Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis that Developed after Herpes Encephalitis: A Case Report and Literature Review

Ömer Bektaş[1] Tutku Tanyel[2] Bilge Aldemir Kocabaş[3] Suat Fitöz[4] Erdal İnce[3] Gülhis Deda[1]

[1] Department of Pediatric Neurology, Ankara University Medical School, Ankara, Turkey
[2] Düzen Laboratories Group, Ankara, Turkey
[3] Department of Pediatric Infection, Ankara University Medical School, Ankara, Turkey
[4] Department of Radiology, Ankara University Medical School, Ankara, Turkey

Address for correspondence Ömer Bektaş, MD, Ankara Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları A.B.D. 06100 Cebeci/Ankara, Turkey (e-mail: bektasomer@gmail.com).

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Abstract

Herpes encephalitis (HE) is among the most common forms of viral encephalitis. Earlier publications indicate the development of acyclovir-refractory choreoathetosis in patients with HE. These reports suggest the development of secondary autoimmunity in the pathogenesis of HE. Combined methylprednisolone and acyclovir treatment reduced the appearance of brain abnormalities relative to treatment with acyclovir alone in a mouse model of encephalitis. We describe a case of a 19-month-old previously healthy girl presenting with sudden onset seizures and loss of consciousness. Initial polymerase chain reaction (PCR) tests for the presence of herpes simplex virus (HSV) were negative as were the tests for the limbic encephalitis antibodies. Steroids were administered with acyclovir to treat suspected autoimmune encephalitis as a result of the patient history of varicella vaccination. HSV PCR testing was positive on the 5th day; however, steroid treatment was continued due to the positive response seen in the patient. Steroid therapy was reduced on the 25th day of treatment due to the development of upper respiratory tract infection and the patient developed orofacial dyskinesia and choreoathetoid movements on the 28th day. Antibodies against *N*-methyl-D-aspartate receptor were detected in the in the serum and cerebrospinal fluid (CSF) on the 28th day. This case is an example of the emergence of autoimmune symptoms in the pathogenesis of HE.

Keywords
- herpes encephalitis
- autoimmune encephalitis
- pediatric
- choreoathetoid movements
- relapse
- dyskinesia

Introduction

Herpes encephalitis (HE) is the most common form of lethal encephalitis in Europe and the United States.[1] Although the use of acyclovir as a selective antiviral agent has resulted in significantly improved patient outcomes, neurological sequelae or even death may occur in as many as 35% of affected individuals.[2] Not all symptoms attributed to HE occur as a result of neural lysis or direct viral invasion, and the general opinion is that direct viral cytotoxicity is unlikely to be solely responsible for relapses of the condition.[3] It has been postulated that secondary autoimmune mechanisms play a role in the pathogenesis of HE, which has led to several studies demonstrating the benefit adjunct steroid therapy in addition to acyclovir.[3]

The association between HE and anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis has been defined in adult[4–8] and pediatric[9–12] case series reports. Adult retrospective studies have also been published;[3] however, the number of prospective

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cases in the literature is limited but includes the case of a child with post-HE anti-NMDAR autoimmunity.[8,10,11] Presented herein is a similar case of a child with post-HE anti-NMDAR encephalitis, presenting with symptoms and magnetic resonance imaging (MRI) findings similar to the previously described cases.[9–12]

Case Report

A 19-month-old girl was brought to the emergency department with drooling and aphasia. The patient's gestational history was unremarkable, and her developmental milestones were normal. The child's parents reported no history of chronic disease but stated that she had been vaccinated for chicken pox 2 weeks earlier. Family medical history was unremarkable. During physical examination, the patient had a focal seizure characterized by drawing of the mouth to the right and clonic jerks in the right arm. Similar seizures occurred twice during early follow-up, spontaneously terminating each time. The initial cranial computed tomographic scan was normal. The patient was hospitalized, and because of the hourly recurrence of seizures, 20 mg/kg of phenytoin was administered followed by 20 mg/kg of phenobarbital.

