Osmangazi Journal of Med, 2025;47(5):828-833
DOI: 10.20515/otd.1638797

Case Report
Olgu Sunumu

Osmangazi Journal of Medicine
e-ISSN: 2587-1579

Cases of Anti-NMDAR Encephalitis Caused by HSV Encephalitis: Two Different Clinical Courses and Prognosis

HSV Ensefalitinin Neden Olduğu Anti-NMDAR Ensefaliti Olguları: İki Farklı Klinik Seyir ve Prognoz

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Informed Consent: The authors declared that informed consent form was signed by the patient.

Copyright Transfer Form: Copyright Transfer Form was signed by all authors.

Author Contribution Rates: Surgical and Medical Practices: ÖÖ, MT, LÖ, PO. Concept: ÖÖ, MT, LÖ,PO. Design: ÖÖ, MT. Data Collection or Processing: ÖÖ, MT, LÖ. Analysis or Interpretation: ÖÖ, MT, LÖ. Literature Search: ÖÖ,LÖ. Writing: ÖÖ,LÖ

Conflict of Interest Disclosure: There is no conflict of interest among the authors.

Sources of Funding: There is no funding/sponsorship for this study.

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

Received :12.02..2025
Accepted :13.02.2025
Published :11.06. 2025

Abstract: The recurrence of symptoms or the emergence of new clinical findings following herpes simplex virus encephalitis (HSVE) can result due to the relapse of the same viral agent, development of a new infectious encephalitis or autoimmune encephalitis. Differences in the presentation, clinical course, and electrophysiological findings of cases may be associated with variations in prognosis. In the first case of anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARE) following HSVE that we presented here, the patient exhibited epileptic seizures, and electroencephalography (EEG) revealed lateralized periodic discharges (LPDs) with plus modifiers. During the follow-up, status epilepticus developed and the patient did not respond to treatment and died. In contrast, the second case of anti-NMDARE following HSVE presented with psychiatric symptoms. EEG revealed LPDs in the form of a monomorphic blunt delta pattern. This patient responded rapidly to first-line treatments and achieved recovery with mild cognitive impairment. The pathogenic processes underlying the differences in clinical course and outcomes remain unclear, emphasizing the need for further research. Early initiation of immunotherapy is critical in patients with poor prognostic indicators after excluding HSVE relapse via polymerase chain reaction testing of cerebrospinal fluid.

Keywords: Herpes simplex virüs encephalitis; autoimmune encephalitis; lateralized periodic discharges; anti-NMDAR encephalitis

Özet: Herpes simpleks virüs ensefaliti (HSVE) sonrası semptomların tekrarlaması veya yeni klinik bulguların ortaya çıkması, aynı viral etkenin nüksü, yeni bir enfeksiyöz ensefalit ya da otoimmün ensefalit gelişimine bağlı olabilir. Olguların başvuru semptomlarındaki, klinik seyirlerindeki ve elektrofizyolojik bulgularındaki farklılıklar, prognozlarındaki değişikliklerle ilişkili olabilir. Burada sunduğumuz HSVE sonrası gelişen anti-N-metil-D-aspartat reseptör ensefaliti (anti-NMDARE) tanılı ilk olgu, epileptik nöbetler ile başvurmuş ve elektroensefalografisinde (EEG) artı modifikatörleri olan lateralize periyodik deşarjlar (LPD) tespit edilmiştir. Takibinde status epileptikus gelişmiş, hasta tedavilere yanıt vermeyerek eksitus olmuştur. Buna karşılık, HSVE sonrası gelişen ikinci anti-NMDARE olgusu psikiyatrik semptomlarla başvurmuş, EEG'sinde monomorfik künt delta paterninde LPD'ler gözlemlenmiştir. Bu hasta birinci basamak tedavilere hızla yanıt vermiş ve hafif bilişsel bozukluk ile iyileşme sağlamıştır. Klinik seyir ve sonuçlardaki farklılıkların altında yatan patogenetik süreçler henüz net değildir ve daha fazla araştırmaya ihtiyaç duyulmaktadır. Beyin omurilik sıvısında polimeraz zincir reaksiyonu testi ile HSVE nüksü dışlandıktan sonra, kötü prognostik göstergelere sahip hastalarda erken immünoterapinin başlatılması kritik öneme sahiptir.

