

Case Report

A Rare Case of Anti-NMDA receptor encephalitis: CMV positivity, *MTHFR* 677T variant and hematoma on neuroimaging

Anti-NMDA Reseptör Ensefalitinin Nadir Bir Olgusu: CMV Pozitifliği, MTHFR 677T Varyantı ve Nörogörüntülemeye Hematom

Basak Gokcay¹, Safa Mete Dagdas², Mehmet Semiz³, Dilek Cavusoglu⁴, Nihal Olgac Dunder⁵

¹Afyonkarahisar Health Science University, Pediatric Neurology, Afyon, Türkiye

²University of Health Sciences, Izmir City Hospital, Pediatric Neurology, Izmir, Türkiye

³University of Health Sciences, Izmir City Hospital, Pediatric Neurology, Izmir, Türkiye

⁴Afyonkarahisar Health Science University, Pediatric Neurology, Afyon, Türkiye

⁵Izmir Katip Celebi University, Pediatric Neurology, Neuroscience, Izmir, Türkiye

ABSTRACT

Herpes simplex virus (HSV) encephalitis represents the leading cause of severe encephalitis in the pediatric population. Recurrence of clinical manifestations is rarely observed. Recurrence is thought to result from secondary autoimmune processes rather than active viral infection. One of the most common etiologies of autoimmunity is anti-NMDA receptor encephalitis. Early recognition is essential for patient outcome in this treatable autoimmune encephalitis. Patients typically present with abnormal behavior and posture, speech disturbances, seizures, movement disorders, dyskinesias, and altered levels of consciousness. We describe a 21-month-old male presenting with fever, diarrhea, vomiting, seizures, and movement disorders.

Keywords: *nmda receptor, anti- nmda receptor encephalitis, hsv enfektion, encephalitis, pediatric*

ÖZET

Herpes simplex ensefaliti çocukluk döneminde ensefalitin en sık nedenidir. Ender olarak klinik semptomların rekürrensi görülür. Rekürrens virus invazyonundan ziyade sekonder otoimmun mekanizma sonucu gelişir. Otoimmunitenin en sık etiyolojilerinden birisi de anti NMDA reseptör ensefalitidir. Tedavi edilebilir otoimmun ensefalit olan bu tabloda hızlı tanı konulması hastalığın prognozu açısından önemlidir. Hastalar anormal davranış ve duruş, konuşma bozukluğu, nöbet, hareket bozukluğu, diskineziler ve bilinç düzeyinde azalma şikayetleri ve bulguları ile başvururlar. Ateş, ishal, kusma, nöbet ve hareket bozuklukları ile başvuran 21 aylık bir erkek olguyu sunuyoruz.

Keywords: *nmda reseptör, anti nmda reseptör ensefalit, hsv enfeksiyonu, ensefalit, pediatrik*

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Correspondence / Yazışma: Dilek Cavusoglu · Afyonkarahisar Health Science University, Pediatric Neurology, Afyon, Türkiye · dilekcavusoglu83@gmail.com

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INTRODUCTION

Autoimmune encephalitides are a group of inflammatory diseases characterized by immune responses directed against cell-surface and synaptic proteins. Anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis is the most common form of autoimmune encephalitis in pediatric patients. Although it is a very rare disease, rapid diagnosis and treatment are essential. It is an acute form of encephalitis caused by an autoimmune reaction against the GluN1 subunit of the NMDA receptor. The onset of this encephalitis is typically marked by neuropsychiatric syndromes(1). The condition manifests with a wide range of symptoms, such as progressive impairment of consciousness, cognitive deficits, seizures, dyskinesias, and autonomic dysfunction(2). A diagnosis of anti- NMDA receptor encephalitis can be made when all three of the following criteria are met, rapid onset of at least four of the six following major groups of symptoms (abnormal behaviour or cognitive dysfunction, speech dysfunction, seizures, movement disorder, dyskinesias, or rigidity/abnormal postures, decreased level of consciousness, autonomic dysfunction or central hypoventilation). At least one of the following laboratory study results, abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush), cerebrospinal fluid (CSF) with pleocytosis or oligoclonal bands. Reasonable exclusion of other disorders(3). Most patients with encephalitis undergo brain magnetic resonance imaging (MRI) at early stages of the disease. Although findings are often normal or non-specific, they may sometimes point to an underlying autoimmune cause(4).