A neurological examination revealed an unconscious patient with spontaneous eye opening who was capable of localizing painful stimuli (Glasgow Coma Scale (GCS) = 10). Deep tendon reflexes were normoactive, although pathological reflexes were absent. A midazolam infusion at an initial rate of 0.1 mg/kg/h failed to terminate the seizures, and doubling the dose was not successful. The seizures were brought under control by the initiation of 20 mg/kg/d intravenous levetiracetam given in two equal doses. The patient developed a transient fever of 38.5°C during follow-up, which prompted empirical treatment with acyclovir and ceftriaxone following lumbar puncture.

The patient's complete blood count and arterial blood gas analysis were normal. Serum biochemistry was also normal, including levels of acute phase reactants, ammonia, and lactate. Cerebrospinal fluid (CSF) analysis following lumbar puncture revealed glucose and protein levels of 54 mg/dL and 22 mg/dL, respectively. On microscopic examination of the CSF, one leukocyte and two erythrocytes were observed in each high-powered field. Both the serum and CSF samples were negative for antibodies against common viral pathogens or mycoplasma. Herpes polymerase chain reaction (PCR) testing of both CSF and serum, performed in two different reference laboratories, was negative (National Reference Laboratory and Ankara University Center Laboratory). Serum and CSF samples were also negative for autoantibodies in the limbic encephalitis panel (Anti-NMDAR, Hu, Ma2, Yo, CV2, Ri, VGKC, LGI-1, CASPR2, GAD, and AMPA). The serum levels of antithyroid peroxidase were normal. In the CSF, no additional oligoclonal bands were seen. A subsequent MR scan of the brain revealed the presence of hyperintense lesions (T2AG and Fluid-Attenuated Inversion Recovery [FLAIR] sequences) that were pronounced in the bilateral insular cortices, perisylvian area, and the temporoparietal area, and less obvious in the bilateral thalami. Restricted diffusion was observed in the same regions (►**Fig. 1 A–D**).

Intravenous immunoglobulins (IVIg) for 5 days at a dose of 400 mg/kg/d and oral prednisolone at a daily dose of 2 mg/kg were given to the patient. Lumbar puncture was repeated on the 5th day of acyclovir treatment. Results of the HSV PCR and HSV IgG index were positive in a second set of CSF samples, confirming the diagnosis of HE. As such, a decision was made to continue steroid and acyclovir treatment, citing the favorable response previously observed in the patient. On the 20th day of treatment, the patient was conscious and capable of expressing herself audibly, although she could not speak. She was also able to walk with support. Steroid administration was reduced on the 25th day to 1 mg/kg/d subsequent to the development of upper respiratory tract infection. On day 28, the patient suddenly developed hallucinations, choreoathetoid movements, and orofacial dyskinesia (►**Video 1**). Lumbar puncture was repeated, and although the CSF was negative for HSV by PCR, anti-NMDAR antibodies were detected (►**Fig. 2**). Antibodies against the NR1 subunit of the NMDA receptor were detected in the patient's serum and CSF using transfected cells produced by Euroimmun Medizinische Labordiagnostika AG (Luebeck, Germany, FA 112d-1005–1). A repeat cranial MRI showed early signs of atrophy in the opercular area (►**Fig. 1 E–H**). Findings from a computerized tomography scan of the thorax and abdomen were unremarkable, and serum levels of the tumor markers alpha fetoprotein and β-human chorionic gonadotropin were normal.

Video 1

Hallucinations along with choreoathetoid movements and orofacial dyskinesia suddenly developed in the patient.
Online content including video sequences viewable at: www.thieme-connect.com/products/ejournals/html/10.1055/s-0034-1387813.

Acyclovir was discontinued and the patient was given pulse methylprednisolone for 3 days at a dose of 30 mg/kg/d. IVIg treatment (400 mg/kg/d) was also administered for a second time. Plasmapheresis was performed three times a week for 3 weeks (nine sessions total). Although partial improvement was observed, second-line treatment with weekly rituximab (375 mg/m^2) and monthly cyclophosphamide (500 mg/m^2) were initiated because of the persistent serum and CSF anti-NMDAR positivity after 3 months.