Anahtar Kelimeler: Herpes simpleks virüs ensefaliti; otoimmün ensefalit; lateralize periyodik deşarjlar; anti-NMDAR ensefaliti

How to cite/ Atıf için: Öcek Ö, Tarı M, Öcek L Ortan P. Anti-NMDAR Encephalitis Caused by HSV Encephalitis: Different Courses and Prognosis, Osmangazi Journal of Medicine,2025;47(5):828- 833

1. Introduction

Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDARE) is an autoimmune encephalitis (AE) characterized by an acute or subacute onset of prodromal symptoms such as headache, nausea, vomiting, and fever, followed by psychiatric manifestations, seizures, memory impairment, speech disturbances, central hypoventilation, altered consciousness, autonomic dysfunction, and movement disorders primarily involving the face and oral region, but also affecting the limbs and trunk [1,2]. While predominantly affecting children and young women, it can also present in males and older individuals, with age-related variations in presenting symptoms. In middle-aged and older adults, initial symptoms often include altered consciousness, memory problems, paranoia, grandiose delusions, hallucinations, mania, anxiety, and insomnia. In contrast, children and young adults typically present with neurological symptoms such as movement disorders, including choreoathetosis, and epileptic seizures [1-3].

The clinical manifestation is attributed to antibodies targeting heteromers of the NR1 and NR2 subunits of the NMDA receptor [1,2]. Since it frequently has a paraneoplastic etiology, malignancy screening is important following diagnosis. Particularly in young women over the age of 18, up to 45% of cases are associated with bilateral or unilateral ovarian teratomas. However, AEs can also be triggered by infections caused by viruses, parasites, bacteria, or even Borrelia [1-4]. Among these, herpes simplex virus (HSV) is a common trigger [4]. It has been reported that 7–25% of patients develop NMDAR antibodies following HSV encephalitis (HSVE), typically within the first three months. The time to development of anti-NMDARE after HSVE is longer in adults but shorter in children [5].

Here, we aim to present two cases diagnosed with anti-NMDARE following HSVE, highlighting their different presentations, clinical courses, and prognoses in the context of the current literature.

2. Case Report

Case 1

A 37-year-old male admitted to the emergency department with fever, nausea, vomiting, speech disturbances, and epileptic seizures characterized by loss of awareness and convulsions in the right arm and leg, which had begun three weeks prior. He had no history of chronic illnesses or medication use. Neurological examination revealed the patient was conscious and globally aphasic but intact muscle strength and no evidence of meningeal irritation. Cranial magnetic resonance imaging (MRI) demonstrated an asymmetric hyperintense lesion in the left medial temporal lobe, hippocampal region, and insular cortex on T2-weighted sequences. Electroencephalography (EEG) showed lateralized periodic discharges with sharp and spike-wave activities of high amplitude in the left temporoparietal region (Figure 1). Cerebrospinal fluid (CSF) analysis confirmed HSV positivity. The patient was diagnosed with HSVE and started on acyclovir (2250 mg/day) for 21 days, after which his neurological symptoms fully resolved. On the 28th day of follow-up, the patient experienced a recurrence of fever and developed altered consciousness. Neurological examination revealed somnolence; the patient opened his eyes in response to verbal stimuli but could not establish cooperation or orientation to time and place, though he localized painful stimuli. Neuroimaging showed slight progression of the previously noted lesion. Repeated CSF analysis revealed 260 leukocytes/mm³ and elevated protein (136 mg/dL). A repeated viral encephalitis panel was negative. Autoimmune and paraneoplastic antibody panel was requested. Repeated EEG findings were consistent with nonconvulsive status epilepticus (NCSE), as the observed patterns were suppressed with diazepam and did not exhibit clinical seizures (Figure 2).