Herpes simplex encephalitis has been most commonly reported in association with the development of subsequent autoimmune encephalitis(5). The classic presentation for an herpes encephalitis starts with a "flu-like" prodrome that is followed by severe headaches, nausea, vomiting, and altered consciousness. Other common symptoms include seizures, cranial neuropathies, cognitive changes, and movement disorders(6).

CASE REPORT

A 21-month-old male was admitted with complaints of diarrhea, vomiting, fever and seizures. Two seizures were described as focal and unresponsive, each lasting approximately 5-10 minutes. On

admission, apart from the patient being lethargic, the rest of the neurological examination was normal. The brain computed tomography (CT) scans showed a hematoma area in the right frontotemporal region compatible with edema around it (Figure.1). Due to the seizure the patient was loaded with phenytoin and then switched to maintenance therapy. A 3% NaCl infusion was started at an anti-edema dose. The patient with intracranial hemorrhage, edema and lethargy was referred to an intensive care unit of another hospital. In blood tests performed at an external center, HSV IgM and HSV IgG positivity were observed. The focal temporal involvement including on neuroimaging findings, papilledema, seizures, and impaired consciousness were pointed to most likely diagnosed HSV encephalitis. Therefore, the patient was empirically treated with acyclovir for 21 days. Unfortunately, lumbar puncture could not be performed due to papilledema. Two days after discharge, he presented to our clinic with restlessness, inability to feed, and meaningless movements. When he was discharged from the other hospital, he had no these complaints. The patient was hospitalized for further evaluation and management. Empirical therapy with acyclovir was initiated for suspected HSV infection. The brain MRI showed sequela atrophic changes and encephalomalacia in the cortico-subcortical areas in the right frontotemporal region on the FLAIR images (Figure.2). The EEG revealed delta brushes activity originating from bilateral temporal regions. On follow-up, the patient developed focal tonic posturing involving either the arm or the leg. The seizures usually lasted for 1-2 minutes. He was treated with carbamazepin, clonazepam and topiramate. Lumbar puncture was performed. This revealed elevated protein (140 mg/dl). Anti-NMDA receptor antibodies were positive in serum and CSF. The patient received IVIG treatment (2 G/kg) for two days and pulse steroid (30 mg/kg/day) for 5 days followed by oral prednisolone (1 mg/kg/day) tapering over 14 days and discontinued. Moreover, the patient presented left hemiparesis (MRC grade 2/5). Difficulty swallowing, involuntary movements, tachycardia, restlessness, and then autonomic dysfunction developed. He was transferred to an intensive care unit. Firstly, the patient was treated with five sessions of plasma exchange. Unfortunately, a positive CMV PCR was detected and he was given ganciclovir treatment for 21 days. Humoral and cellular immunities were investigated, but no evidence of immunodeficiency was found. Additionally,

expanded immunodeficiency genetic panel revealed no disease-causing variant. Then, he was treated with rituximab (375 mg/m²) for four doses. Clinically rituximab provided a significant improvement of autonomic instability and motor deficits. Furthermore, MRI cerebral venography revealed venous sinus thrombosis in the right main and superficial veins. Comprehensive thrombophilia evaluation revealed the *MTHFR* C677T homozygous variant. He was treated with low-molecular-weight heparin 1 mg/kg twice daily for 20 days and then reduced to single dose. At discharge, his neurological examination revealed left hemiparesis (MRC grade 4/5) and head and neck control in sitting only with support. During follow-up, the patient revealed epileptic spasms with the EEG pattern of hemi-hypsarrhythmia related to the underlying structural abnormality.



Figure 1. Hematoma area in the right frontotemporal region.

DISCUSSION

Herpes simplex encephalitis is the most commonly reported viral infection associated with the development of subsequent autoimmune encephalitis. Recent studies have identified autoantibodies targeting neuronal antigens, most commonly against NMDA receptors. The major group of symptoms criteria include rapid onset (less than 3 months) of at least four of six major groups of clinical symptoms: abnormal psychiatric, behavior or cognitive dysfunction; speech dysfunction (pressured speech, verbal reduction, mutism); seizures; movement disorder, dyskinesias, or

rigidity/abnormal postures; decreased level of consciousness; and autonomic dysfunction or central hypoventilation(8). While psychiatric symptoms predominate in adults, children usually present with prominent neurological manifestations(9). A diagnosis of NMDA encephalitis is confirmed by a combination of CSF, EEG, and brain MRI. The pleocytosis demonstrates in CSF(10). A definite diagnosis can be provide in the presence of one or more of the six major group of symptoms and positive NMDAR antibodies. The NMDA receptor in the CSF is more sensitive and specific than anti-NMDAR antibodies in the serum samples(8). In the present case, CSF analysis revealed pleocytosis and the presence of anti-NMDAR antibodies. EEG of our patient also demonstrated extreme delta brush activity, a characteristic finding in anti-NMDA receptor encephalitis. Autoimmune encephalitis should be considered in patients with a prior history of viral encephalitis who develop movement disorders, seizures, fever, or neuropsychiatric symptoms(11).