Second-line immunotherapy was administered for approximately 6 months. The patient received a total of 12 doses of rituximab and 6 doses of cyclophosphamide. After second-line immunotherapy, anti-NMDAR antibody was negative both in serum and in CSF. As a result, the patient's clinical condition showed significant improvement. The patient's dyskinetic movements disappeared. She was aware of her environment, yet she was unable to speak. In addition, she

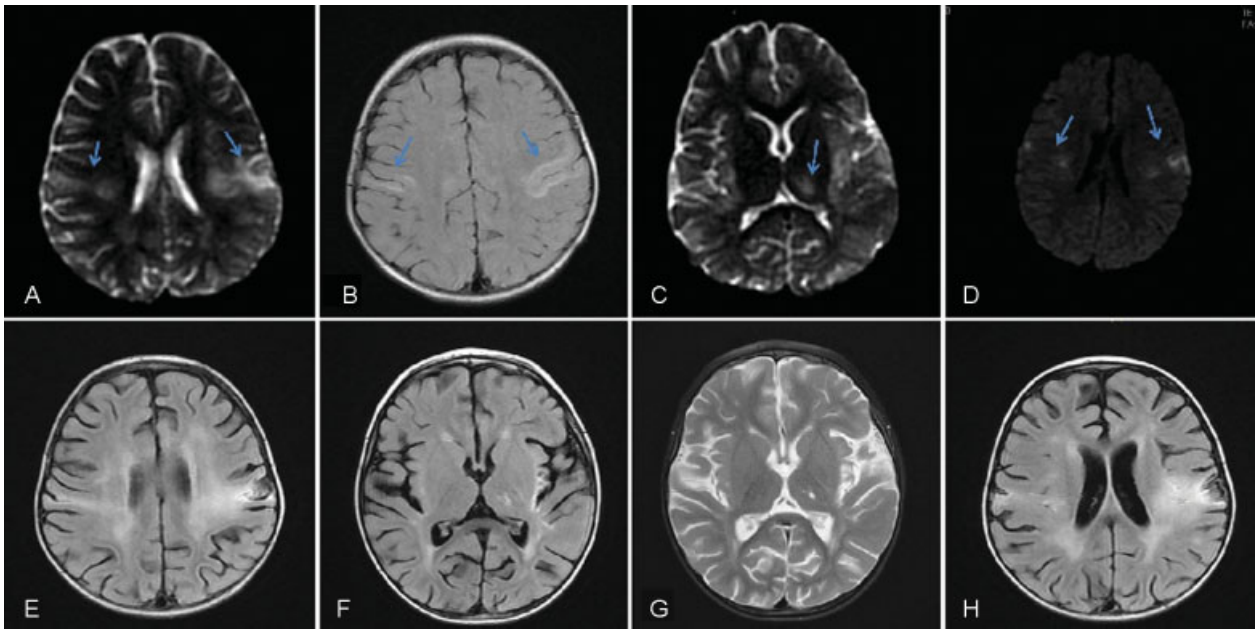

Fig. 1 Magnetic resonance imaging (MRI) findings of a patient who developed herpes simplex encephalitis (HSE) followed by anti-*N*-methyl-D-aspartate (anti-NMDAR) encephalitis. (A–D) The MRI findings during the first week of HSE. (A, B) Increased T2 and T2-FLAIR signal were demonstrated in the left medial temporal lobe, right insula, posterior basal ganglia, and bilateral opercular regions, and (C, D) increased signal in diffusion-weighted images. Arrows signify increased signal (hyperintensity). (E–H) The MRI obtained during admission for anti-NMDAR encephalitis, 1 month after HSE onset, showed no additional changes other than the interval evolution of areas of encephalomalacia in opercular regions and hippocampal atrophy.

