CASE REPORT

Autoimmune Encephalitis Due to COVID-19 in a Young Patient

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Abstract

Autoimmune encephalitis is an inflammatory condition caused by different factors, including viral infections, diagnosed after ruling out other causes of encephalitis. The current study reported novel autoimmune encephalitis in an 11-year-old girl who presented with seizures, cognitive dysfunction, and neurological impairments. During the admission, the researchers observed high levels of anti-N-methyl-D-aspartate receptor (NMDAR) antibodies in the cerebrospinal fluid (CSF). Besides, she had positive anti-COVID-19IgG. Therefore, the diagnosis of COVID-19-induced autoimmune encephalitis was specific. The patient received anti-epileptic, anti-viral drugs, IVIG, and rituximab and was discharged with remission. The case diagnosis was made by anti-NMDAR antibodies, which highlights the importance of this diagnostic tool. Similar cases have been reported earlier, but the point of this case was her younger age compared to the previous cases and her developing neurological deficit before COVID-19 presentations.

Keywords: Autoimmune encephalitis; COVID-19; Infection.
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Introduction

Autoimmune encephalitis is an inflammatory condition in the brain mainly due to immune responses against self-antigens expressed in the central nervous system (1). Different etiologies and complex differential diagnoses have been reported for autoimmune encephalitis (2). The main presentations of autoimmune encephalitis are deficits in memory and cognition, followed by a decrease in the levels of consciousness. Based on the evidence, the most common differential diagnosis of autoimmune encephalitis could be primary psychiatric disorders, malignant catatonia (MC), neuroleptic malignant syndrome, viral encephalitis, and encephalitis lethargica (3). The diagnosis of this disease is mainly conducted by the use of imaging studies, electroencephalography (EEG), and the presence of antibodies in the cerebrospinal fluid (CSF) (4). COVID-19 pneumonia is caused by the SARS-COV2 virus responsible for the latest pandemic (5). According to recent studies, the SARS-COV2 virus could have neurotropic activities leading to encephalopathy with various neurological symptoms (6). So far, only a few cases of encephalitis due to COVID-19 have been reported, but the current study presents an 11-year-old girl showing autoimmune encephalitis and is later diagnosed with COVID-19 infection.

Case presentation

The current report presented an 11-year-old girl admitted to the medical center due to fever and seizure. Based on the history, almost ten days before admission, she had signs of behavioral disorders and cognition impairment followed by fever and seizure. By admission, she had a fever (oral temperature= 38.3º C) and tachycardia (heart rate= 127 beats/minute) but had normal blood pressure and respiratory rate. The physical examinations of multiple systems did not reveal pathologic findings. In addition, she did not have dermatologic problems or hepatosplenomegaly. Based on neurologic examinations, she was conscious but was not oriented about the time and place (impaired cognitive attention). Examinations of cranial nerves, force and tone of limbs, and deep tendon reflex (DTR) were normal. She did not cooperate with the gait examination.

The patient underwent a brain MRI with contrast and EEG for diagnostic purposes. The result of the brain MRI was normal, but the EEG showed generalized slowing. Afterward, the lumbar puncture (LP) was conducted after brain MRI, and the SCF was checked for any infectious, inflammatory, or autoimmune markers. The results of LP were normal pressure and normal appearance fluid, glucose, RBC, WBC and protein (RBC= 20, WBC= zero (normal range: <5), protein= 9.6 mg/dL (normal range: 20-45), and glucose= 51 mg/100 mL (normal range: >50)) that were suggestive for no bacterial or viral infections. However, the anti-N-methyl-D-aspartate receptor (NMDAR) antibody was highly positive in both serum and CSF (1/320 for both), highly suggestive of autoimmune encephalitis. Other laboratory data at the time of admission are presented in Table 1. The laboratory data of the autoimmune panel of the patient are summarized in Table 2.

