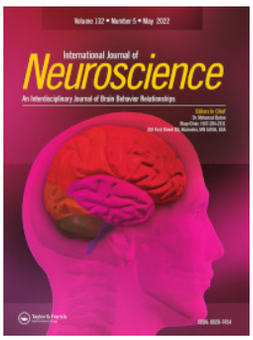

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CASE REPORT

Clinical outcome in an infant with anti-NMDA receptor encephalitis: case report and literature review

Dilek Cavusoglu[a], Cigdem Ozer Gokaslan[b] and Nihal Olgac Dundar[c]

[a]Department of Pediatric Neurology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyon, Turkey; [b]Department of Radiology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyon, Turkey; [c]Department of Pediatric Neurology, Faculty of Medicine, İzmir Katip Celebi University, Izmir, Turkey

ABSTRACT

Anti N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disease that often presents with various neurological and neuropsychiatric symptoms. Although most reported cases occur in children, only a limited number of studies on children are available. The subject of this case report is an 8-month-old female who presented with fever, vomiting, and seizure. She was diagnosed with encephalitis and treated with acyclovir. After 21 days, she showed irritability, seizure, orolingual-facial dyskinesias, choreodystonic movements, hemiparesis, dysphagia, strabismus, lack of interest in light and objects. Clinical signs, neuroimaging findings, and serum analysis of anti-NMDAR antibodies confirmed the diagnosis of anti-NMDAR encephalitis. After the first line of treatment, she showed full recovery. We update the infants with anti-NMDAR encephalitis in the literature. Clinical outcomes suggest that patients with anti-NMDAR encephalitis are mostly poor in the infants, excluding our case. We propose that early and appropriate treatments are critical for timely diagnosis and rapid improvement.

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KEYWORDS
Anti-NMDAR encephalitis; neuroimage; infant; outcome

What is known

- Encephalitis caused by antibodies to the NMDA receptor is well defined.
- Anti-NMDA receptor encephalitis is still the most overlooked cause of encephalitis in children.
- Anti-NMDA receptor encephalitis in infants is quite uncommon

What is new

- Clinical outcomes suggest that patients with anti-NMDAR encephalitis are mostly poor in the infants except this case.

Introduction

The anti N-methyl-D-aspartate (NMDA) receptors are glutamate-gated cationic channels localized in the brain with significant synaptic transmission and plasticity. The structures of the channels occur through combinations of GluN1, GluN2, and GluN3 subunits. As a result of immunoglobulin G subclass G1 autoantibodies connecting with extracellular areas of the GluN1 subunits, the layer NMDA receptors become antibody-mediated. The reduction of receptors, therefore, causes synaptic dysfunction that presents as distinctive clinical findings [1]. Encephalitis caused by antibodies to the NMDA receptor is well defined, but it is still the most overlooked cause of encephalitis in children, although 35-40% of anti-NMDAR encephalitis occurs in this patient group [2]. Reports of infant anti-NMDAR encephalitis, however, are quite rare. Here, we present a case of diagnosed anti-NMDAR encephalitis in an infant who responded well to treatment and describe infant anti-NMDAR encephalitis as currently reported in the literature.

Case presentation

An 8-month-old girl presented with fever, vomiting, and seizure. Cranial computed tomography results were normal. Tests of cerebrospinal fluid revealed

CONTACT Dilek Cavusoglu dilekcavusoglu83@gmail.com Department of Pediatric Neurology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Ali Çetinkaya Kampüsü Dörtyol Mah. 2078 Sok. No. 3/4 Afyonkarahisar, Afyon, 03100, Turkey

pleocytosis (50 cells per mm3) and raised protein (60 mg/dL). However, we could not study HSV in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) because it was not available at that time in the hospital. Intravenous acyclovir was administered for 14 days. She improved clinically and was discharged home. After 21 days, she developed irritability, seizures, orolingual-facial dyskinesias, choreodystonic movements, hemiparesis, dysphagia, lack of interest in light and objects, and strabismus. A second course of aciclovir was started. Brain magnetic resonance imaging (MRI) revealed T2 and FLAIR signal hyperintensity and atrophy, predominantly in the right temporo-occipital lobes, with cortex and adjacent white matter involvement [Figure 1A–C]. Laboratory tests for serum levels of lactate, ammonia, and cortisol vitamin B12; thyroid function tests; and tandem mass spectrometry screening for amino acids and acylcarnitines, urinary organic acids, and very-long-chain fatty acids showed normal results. In addition, serological results for serum herpes simplex virus (HSV) 1 and 2 immunoglobulin M (IgM) and IgG; mycoplasma pneumonia IgM and IgG; antinuclear antibody (ANA); and anti-double-stranded DNA (ds-DNA) antibody were all negative. The diagnosis was initially considered anti-NMDA receptor encephalitis, based on the clinical features and neuroimaging findings. The patient, therefore, received intravenous immunoglobulin (IVIG) 2 g/kg and then high-dose intravenous methylprednisolone (5-day pulse IV methylprednisolone 30 mg/kg/d), followed by oral prednisolone 2 mg/kg/d with slow tapering for 3 months. Subsequent serum analysis confirmed anti-NMDAR antibodies. At 15 days' follow-up, no neurological symptoms were present. During 18 months' follow-up, the patient showed normal psychomotor development, despite previously described MRI findings including T2 and FLAIR signal hyperintensity and atrophy, predominantly in the right temporo-occipital lobes, with cortex and adjacent white matter involvement.