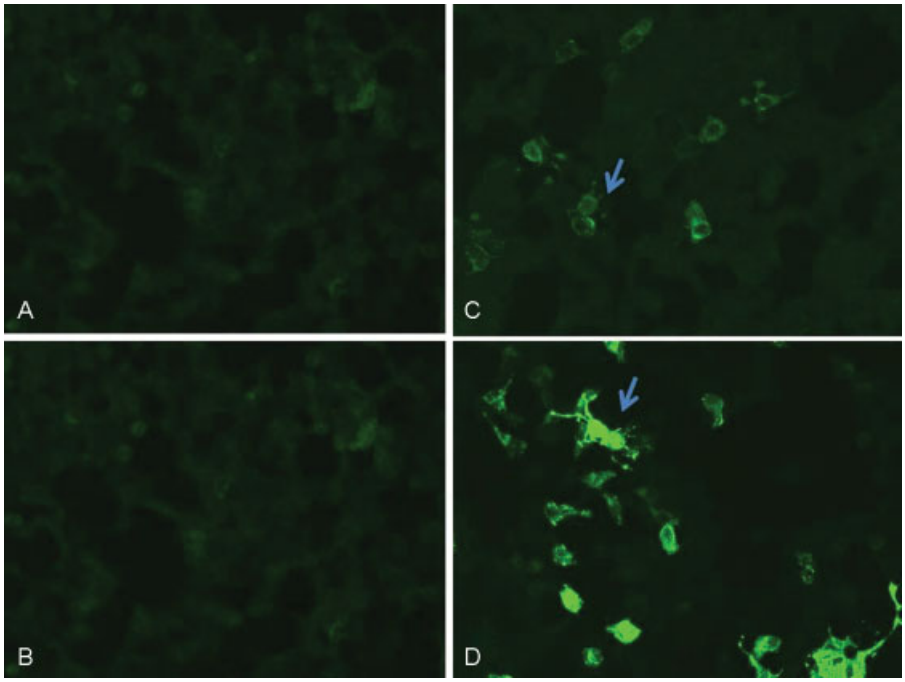

Fig. 2 Immunofluorescent microscopy reactivity of cerebrospinal fluid and blood at disease onset (A and B) were negative, whereas receptor antibodies (C and D) were present in serum and cerebrospinal fluid (CSF) on the 28th day. Antibodies against the NR1 subunit of the *N*-methyl-D-aspartate (NMDA) receptor were detected using transfected cells produced by Euroimmun. NR1-transfected cells (A, B, C, and D; original magnification ×200). The arrows represent immunopositive staining of transfected human embryo kidney (HEK) cells overexpressing the NR1 subunit of NMDARs. Arrows signify increased signal (hyperintensity). (The CSF sample is much more reactive than the blood sample.)

Table 1 Summary of pediatric cases with anti-NMDAR encephalitis secondary to Herpes encephalitis

Study	*n*	Identification[a]	Detection Time[a]	Ages/gender	MRI (T2) Lesions	Clinical presentation[a]	Treatment	Outcome
Armangue et al[11]	5	Prospective	After 1–4 wk from post-HE	2 mo/M	Extensive bilateral occipital, right temporal	Choreoathetosis, irritability, and sleep disorder	–	Day 130: Improved; deficits in visual tracking
				28 mo/F	Extensive bilateral temporal	Fever, agitation, insomnia, and choreoathetosis	IvMP, IVIg, Ritux, and CycP	Two years: Improved; normal exam, residual biopercular syndrome
				6 mo/F	Extensive bilateral temporal	Fever, irritability, insomnia, choreoathetosis, and unresponsiveness	IvMP, IVIg, Ritux, and CycP	Day 210: Partial improvement: no chorea, residual dysphagia, and hemiparesis
				8 mo/M	Extensive bilateral fronto-temporal	Irritability, unresponsiveness, seizures, and choreoathetosis	IvMP, IVIg, Ritux, and CycP	Day 120: Slight improvement
				24 y/M	Extensive bilateral temporal, insular	Progressive mania, irritability, disorientation, and memory dysfunction	IvMP	Day 119: Improved; residual memory impairment
Mohammad et al[12]	1	Prospective	After 15 d from post-HE	7 y/M	Unilateral temporal cortical and white matter lesions	Encephalopathy, chorea, dystonia, and dysautonomia	IVIg, and CycP	9 mo; residual motor and cognitive deficit
Hacohen et al[10]	2	Retrospective	After 4–5 wk from post-HE	10 mo/F	Unilateral temporal and frontoparietal	Orofacial dyskinesia, choreoathetosis, and cognitive regression	IVIg	Residual motor and cognitive deficit
				3 y/F	Left temporal lobe, right mesial, temporal lobe	Orofacial dyskinesia, choreoathetosis, and seizures	IVIg, MMF, and Ritux	Residual, cognitive, deficit
Armangue et al[9]	1	Retrospective	After 4 wk from post-HE	2 y/F	Right medial temporal lobe, right insula, posterior basal ganglia, and bilateral opercular regions	Fever, agitation, orofacial dyskinesia, and choreoathetosis	IVIg, Ritux, and CycP	Residual motor and cognitive deficit
Our case	1	Prospective	After 28 d from post-HE	19 mo/F	Left medial temporal lobe, right insula, posterior basal ganglia, and bilateral opercular regions	Orofacial dyskinesia and choreoathetosis	O-MP, IVIg, pl-ph, Ritux, and CycP	9 mo; residual motor and cognitive deficit