As a result, treatments of autoimmune encephalitis were initiated, including five time of corticosteroid pulses (30 mg/kg), five times plasmapheresis, and IVIG (2 gr/kg). The seizures of the patient were controlled using levetiracetam (levebel) (30 mg/kg/day) and Clobazam (10 mg, one tablet every 12 hours). During the admission, the patient had a fever (T= 38.5º C) and rashes on the trunk and

limbs. Therefore, evaluations were performed to assess the possibility of a multisystem inflammatory syndrome in children (MIS-C). As a result, the researchers checked the anti-COVID-19 antibodies for the patient, and the results revealed positive anti-COVID-19 IgG (16.11 RU/mL). These findings suggested a possible relationship between COVID-19 infection and autoimmune encephalitis.

However, this research evaluated multiple factors that could result in autoimmune encephalitis, including thyroid functions and rheumatologic factors. Ultrasound also evaluated the thyroid gland thoroughly, but no pathologies were observed. The patient had normal thyroid function tests, negative anti thyroperoxidase (TPO) antibodies, normal levels of ANA, Anti-ds DNA, and anticardiolipin (Table 1). The patient underwent abdominal ultrasound imaging to screen tumors, and a dermoid cyst was observed in the right ovary with a size of 6 mm. During the hospitalization, an abdominal distention was detected, and with suspicion of a dermoid cyst being the etiology of the abdominal distension, the patient underwent a surgical operation to remove the cyst. Based on pathologic results, the diagnosis for the extracted tissue was a dermoid cyst.

The patient did not respond to corticosteroids, plasmapheresis, and IVIG treatments during the hospitalization. However, the corticosteroid treatments with a 2 mg/kg dosage continued until discharge. The patient was bedridden, unable to talk, and had no cognitive attention. Afterward, rituximab was administered with the dosage of 375 $mg/m,^2$ which resulted in significant development of cognitive condition and consciousness within one week. The patient's general condition improved so she could talk, sit and walk, and she was discharged with full recovery after one month. Follow-up of the patient for the second dosage of rituximab after two weeks indicated full recovery of the patient, and no cognitive impairments or seizures were reported.

Table 1. Laboratory data of the patient by the time of admission.

Variable	Amount
White blood cells	22200
Lymphocyte	6.9
Neutrophil	90
Hemoglobin	14.9
Mean corpuscular volume	74.9
Platelet	470000
Erythrocyte sedimentation rate	81
Uric acid	7
Direct bilirubin	0.2
Partial thromboplastin time	27
INR	1.2
Na	149
Creatinine	0.68
Aspartate transaminase	11
Alanine transaminase	13
Lactate dehydrogenase	498
Ferritin	65.4
C-reactive protein	4.3
Troponin	Negative
D-dimer	288
Thyroid-stimulating hormone	0.4
Anti TPO	<1
Anti-HIV antibody	0.2
Anti-HCV antibody	0.3
HSV PCR	Negative
2ME	Negative
Procalcitonin	0.34
Sars-covid anti-spike IgG	16.11
Sars-covid neutralization (RBD) IgG	0.53
Antinuclear antibodies	1.9
Anti-ds DNA	3.3
Anti TTG	1.8

Table 2. The autoimmune panel of the patient.

Variable	Amount
Autoimmune encephalitis panel in CSF	
Anti-Glutamate receptor: Type NMDA	> 1:320
Anti-Glutamate receptor: Type AMPA	<1:10
Anti- Gamma amino butyric acid: GABA receptors antibodies	<1:10
Anti- LGII	<1:10
Anti-CASPR2	<1:10
Autoimmune encephalitis panel in serum	
Anti-Glutamate receptor: Type NMDA	> 1:320
Anti-Glutamate receptor: Type AMPA	<1:10
Anti- Gamma amino butyric acid: GABA receptors antibodies	<1:10
Anti- LGII	<1:10
Anti-CASPR2	<1:10

Discussion

The current study reported a young case of autoimmune encephalitis that was probably related to COVID-19 infection. The presented case was diagnosed via highly positive anti-NMDAR antibody levels in the CSF and positive anti-COVID-19 IgG. Some previous studies have reported in some the association between COVID-19 and autoimmune encephalitis.