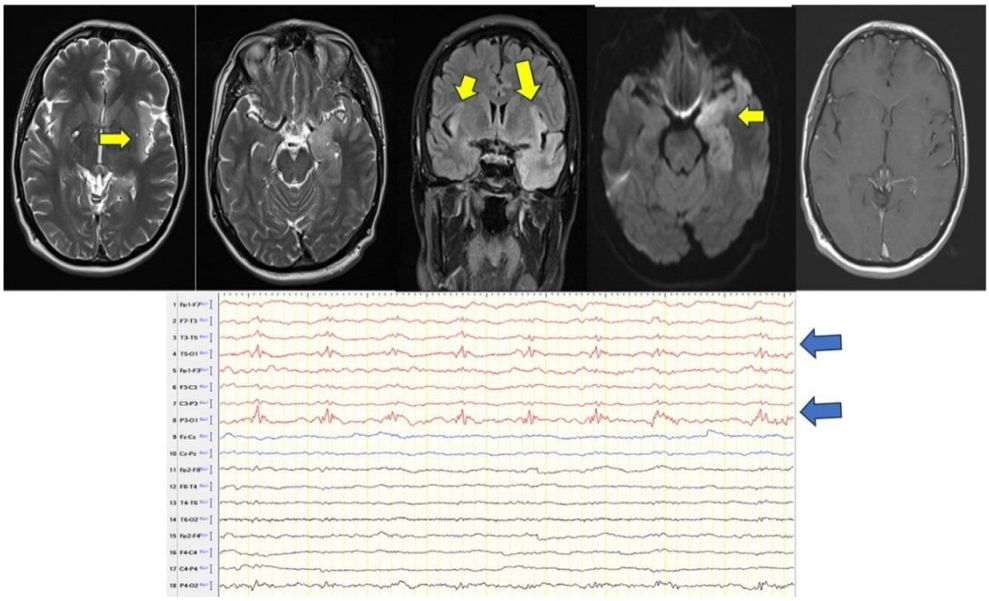

Figure 1. Cranial MRI and EEG examinations of the first case at the time of presentation. MRI demonstrated an asymmetric hyperintense lesion in the left medial temporal lobe, hippocampal region, and insular cortex (yellow arrows). EEG showed lateralized periodic discharges with sharp and spike-wave activities of high amplitude in the left temporoparietal region (blue arrows).

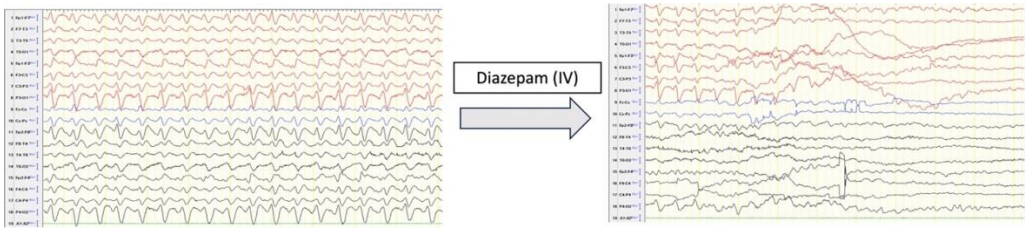

Figure 2. EEG findings were compatible with NCSE in the follow-up of the first case. Epileptiform discharges supressed after diazepam.

Due to lack of consciousness and continued EEG findings levetiracetam (3000 mg/day), phenytoin (300 mg/day), and lacosamide (400 mg/day) were started respectively. He was admitted to the neurology intensive care unit (ICU) for monitoring. Subsequent EEG revealed suppression of epileptic activity in the right hemisphere, with decreased amplitude of discharges in the left hemisphere, although prominent discharges persisted in the frontotemporal regions. His CSF was found to be positive for anti-NMDAR antibodies and we diagnosed his as having anti-NMDARE. The patient received 1000 mg/day of intravenous methylprednisolone (IVMP) for 10 days. Due to persistent altered consciousness, the patient was treated with intravenous immunoglobulin (IVIG) at 0.4 g/kg/day for five days. Malignancy screening was unremarkable. On the 40th day of follow-up, the patient's clinical condition deteriorated, with worsening consciousness. A new EEG revealed generalized slow-wave activity in the delta frequency range without epileptic discharges. The patient underwent seven cycles of plasmapheresis and than was treated with rituximab. Despite these interventions, focal seizures accompanied by oral automatisms recurred. EEG showed a re-emergence of periodic discharges and interictal fast rhythmic activity (plus modifiers). The patient was intubated and managed with midazolam, followed by thiopental infusion. Burst suppression patterns were

observed on EEG. The patient's condition continued to detoriate and sepsis developed during follow-up, and he died on the 67th day of hospitalization.