Abbreviations: CycP, monthly intravenous cyclophosphamide; F, female; HE, herpes encephalitis; IVIg, intravenous immunoglobulins; IvMP, intravenous methylprednisolone; M, male; mo, months; MRI, magnetic resonance imaging; MMF, mycophenolate mofetil; O-MP, intravenous methylprednisolone; NMDAR, *N*-methyl-D-aspartate; pl-ph, plasmapheresis; Ritux, Rituximab; y, years.
[a]Equal of anti-NMDAR ab.

was able to sit unsupported and crawl, but she remained unable to walk (►**Video 2**).

Video 2

The clinical presentation after second-line immunotherapy.
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Discussion

Following the description of the first pediatric case of anti-NMDAR encephalitis in 2007,[13] several additional cases have been identified.[14] The anti-NMDAR encephalitis than any other viral encephalitis is more common among patients who are younger than 30 years.[15] Pediatric cases resembling the present case have been previously described (►**Table 1**).[9–12] Anti-NMDAR encephalitis after HE occurs most commonly in children younger than 3 years and in middle-aged adults (mean, 53 years), with disease being more common among females in both populations. Anti-NMDAR positivity occurs at 1 to 4 weeks after HE in both adults and children, and was first noted at day 28 in the present case. In almost all the cases, involvement of the temporal region can be seen in MRI. Among pediatric cases, choreoathetosis occurs in 90% of individuals, seizures in 20%, and neuropsychiatric symptoms in 10% of patients. Choreoathetosis was observed in the initial stages of the present case. Among adult cases, seizures occur in 25% and neuropsychiatric symptoms in 38% of patients.[3,9–12]

The combination of acyclovir and corticosteroids for the treatment of HSV encephalitis was associated with improvement in earlier studies. Severe clinical outcomes of HSV encephalitis are associated with immunocompetent patients.[16] The most likely explanation for the development of anti-NMDAR encephalitis following HSV encephalitis is that virus-induced neuronal damage triggers a primary autoimmune response against NMDAR subsequent to the presentation of antigens which are normally shielded from the immune system.[3,17]

First-line immunotherapy, second-line immunotherapy, and tumor removal are the established treatments for anti-NMDAR encephalitis.[18] Teratoma has not been reported in cases with anti-NMDAR encephalitis secondary to HE. As many as 94% of the anti-NMDAR encephalitis case patients given first-line immunotherapy improve within the first 4 weeks;[18] however, pediatric cases with anti-NMDAR encephalitis secondary to HE are more resistant to treatment. Two cases (20%) improved with first-line immunotherapy and seven patients (70%) required second-line immunotherapy in a previous study. Similarly, partial improvement was observed to first-line immunotherapy in our patient to first-line immunotherapy.[9–12] Unlike previous cases, we administered early oral steroids and performed plasmapheresis, resulting in notable improvement. A total of 12 doses of rituximab and 6 doses of cyclophosphamide therapy resulted in substantial improvement, similar to other cases in the literature. Still, when the results of the treatment are taken into account, residual motor and cognitive deficits are observed in almost all pediatric cases with anti-NMDAR encephalitis secondary to HE. It is difficult to separate the effects of HE and anti-NMDAR autoimmunity on neurological sequelae. Choreoathetosis and orofacial dyskinesias occur in some patients during the first month of HE as a result of unknown etiologic factors.[19–21] The abnormal movements may last several months or years and are refractory to anti-epileptics and dopamine receptor antagonists.[19] These observations suggest a postinfection immune-mediated etiology.[19–21]

We present a case of a child with anti-NMDAR encephalitis secondary to HE encephalitis. The positive response observed following steroid use is supported by a recent retrospective study.[3] In this context, previously reported cases of patients with HE developing choreoathetosis refractory to acyclovir treatment,[19] patients with persistent postencephalitic seizures despite clearance of a herpes infection,[22] and HSV encephalitis patients who responded to corticosteroids[23] warrant reevaluation.

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