In 2021, Mulder and colleagues reported that a 40-year-old male with autoimmune encephalitis presented with MC. The reported case had COVID-19 infection prior to developing symptoms, and he had negative results for antibodies against NMDAR, glutamic acid decarboxylase, contactin-associated protein-like 2, leucine-rich, glioma inactivated 1, and ganglioside antibodies in serum and CSF. The patient was then diagnosed with autoimmune encephalitis following COVID-19 infection and received plasmapheresis and IVIG (7). Zuhorn and others presented another case in 2021.The reported case was a 54-year-old male diagnosed with COVID-19 by a positive RT-PCR test for SARS-CoV-2. The clinical presentations of this case were clinical deterioration and neuropsychiatric symptoms, including aggressiveness, disorientation, and stupor, even before respiratory deterioration. The reported patient was diagnosed by brain MRI based on the claustrum sign. No immunological markers were detected in the case (8). As indicated, the presented cases of COVID-19-induced autoimmune encephalitis had negative markers, while our case had highly positive anti-NMDAR antibody levels in the CSF.

The critical point is that patients with viral encephalitis usually have no positive anti-NMDAR antibody, but in the presented case, the CSF biochemical parameters were completely normal. Consequently, believingly, the symptoms were triggered by high titers of anti-NMDAR antibodies that resulted in autoimmune encephalitis and

central nervous system (CNS) complications. Notably, the anti-NMDAR antibody could be detected both in serum and in patients' CSF and positive CSF tests indicated definite diagnosis of autoimmune encephalitis. Based on previous reports, the differential diagnosis of autoimmune encephalitis is primary psychiatric disorders, MC, neuroleptic malignant syndrome, viral encephalitis, and encephalitis lethargica (9-12). Another point is that this study assumed para-neoplastic causes for the autoimmune encephalitis due to a dermoid cyst in the ovary, but this could not justify the positive anti-NMDAR antibody in the CSF. However, the researchers believe that the excision of the dermoid cyst could have contributed to the patient's improvements. Nevertheless, there is a lack of evidence showing possible para-neoplastic effects of dermoid cysts. As Dalmau et al. explained in 2017, autoimmune and paraneoplastic encephalitis could have similar conditions and symptoms, primarily due to ovarian cancer (12).

Correspondingly, recent cases have focused on anti-NMDAR antibody-causing encephalitis. Monti et al. reported a similar case to our patient in 2020. They presented a 50-year-old man who developed COVID-19 infection symptoms associated with focal motor seizures, impaired awareness, and oro-facial dyskinesia/automatisms. The autoimmune encephalitis diagnosis was made by positive anti-NMDAR antibody, and the patient received methylprednisolone, IVIG, plasma exchange, and antiseizure drugs/anesthetics to control refractory/super refractory status (SRSE), as well as empirical therapies used for SAR-CoV-2 infection (13). This case also highlighted the importance of anti-NMDAR antibodies as diagnostic results in autoimmune encephalitis. Another study by Zandifar et al. demonstrated the link between COVID-19 infection and anti-NMDAR encephalitis. They emphasized the importance of this marker as a powerful diagnostic tool in possible cases (14). Panariello et al. presented another case as a 23-year-old Ecuadorian male presented with a COVID-19 infection with neurological presentations suggestive of encephalitis. The CSF analysis of the case was normal except for increased protein levels and positive anti-NMDAR antibody (15). All these data show the importance of anti-NMDAR antibodies in diagnosing COVID-19-induced autoimmune encephalitis.

Another point of this study's case was that the age of the presented case was lower than most previously reported cases, and the patient had no COVID-19 infection symptoms prior to developing seizure and encephalitis. The normal parameters of CSF biochemical analysis were a clue for diagnosing autoimmune encephalitis definitely diagnosed by positive anti-NMDAR antibodies. The COVID-19 pandemic has become a global crisis that continues in Iran and other developing countries. Assumedly, autoimmune encephalitis might be detected in some infected cases, and particular diagnostic and therapeutic strategies should be developed. The current study suggests that physicians should pay more attention to the incidence of autoimmune encephalitis in cases with COVID-19 infection.

