
Faiq B. Basa¹, Stefania Moramarco², Leonardo Emberti Gialloreti²

¹Internal Medicine Department, Rizgary Teaching Hospital, Erbil, Iraq.
²Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy.

Abstract

Covid-19 infection frequently causes neurological symptoms. One of the mechanisms of indirect nervous system involvement is through inflammatory response and immune dysregulation. There are few recorded cases of indirect involvement of CNS by auto-antibodies. We present a case of a 6-year-old Iraqi boy with anti-N-methyl-d-aspartate receptor (anti-NMDAR) autoimmune encephalitis, associated with Covid-19. He presented with recent repeated attacks of refractory focal seizures preceded by behavioral changes. Serum and CSF anti-NMDAR antibodies were positive. Early recognition and treatment of autoimmune encephalitis are crucial as the prognosis is promising with early immunotherapy. Autoimmune encephalitis should be included in the main differential diagnosis whenever refractory epilepsy or new onset status epilepticus is faced. In the era of COVID-19, high vigilance is required as a possible association may increase autoimmune encephalitis incidence.

Introduction

The new coronavirus disease (Covid-19) was initially detected in Wuhan, China, in December 2019 [1]. There are now established Covid-19 cases with neurological symptoms, which developed either through direct harm of the central nervous system (CNS) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or via autoimmune processes [2, 3]. Several neurological complications have been described: encephalitis, meningitis, cerebrovascular diseases, acute disseminated encephalomyelitis (ADEM), and encephalopathies [4, 5].

Encephalitis is an inflammatory condition affecting the brain. Its etiologies are diverse. There are two main types of immune mediated encephalitis: (1) the paraneoplastic encephalitis syndromes, often associated with antibodies against intracellular neuronal proteins (onconeuronal proteins) [6]; (2) encephalitis syndromes associated with antibodies against neuronal cell surface/synaptic proteins, known as autoimmune encephalitis (AE) [7]. While paraneoplastic encephalitis syndromes are invariably cancer-related, autoimmune encephalitis syndromes may occur in the presence or absence of cancer.

AE includes a spectrum of disorders depending on the type of autoantibodies that are directed against various receptors and synaptic receptors and channels. The most common type of AE is the anti-N-methyl-d-aspartate receptor (anti-NMDAR) encephalitis, which was first described by Dalmau and colleagues in 2008 [8].

More recently, many new antibodies targeting neuronal surface antigens and synaptic proteins causing different forms of AE have been discovered, including those caused by autoantibodies targeting GABAB-R, GABAA-R, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), and contactin associated protein-like 2 (CASPR2), leucine-rich glioma inactivated 1 (LGI1), dipeptidyl-peptidase-like protein 6 (DPPX), Ig LON5, and others [9].

Keywords:
Autoimmune encephalitis, Covid-19, refractory seizures, Anti-NMDA receptor encephalitis.
Additionally, AE might be the diagnosis behind new onset refractory seizure or status (NORSE), atypical movement disorders, rapidly progressive dementia of unknown etiology, or psychiatric and behavioral disturbances, sometimes mistaken for primary psychiatric illnesses [10].

In addition to the established association of AE with tumors like, e.g., ovarian teratoma in anti-NMDAR encephalitis, also the possibility of an association with SARS-CoV-2 infection arose. At present, there are few reported cases with positive anti-NMDAR encephalitis in association with COVID-19 [11, 12]. Nevertheless, this possible association will need more attention when neurologists, psychiatrists, and physicians face cases of unexplained refractory seizure and/or psychiatric manifestation.

Here, we report a unique case of a 6-year-old boy who presented with repeated attacks of refractory focal seizures, associated with autoimmune encephalitis.

**Case report presentation**

The parents of a 6-year-old boy from Erbil, Iraq, with normal perinatal and developmental history and no other known medical illnesses noticed an unusual decreased physical and cognitive activity, as new-emerging eating disorders. After a few days, while sleeping, the child developed abnormal body movements restricted to the left face and left body side with impaired consciousness. Therefore, he was taken to a pediatric emergency department.

