed to be positive for COVID-19 after their anti-NMDAR encephalitis related symptoms had appeared. The neurological manifestations of COVID-19 are similar to those of the anti-NMDAR encephalitis. Approximately 36.4% of patients with COVID-19 showed neurologic symptoms[46] making it difficult to distinguish whether the first neuropsychiatric symptoms are due to COVID-19 or anti-NMDAR encephalitis.

To the best of our knowledge, this is the first reported case of anti-NMDAR encephalitis suspected to be triggered by COVID-19, in East Asia. One recent study reviewed cases of autoimmune encephalitis in COVID-19 and suggested that their prognosis was relatively good.[7] Our case had relatively good psychological symptoms due to COVID-19 or anti-NMDAR encephalitis.

There are some ambiguities related to the case. It is unclear whether the patient’s neuropsychiatric symptoms were due to COVID-19 or anti-NMDAR encephalitis. In addition, it cannot be conclusively assumed that the patient’s ovarian teratoma in the case had existed ever since the COVID-19 exposure. However, it can be concluded that when a patient with COVID-19 exhibits neuropsychiatric symptoms, anti-NMDAR encephalitis should be considered as a comorbidity.

Moreover, in the present case, we did not evaluate the CSF for Interleukin-6 (IL-6) or SARS-CoV-2. In COVID-19, a cytokine storm occurs and IL-6 increases during the inflammatory phase of COVID-19. In particular, elevated IL-6 levels in the CSF lead to increased production of autoantibodies in anti-NMDAR encephalitis.[10,17] Hence, CSF needs to be tested for IL-6 to clarify whether COVID-19 and anti-NMDAR encephalitis occurred during a similar duration of time by coincidence or they had a causal relationship.

To date, only a few cases of anti-NMDAR encephalitis triggered by COVID-19 have been reported. We report a case of anti-NMDAR encephalitis occurring after COVID-19 exposure in South Korea and compare the results with those of previous studies. COVID-19 may act as a trigger for the occurrence of anti-NMDAR encephalitis.

If a patient shows neuropsychiatric symptoms after COVID-19, suspecting an association with anti-NMDAR encephalitis is essential and the symptoms should not be regarded as an exclusive manifestation of COVID-19. With the accumulation of cases and data related to COVID-19 and anti-NMDAR encephalitis, we can anticipate to determine the epidemiology, establish an algorithm for effective treatments, and predict the prognosis of anti-NMDAR encephalitis following COVID-19 exposure.

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Author contributions

Conceptualization: Hyesun Lee, Hyuk Sung Kwon.
Data curation: Hyesun Lee.
Investigation: Hojin Choi, Seong-Ho Koh, Kyu-Yong Lee, Young Joo Lee, Hyesun Lee, Hyuk Sung Kwon.
Supervision: Hojin Choi, Seong-Ho Koh, Kyu-Yong Lee, Young Joo Lee, Hyuk Sung Kwon.
Visualization: Hyesun Lee.
Writing – original draft: Hyesun Lee, Hyuk Sung Kwon.
Writing – review & editing: Hyesun Lee, Hyuk Sung Kwon.

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