Case Report / Olgu Sunumu

DOI: 10.4274/cayd.galenos.2024.45087
J Pediatr Emerg Intensive Care Med 2024;11:137-40

Diagnostic Challenges in a Nine-year-old Boy with ADEM and Longitudinal Extensive Transverse Myelitis

ADEM ve Longitudinal Ekstensive Transvers Miyelitli Dokuz Yaşında Bir Erkek Çocukta Tanı Zorlukları

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Abstract

Acute disseminated encephalomyelitis (ADEM), or postinfectious encephalomyelitis, is a demyelinating central nervous system disease that typically presents with multifocal neurologic symptoms and encephalopathy. Numerous pathogens have been associated with ADEM, and the implicated viruses include coronavirus, coxsackie, cytomegalovirus, Epstein-Barr, herpes simplex, hepatitis A, HIV, influenza, measles, rubella, varicella zoster, and adenovirus. Although severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection has been associated with ADEM, the incidence is quite low. We present the case of a 9-year-old boy with ADEM plus longitudinal extensive myelitis who had a SARS-CoV-2 infection history and acute adenovirus infection. We evaluated the diagnosis and treatment challenges. Although our patient had severe neurological respiratory failure requiring intubation and tetraplegic flaccid paralysis, he had a total recovery before hospital discharge.

Keywords: ADEM, adenovirus, COVID-19, transverse myelitis, children, rituximab

Öz

Akut dissemine ensefalomiyelit (ADEM) veya postenfeksiyöz ensefalomiyelit, tipik olarak multifokal nörolojik semptomlar ve ensefalopati ile ortaya çıkan, demiyelinizan bir merkezi sinir sistemi hastalığıdır. Çok sayıda patojen ADEM ile ilişkilendirilmiştir ve ilişkili virüsler arasında koronavirüs, koksaki, sitomegalovirüs, Epstein-Barr, herpes simpleks, hepatit A, HIV, grip, kızamık, kızamıkçık, varicella zoster ve adenovirüs yer alır. Şiddetli akut solunum sendromu-koronavirüs-2 (SARS-CoV-2) enfeksiyonu ADEM ile ilişkilendirilse de görülme sıklığı oldukça düşüktür. SARS-CoV-2 enfeksiyon öyküsü ve akut adenovirüs enfeksiyonu olan, ADEM ve eşlik eden longitidünal yaygın transvers miyelitli 9 yaşında bir erkek hastayı sunduk. Tanı ve tedavi zorluklarını değerlendirdik. Hastamızda entübasyon gerektiren ciddi nörolojik solunum yetmezliği ve tetraplejik flask paralizi olmasına rağmen hastaneden taburcu olmadan tamamen iyileşti.

Anahtar Kelimeler: ADEM, adenovirüs, COVID-19, transverse myelit, rituksimab

Introduction

Acute disseminated encephalomyelitis (ADEM), also known as postinfectious encephalomyelitis, is a demyelinating central nervous system disease that typically presents with multifocal neurologic symptoms and encephalopathy.[1] A febrile or viral infection precedes ADEM. Neurological complications following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Coronavirus disease-2019 (COVID-19) infection have been reported in the literature, ranging from acute to weeks following infection with SARS-CoV-2.[2] There are only a few case reports in the literature about postvoid or COVID-related ADEM in children.[3] We know that adenoviral infection can also result in neurological dysfunction and ADEM.[4] Here, we present the case of a 9-year-old boy with ADEM plus longitudinal extensive transverse myelitis (LETM) and evaluate the diagnosis and treatment challenges.