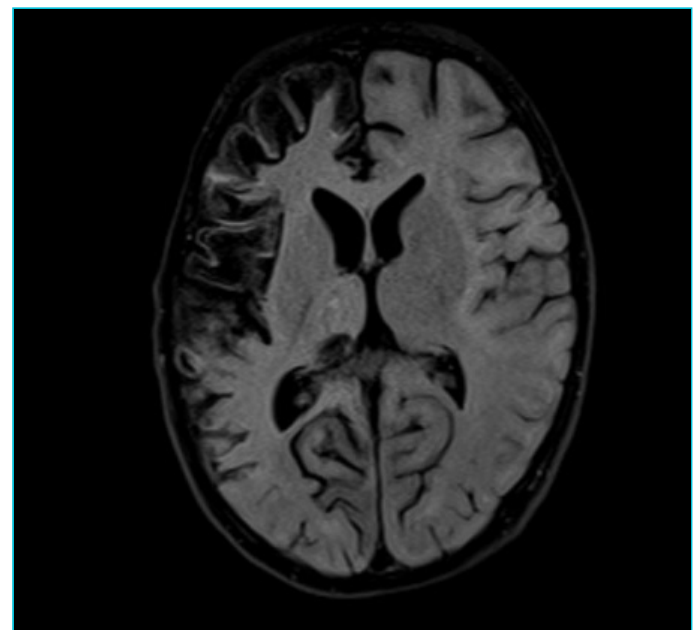


Figure 2. Axial fluid attenuated inversion recovery (FLAIR) image showed sequela atrophic changes and encephalomalacia in the cortico-subcortical areas in the right frontotemporal region on brain MRI.

The first-line treatment for anti-NMDA receptor encephalitis comprises corticosteroids, IV immunoglobulin, and plasmapheresis, while second-line options include rituximab and cyclophosphamide. In patients who are refractory to first-line treatment, like our case, second-line immunotherapy may enhance clinical outcomes(13).

Sinus venous thrombosis (SVT) is the result of thrombosis in the cerebral venous sinuses, leading to impaired venous drainage. Endothelial damage, venous stasis, and hypercoagulability contribute to thrombus formation. The most common risk factors include dehydration, infection, and coagulopathy(14). In our patient, both HSV and CMV infection, anti-NMDA receptor encephalitis and the presence of a homozygous *MTHFR* C677T mutation, a thrombophilia gene, may have contributed to the development of thrombosis. SVT and also HSV and CMV infection can result in intracranial hematoma or hemorrhagic infarction. We believe that anti-NMDA receptor encephalitis should be considered in patients presenting with seizures, involuntary movements, and altered levels of consciousness especially if there is a history of HSV infection. The diagnosis should be confirmed using imaging, EEG, and CSF analysis; the underlying cause should be investigated, and treatment should be initiated promptly

Physical therapy and rehabilitation are significant for these patients. We want to present a rare case of coexistence of NMDA encephalitis, CMV positivity in CSF, and *MTHFR* C677T homozygous mutation with hematoma on neuroimaging.

CONCLUSION

Physical therapy and rehabilitation are significant for these patients. We want to present a rare case of coexistence of NMDA encephalitis, CMV positivity in CSF, and *MTHFR* C677T homozygous mutation with hematoma on neuroimaging.

Patient Consent Form / Hasta Onam Formu

The parents' of this patient consent was obtained for this study.

Conflict of Interest / Çıkar Çatışması

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

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Author Contributions / Yazar Katkıları

Concept: BG,DC; design: BG,DC; supervision: NOD; materials: SMD,MS; data collection and/or processing: BG,SMD,MS; analysis and interpretation: DC,NOD; literature review: BG,DC; writing manuscript: BG,DC; critical reviews: NOD. All authors contributed to the final version of the manuscript and discussed the results and contributed to the final manuscript.

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