In Conclusion

Here, the present study reported an 11-year-old girl with seizure and cognitive impairment who was later diagnosed with autoimmune encephalitis due to COVID-19 infection. The case diagnosis was made by anti-NMDAR antibodies, which highlights the importance of this diagnostic tool. Similar cases have been reported earlier, but the point of this case was her younger age compared to

the previous cases and her developing neurological deficit before COVID-19 presentations.

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Author's Contribution

Forogh Derakhshani:Substantial contributions to the conception, design of the work; the acquisition, analysis, interpretation of data for the work, Drafting the work, Final approval of the version to be published, Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy Neda Hoseini: Substantial contributions to the conception, design of the work; the acquisition, analysis, interpretation of data for the work, Drafting the work, Final approval of the version to be published, Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Dubey D, Pittock SJ, Kelly CR, McKeon A, Lopez-Chiriboga AS, Lennon VA, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. Annals of neurology. 2018;83:166-77.
2. Harutyunyan G, Hauer L, Dünser MW, Karamyan A, Moser T, Pikija S, et al. Autoimmune encephalitis at the neurological intensive care unit: etiologies, reasons for admission and survival. Neurocritical care. 2017;27:82-9.
3. Armangue T, Petit-Pedrol M, Dalmau J. Autoimmune encephalitis in children. Journal of child neurology. 2012;27:1460-9.
4. Hermetter C, Fazekas F, Hochmeister S. Systematic review: syndromes, early diagnosis, and treatment in autoimmune encephalitis. Frontiers in neurology. 2018;9:706.
5. Velavan TP, Meyer CG. The COVID-19 epidemic. Tropical medicine & international health. 2020;25:278.
6. Filatov A, Sharma P, Hindi F, Espinosa PS. Neurological complications of coronavirus disease (COVID-19): encephalopathy. Cureus. 2020;12.
7. Mulder J, Feresiadou A, Fällmar D, Frithiof R, Virhammar J, Rasmusson A, et al. Autoimmune encephalitis presenting with malignant catatonia in a 40-year-old male patient with Covid-19. American Journal of Psychiatry. 2021;178:485-9.
8. Zuhorn F, Omaimen H, Ruprecht B, Stellbrink C, Rauch M, Rogalewski A, et al. Parainfectious encephalitis in COVID-19:"the claustrum sign". Journal of neurology. 2021;268:2031-4.
9. Dalmau J, Rosenfeld MR, DeAngelis L, Eichler AF. Paraneoplastic and autoimmune encephalitis. UpToDate. 2017.
10. Sansing LH, Tüzün E, Ko MW, Baccon J, Lynch DR, Dalmau J. A patient with encephalitis associated with NMDA receptor antibodies. Nature Clinical Practice Neurology. 2007;3:291-6.
11. Gable M, Gavali S, Radner A, Tilley D, Lee B, Dyner L, et al. Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. European journal of clinical microbiology & infectious diseases. 2009;28:1421-9.
12. Dale RC, Irani SR, Brilot F, Pillai S, Webster R, Gill D, et al. N-methyl-D-aspartate receptor

antibodies in pediatric dyskinetic encephalitis lethargica. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society. 2009;66:704-9.

13. Monti G, Giovannini G, Marudi A, Bedin R, Melegari A, Simone AM, et al. Anti-NMDA receptor encephalitis presenting as new onset refractory status epilepticus in COVID-19. Seizure. 2020;81:18.
14. Zandifar A, Badrfam R. COVID-19 and anti-N-methyl-d-aspartate receptor (anti-NMDAR) encephalitis: Are we facing an increase in the prevalence of autoimmune encephalitis? Journal of Medical Virology. 2021;93:1913-4.
15. Panariello A, Bassetti R, Radice A, Rossotti R, Puoti M, Corradin M, et al. Anti-NMDA receptor encephalitis in a psychiatric Covid-19 patient: a case report. Brain, behavior, and immunity. 2020;87:179.