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Received/Geliş Tarihi: 20.08.2023 **Accepted/Kabul Tarihi:** 17.05.2024

Case Report

A nine-year-old previously healthy boy presented to the emergency room with a history of fever, nausea, vomiting, and diarrhea. He was unconscious; his Glasgow Coma scale (GCS) 8 (E:2, V:2, M:4), and his brain computed tomography and diffusion brain magnetic resonance imaging (MRI) were normal. His parents' COVID-19 tests were positive, and he lost his sense of smell 6 weeks ago. On admission to our pediatric intensive care unit (PICU), the patient was unconscious and there was no nuchal rigidity. His GCS was 8-10, pupils were bilaterally equal and reactive to light, deep tendon reflexes (DTR) were negative, and the Babinski sign was bilaterally positive. His basic laboratory markers (such as hemogram, electrolytes, liver function tests, and kidney function tests) were normal, but he had elevated inflammatory markers (such as C-reactive protein and sedimentation). His nasopharyngeal swap and stool analysis revealed an acute adenovirus infection. A summary of his autoimmunity and infection laboratory results is shown in Table 1. His antinuclear antibody was positive. However, no other findings supported vasculitis or lupus.

Empirical ceftriaxone and acyclovir treatment were started. His EEG showed a delta coma. Brain MRI revealed bilateral symmetric patchy and confluent white matter lesions in the centrum semiovale and periventricular region as well as in the brainstem compatible with ADEM (Figure 1a). The whole spinal MRI showed multiple patchy expansile T2 hyperintense intramedullary lesions predominantly involving the central part of the spinal cord, which tended to merge with each other and extend longitudinally, suggesting acute LETM (Figure 2).

We initially treated the patients with 1 g/kg/day intravenous immunoglobulin for 2 days and 30 mg/kg/day IV methylprednisolone for 5 days. We continued with IV methylprednisolone, starting on 1 mg/kg/day and tapered over 3 weeks. His symptoms continued progressively after his initial treatment, and we started total plasma exchange

Table 1. Summary of infections and autoimmunity laboratory findings

Infections		**Autoimmunity**	
PCR SARS-CoV-2:	Negative	Anti-ds-DNA:	Negative
Anti-SARS-CoV-2 IgG:	Positive (986 U/mL)	ANA screening:	Positive
HIV ½:	Negative	Anti-SSA (anti-Ro):	Positive
HSV 1/2 IgG and IgM:	Negative	Anti-SSB (anti-La):	Negative
HTLV I/II:	Negative	C3 (N: 88-201 mg/dL):	98 mg/dL
CMV IgG and IgM:	Negative	C4 (N: 15-45 mg/dL):	13.5 mg/dL
EBV IgG, IgM, EBNA:	Negative	Anti-MPO and anti-PR3:	Negative
Blood cultures:	Negative	Anti-phospholipid antibodies:	Negative
Viral respiratory PCR panel:	Adenovirus positive	ESR (N: <15 mm/h):	42 mm/h
Cerebrospinal fluid			
Cells:	57/mm^3 (mononuclear)	**Cerebrospinal fluid**	
Proteins:	94 mg/dL	Anti-MOG:	Negative
Glucose:	70 mg/dL	Anti-AQP4:	Negative
PCR SARS-CoV-2:	Negative	Oligoclonal bands:	Negative
PCR multiple viral panels:	Negative		
Cultures (bacterial, fungal, mycobacterial):	Negative		

ANA: Antinuclear antibodies, AQP4: Aquaporin-4, C: Complement, CMV: Cytomegalovirus, EBV: Epstein-Barr virus, ESR: Erythrocyte sedimentation rate, HIV: Human immunodeficiency virus, HSV: Herpes simplex virus, HTLV: Human T-lymphotropic virus, MOG: Myelin oligodendrocyte glycoprotein, N: Normal range/value, PCR: Polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2