After admission, the focal seizures, altered consciousness, and fever continued for two weeks. Consequently, he had to be intubated for 5 days in a Respiratory Care Unit (RCU), from which he was discharged after the seizures became less frequent. As per clinical findings, the patient was drowsy and mute, he had orofacial dyskinesia, and spastic quadripareisis, with infrequent focal seizures.

**Figure 1:** MRI showing bilateral deep white matter cerebral hemispheres increased T2/Flair signal and mild brain atrophy.
A brain MRI showed bilateral deep white matter cerebral hemisphere increased T2/FLAIR signal (Fig.1). EEG detected diffuse slowing and abnormal epileptic discharge (Fig.2).

Cerebrospinal Fluid (CSF) was clear and colorless. CSF glucose level was 55.7 mg/dL, and CSF total protein 14.6 mg/dL. No abnormal cells were detected. CSF oligoclonal bands (OCB) were positive. Real-time polymerase chain reaction (RT-PCR) assay was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Central Nervous System (CNS) tuberculosis and Viral Encephalitis were excluded by Cerebrospinal fluid polymerase chain reaction (CSF-PCR) assays. Serum and CSF anti-NMDA receptor IgG Ab were positive.

The therapeutic intervention started with intravenous (IV) methylprednisolone therapy (15 mg/kg/day) for 5 days, followed by intravenous immunoglobulin (IVIG), according to the high-dose immunomodulatory therapy strategy (1,000 mg/kg), for 5 days [13]. Anti-seizure medication (ASM) was commenced as well.

In the following weeks a mild improvement in terms of enhanced consciousness, limbs movements, and weight gain was observed. Therefore, the nasogastric tube was removed, and oral feeding restarted. We monitored the child through regular evaluations and biochemical analyses until complete clinical recovery. ASM was not discontinued. The overall treatment was well tolerated.

**Discussion**

Autoimmune encephalitis is a condition that can be easily missed as it is not commonly considered in the differential diagnosis of various medical presentations. However, such diagnosis should be always taken into consideration when a person, particularly a child, presents with a new onset of refractory status epilepticus (NORSE) and/or new behavioral or psychiatric conditions. An early diagnosis of AE is essential, as the treatment is different from other conditions. With correct timely interventions the outcome is frequently favorable.

Though SARS-CoV-2 virus rarely invades the nervous system, Covid-19 infection frequently causes neurological symptoms like headache, delirium, anosmia, and dysgeusia [14]. One of the mechanisms of indirect nervous system involvement is through inflammatory response and immune dysregulation. There are few recorded cases
of indirect involvement of CNS by auto-antibodies that are directed against the surface and synaptic protein. This case is one of the rare cases of Anti-NMDA antibody autoimmune encephalitis that is associated with Covid-19 infection [15]. It indicates that in the era of COVID-19, high vigilance is required as a possible association may increase AE incidence.

A recent systemic review that analyzed 16 studies, including a total of 161 patients with NORSE [16], showed that the most frequent cause was AE. In addition to the well-known association with teratoma and cancer, AE, and specifically Anti-NMDA receptor Ab encephalitis, could be associated with a SARS-CoV-2 infection, either concomitantly or as post-infection manifestation. In this reported case, immunotherapy, in addition to anti-seizure medication, showed to be effective.

The main limitation of this report is the relatively short follow-up period. Observation of the child is ongoing to detect possible medium- or long-term consequences.

Conclusion

This case demonstrated that autoimmune encephalitis should be always considered when facing a new onset of refractory epilepsy and/or abnormal behaviors, and that it could be associated with SARS-CoV2 infection. Early diagnosis of an autoimmune encephalitis and ensuing correct treatment can be lifesaving.

Statement of Ethics: The parents of the child involved in this study have given their written informed consent to publish his case (including the publication of images). Ethical approval is not required for this study in accordance with national guidelines.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Funding Sources: This case report required no funding.

References