Case 2

A 35-year-old female admitted to our clinic with nonsensical speech, somnolence, paranoid thoughts of harmed by her relatives, inability to recognize her husband and children, and suspicious behaviors. Her medical history revealed that she had been admitted to another hospital four weeks ago due to altered consciousness and seizures. At that time, her EEG showed high-amplitude sharp-wave discharges in the left temporal regions, and cranial MRI revealed an edematous lesion involving the cortex and subcortical areas of the left temporofrontal lobe, including the insular cortex and hippocampus, without contrast enhancement. CSF analysis confirmed HSVE, for which she was treated with 21 days of acyclovir (750 mg/day) and levetiracetam (1000 mg/day). She was discharged with normal EEG findings and full resolution of her neurological symptoms. However, psychotic symptoms emerged eight days after discharge, the patient was taken to a psychiatry outpatient clinic by her family, where antipsychotic treatment was recommended. Due to her persistent symptoms, she admitted to our clinic. In our neurological examination she was conscious, sensorily aphasic, and exhibited full muscle strength but had persecutory delusions and referential ideation. Cranial MRI showed that the lesion had developed mild hemorrhagic characteristics and exhibited contrast enhancement. EEG demonstrated lateralized periodic discharges with a monomorphic blunt delta wave pattern in the left temporoparietal region (Figure 3). CSF analysis revealed elevated protein levels (71 mg/dL), the viral encephalitis panel was negative and anti-NMDAR antibodies was found to be positive therefore the patient was diagnosed as anti-NMDARE. Levetiracetam was discontinued and valproic acid (1000 mg/day) and olanzapine (5 mg/day) were started. Her agitation and persecutory delusions subsequently diminished. She received 1000 mg/day of IVMP for five days. Due to incomplete resolution of her clinical symptoms, she was additionally treated with IVIG at 0.4 g/kg/day for five days. Malignancy screening revealed no abnormalities. The patient's psychotic symptoms and EEG findings were resolved, and she was discharged. At her follow-up one month later, she demonstrated full recovery except for mild cognitive impairment.

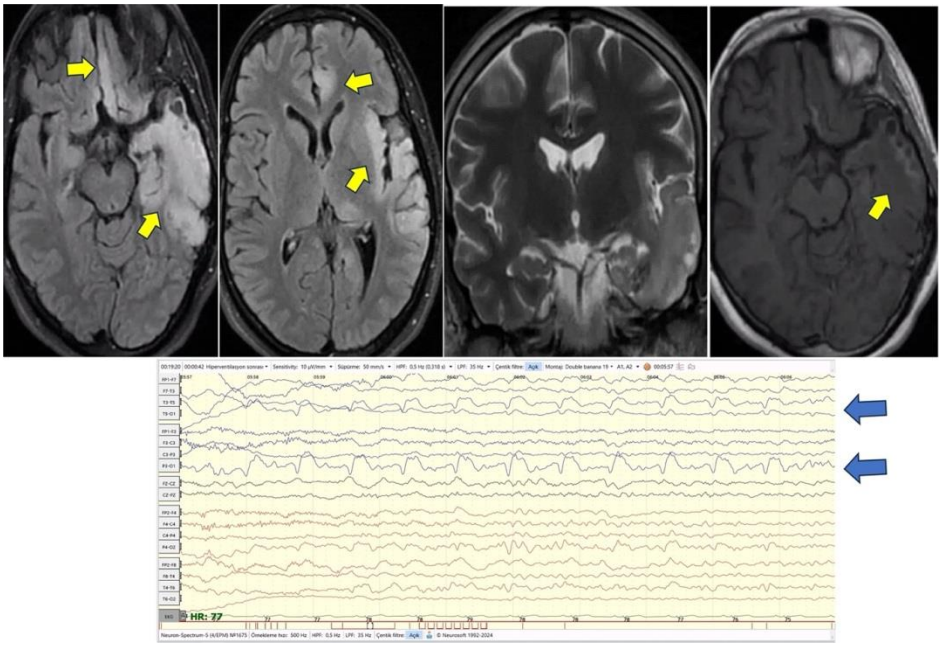

Figure 3. Cranial MRI and EEG examination of the second case at 6 weeks after HSVE. MRI showed that the lesion had developed mild hemorrhagic characteristics and exhibited contrast enhancement (yellow arrows). EEG demonstrated lateralized periodic discharges with a monomorphic blunt delta pattern in the left temporoparietal region (blue arrows).

3. Discussion

Despite the similarity in age between two cases, their clinical courses and outcomes were strikingly different. While the first patient presenting with altered consciousness and refractory epileptic seizures, did not respond to treatment and had a fatal outcome, the second patient, whom characterized by psychiatric symptoms, demonstrated a rapid recovery. These disparities in presentation, clinical progression, and therapeutic response may reflect the influence of distinct antibody profiles and underlying pathogenic mechanisms.