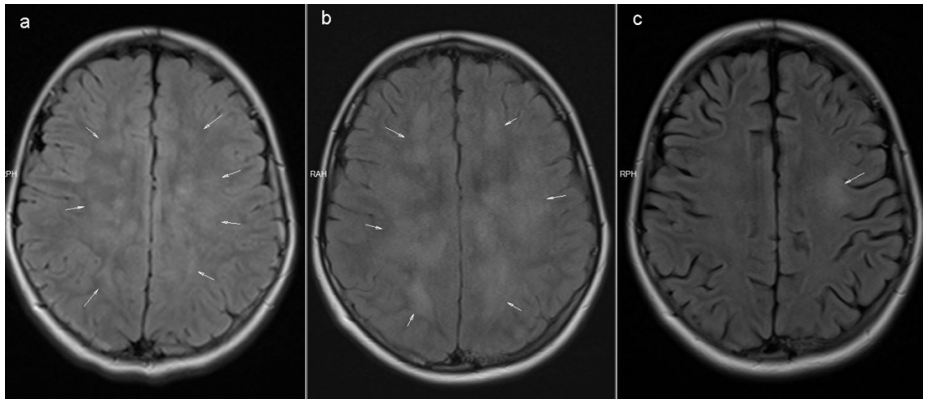

Figure 1. (a-c): Axial plane flair sequence of the patient on admission (a) demonstrates bilateral symmetric patchy and confluent white matter lesions in the centrum semiovale (arrows). One week later, the axial plane flair sequence of the follow-up MRI (b) shows that the white matter lesions coalesced over the 1-week period (arrows). One month later (c), the lesions substantially disappeared except for the left frontal cortical-subcortical lesion (arrow)
MRI: Magnetic resonance imaging

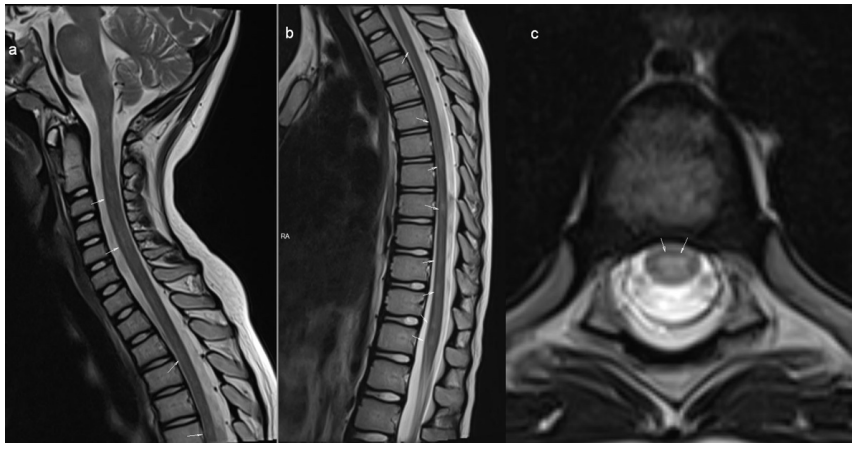

Figure 2. (a-c): Sagittal plane T2-weighted images of the spinal cord (a, b) reveal multiple patchy expansile T2-hyperintense lesions that tend to merge with each other, compatible with longitudinally extensive spinal cord involvement (arrows). Note the extension into the brainstem. An axial plane T2-weighted image of the spinal cord (c) demonstrates the central involvement of the cord (arrows)

(PLEX) on the third day and continued for 6 consecutive days. On the fifth day of PICU admission, we intubated him because of neurogenic respiratory failure. On his 10th day of PICU admission, he was intubated, his four limb muscle strength was 1/5, and his DTRs were negative. We performed a new brain MRI and observed that his white matter lesions were extended (Figure 1b). We gave him rituximab on the 11th day of admission and continued it once a week for a total of four doses. We extubated him on his 14th day, and he started to eat orally and did not require respiratory support or oxygen on his 17th day of PICU admission. He received physiotherapy support in all his PICU days. We transferred him to the pediatric ward on his 18th day in the PICU. We performed a new brain and spinal MRI and observed that all his lesions regressed (Figure 1c). He was discharged on the 38th day of his hospital stay. His examination on discharge showed that his four limb muscle strength was 5/5, DTR was normoactive, Babinski's sign was negative, and he was able to eat and walk without support.

Discussion

ADEM is an autoimmune disorder of the central nervous system that is triggered by environmental stimuli in genetically susceptible individuals.[1] Numerous pathogens have been associated with this disorder. Implicated viruses include coronavirus (and SARS-CoV-2 infection), coxsackie, cytomegalovirus, Epstein-Barr, herpes simplex, hepatitis A, HIV, influenza, measles, rubella, varicella zoster, and adenovirus.[1] Encephalopathy, the main characteristic feature of ADEM, develops within 7 days of prodromal symptoms. Neurological symptoms may include behavioral changes, confusion, irritability, restlessness, and coma.[2] Our patient had all these clinical features.