The pathogenesis of anti-NMDARE following HSVE remains unclear. Potential mechanisms include molecular mimicry, neuronal damage leading to expose the NMDA receptors to the immune system, altered NMDA expression post-HSV infection, immune system modulation by HSV, and misrecognition of NMDA receptors [6]. In a retrospective cohort study conducted in 2012 by Prüss et al. [7] NMDAR antibodies detected approximately 30% of HSVE patients. Leypoldt et al. [8] first reported anti-NMDARE following HSVE in an adult after it was identified in a pediatric patient in 2013.

Symptom recurrence or emergencing of new clinical findings after HSVE often complicate the diagnosis. The presence of new hemorrhagic or necrotic lesions on neuroimaging, detection of HSV deoxyribonucleic acid (DNA) by polymerase chain reaction in CSF, and response to acyclovir treatment may help to suggest HSVE relapse. In contrast, stable MRI findings or lesion enlargement as observed in our first case, negative viral encephalitis panel, and unresponsiveness to antiviral treatment indicates AE [9]. Contrast enhancement of lesions may occur in HSVE due to blood-brain barrier disruption [10]. In the second case, the emergence of mild contrast enhancement and hemorrhagic features on repeated MRI, were suggested that HSE relapse. However, the detection of anti-NMDAR antibodies and the absence of HSV DNA in CSF supported the diagnosis of anti-NMDARE in both cases.

Autoimmune encephalitis presents with diverse clinical manifestations, which are largely dependent on the different neuronal antigens and specific brain regions targeted by the autoimmune process [11]. In children and young adults, anti-NMDARE following HSVE commonly manifests as movement disorders and seizures, while adult patients frequently present with psychiatric symptoms and cognitive dysfunction. Due to the nature of initial symptoms, up to 70–77% of adult female patients are misdiagnosed with psychiatric disorders after being evaluated by psychiatrists [1,2]. Similarly, our second case presented with psychotic symptoms and was misdiagnosed with a psychiatric disorder.

Seizures occur nearly half of anti-NMDARE cases, either as an initial symptom or during the disease course. Generalized tonic-clonic seizures are most common, but focal seizures with or without impaired awareness may also occur [12,13] As in our first case, SE has been reported to be significantly associated with morbidity and mortality in anti-NMDARE. In a study of 109 cases by Liu X et al. [13] seizures occurred in 80.7% during the acute phase, with 25% experiencing non-refractory SE, 14.8% refractory SE, and 10.2% super-refractory SE. Certain EEG features, such as lateralized periodic discharges (LPDs) expecially with plus modifers (LPDs with rhythmic delta activity, fast activity, superimposed rapid sharp, spike waves) are linked to higher seizure and mortality risk. Both of our cases exhibited LPDs on their EEGs. Literature indicates that 58–100% of patients with LPDs experience clinical seizures [14]. LPDs of our first case was exhibiting plus modifiers, he presented with seizures and progressed to SE with a fatal outcome. In contrast, the second case, whom with monomorphic blunt delta patterned LPDs, did not experience seizures during follow-up and recovered fully except for mild cognitive symptoms.

Anti-NMDARE following HSVE typically responds well to immunotherapy in children older than four years [2]. Except HSVE, corticosteroids are the first-line treatment for autoimmune encephalitis. The treatment of post-HSVE anti-NMDARE remains debated. The literature suggests combining corticosteroids with antiviral therapy. IVIG is another acute-phase treatment, often administered as 0.4 g/kg/day for five days, with a repeat course if symptoms persist. Plasma exchange may also be used. Refractory cases may also require cyclophosphamide or rituximab [1-3]. All treatment steps were implemented in our first case but no success was achieved, whereas the

second case improved with corticosteroids and IVIG.

The prognosis of anti-NMDARE following HSVE is less satisfactory than isolated AE. Prolonged ICU stays, recurrent seizures, and development of SE significantly increase morbidity and mortality. In long-term follow-up may reveal persistent seizures or cognitive impairments [2,3,7]. Our first patient, who developed refractory seizures and SE, died during ICU follow-up, while the second patient achieved full recovery except for mild cognitive deficits.

It is essential to recognize that anti-NMDARE can occur following HSVE. The prognosis of patients varies significantly depending on clinical presentation, course, electrophysiological features, and treatment response. Future studies which will investigate the clinical significance and mechanisms of intracellular and neuronal surface antibody production may provide further insights into these differences.

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