The pathophysiology of acute and post-acute neurologic manifestations of COVID-19 is likely multifactorial. Each of the following mechanistic pathways could interactively or independently cause disease: direct viral invasion and replication in the CNS, large vessel or microvascular insufficiency due to vasoconstriction or occlusion, non-specific effects of severe systemic COVID-19 illness or treatment, and immune system dysregulation and autoimmunity targeting cells, including myelin, neurons, axons, and oligodendrocytes.[1,2] The non-specific characteristic of COVID-19-related myelitis makes the diagnosis challenging, and it is mandatory to include several differential diagnoses, including other causes of infectious and metabolic syndromes.[5] Our case may have had immune system dysregulation due to COVID-19 and direct viral invasion due to adenovirus. However, our cerebrospinal fluid (CSF) examination did not show adenovirus in the patient's CSF.

Ismail II and Salama S reviewed the literature on COVID-19-related demyelinating diseases and found that 71/78 patients (90%) presented with encephalopathic clinical symptoms. There were 40 cases of transverse myelitis (TM), of which 24 were isolated TM and 16 were part of diffuse demyelinating processes. LETM was the most frequent future of spinal involvement reported in 19 of 24 (72.5%) cases of isolated TM.[6] They evaluated 20 children with ADEM with a median age of 9 years and 5 of 20 patients with myelitis. Similar to adults, 4 of 5 patients with myelitis showed LETM in children.[6]

Our patients also had ADEM with LETM and an acute adenovirus infection. Adenoviral infection can also result in neurological dysfunction and ADEM, and the lack of adenovirus in the CSF does not exclude CNS involvement.[4]

MIS-C may cause neurologic dysfunction in children.[7] Our patient had a positive COVID-19 serologic test but did not completely meet the MIS-C criteria.

The treatments might be divided into two categories: treatments addressed to the cause and immunological treatments to reduce inflammation and exacerbate the immune response that causes myelitis. Antibiotics and antivirals can be used to treat primary causes. We used empirical ceftriaxone and discussed cidofovir; however, we did not administer it. Because cidofovir has many side effects, our patient was in the late period of his adenovirus infection, and we did not demonstrate it in CSF. The immunological treatments are corticosteroids, immunoglobulins, PLEX, and rituximab in severe cases.[8] Corticosteroids should be started as soon as possible after diagnosis (methylprednisolone 30 mg/kg/day up to 1 g for 3 to 7 days), and PLEX is indicated if corticosteroid treatment fails.[8] In severe cases, rituximab may be used if the other first-line treatment fails. We used rituximab for 4 weeks for our patient because the clinical situation worsened after primary treatment.

The outcome of the children population was favorable in 13/20 (65%) COVID-19-related TM patients.[5] Rodríguez de Antonio et al.[4] demonstrated that only 1/18 patients had total recovery. Although our patient had severe neurological respiratory failure requiring intubation and tetraplegic flaccid paralysis, he had a total recovery before hospital discharge.

In Conclusion, COVID-19-related demyelinating diseases are rare and life-threatening in children. Early diagnosis and appropriate treatment are critical for lifesaving outcomes.

Acknowledgments

We did not use any funding for this study. EA drafted the manuscript. EA, MUY, EA, TH, and EBD provided clinical data. EA, MUY, and EA participated in a literature search. All authors contributed to the study and approved the submitted version.

Ethics

Informed Consent: Informed consent was obtained from our patient's family. However, written consent was not obtained because the publication was retrospective and did not show patient personal information.

Authorship Contributions

Surgical and Medical Practices: E.A., M.U.Y., E.Az., Concept: E.A., M.U.Y., E.Az., T.H., Design: E.A., M.U.Y., E.Az., T.H., Data Collection or Processing: E.A., B.D., Analysis or Interpretation: E.A., B.D., H.T., Literature Search: E.A., M.U.Y., E.Az., T.H., Writing: E.A., M.U.Y., E.Az., T.H., B.D., H.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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