Discussion

The subject of this case report is an 8-month-old female with anti-NMDA encephalitis who showed clinically marked improvement after treatment. We also reviewed 13 previous infant cases of anti-NMDA encephalitis for clinical manifestations, brain MRI, treatments, outcomes, and triggers [Table 1].

Clinical findings varied widely and included neuropsychiatric symptoms, movement disorders, seizures, autonomic dysfunction, insomnia, and speech disorders [14]. Children are more likely to present neurologic manifestations in anti-NMDAR encephalitis [1], and in all of the infants, clinical presentations also included altered mental status, movement disorders, fever, and/or seizures [Table 1]. In our patient fever, seizure, irritability, orolingual-facial dyskinesias, and choreodystonic movements were present.

Markers of viral infections overlapping NMDAR antibodies suggest a trigger of NMDAR antibodies during a second stage of immune-mediated encephalopathy after a viral infection [13]. Although viral infections are commonly responsible for anti-NMDAR encephalitis, a 6 month-old male [case 1] was reported after tuberculous meningitis [Table 1]. In our infant group, 7 patients (53%) had HSV-1 in the CSF samples, confirmed by PCR. In addition, PCR findings for 1 patient [case 10] were positive for HSV-2. Conversely, we could not study HSV in the CSF by PCR because it was not available at that time in the hospital, and therefore, in this patient, HSV could not be excluded as an immunological trigger related to anti-NMDAR encephalitis.

Some studies found abnormal MRI in 35% to 55% of children with anti-NMDAR encephalitis at the time of diagnosis [14, 15]. The abnormal MRIs, however, commonly show T2 or FLAIR signal hyperintensity in the hippocampi, cerebellum, or cerebral cortex, insular regions, basal ganglia, and brainstem, with or without transient meningeal enhancement [1, 15]. In infants with anti-NMDAR encephalitis, brain MRI primarily

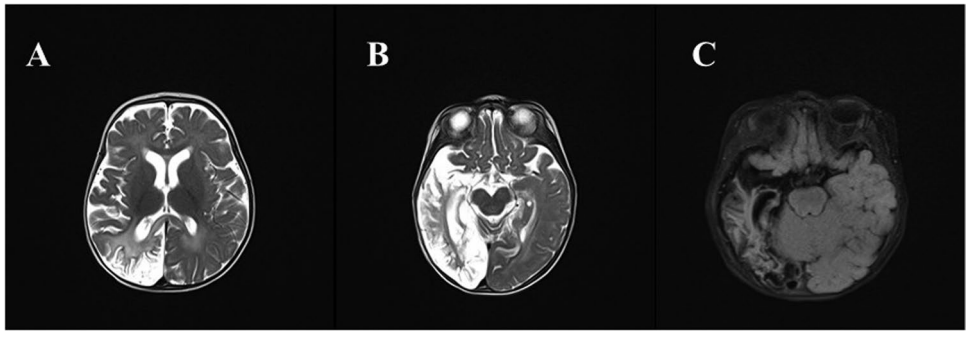

Figure 1. A-C. Axial T2 and FLAIR magnetic resonance imaging (MRI) showed signal hyper-intensity and atrophy predominantly in the right temporo-occipital lobes with the involvement of the cortex and the adjacent white matter.

Table 1. Prior reports of anti-NMDA receptor encephalitis in infants.

Reference	Case No.	Age(months)/ sex	Clinical presentations	MRI	Treatment	Other features	Outcome
Goenka *et al.* [3]	1	6/M	F, AMS	Diffuse basal enhancement with enhancing exudates	IVIG, steroids	Post-tuberculous meningitis	Global developmental delay
Goenka *et al.* [3]	2	5/M	Irritability, F, Sz (focal), choreiform movement	Unremarkable MRI	IVIG, MP, Rtx	None	Global developmental delay
Wickström *et al.* [4]	3	11/F	Sz, severe behavioral change, irritability, sleep disturbance, CAM	Changes typical for HSE with destruction of basal frontal lobe, insula, and anterior temporal lobe of the left side.	IVIG, steroids, acyclovir	HSV-1 PCR (+) in CSF	Intractable epilepsy, delayed cognitive and speech development, hyperactivity
Kim *et al.* [5]	4	7/F	Sz, irritability, Myoclonus, Dystonic spasms, developmental regression	Mild amount of bilateral subdural fluid collection	IVIG, steroids	None	mRS of 4
Bashiri *et al.* [6]	5	10/F	F, Sz, vomiting, irritability, orofacial dyskinesia, CAM, AMS	Gadolinium enhanced with bilateral asymmetrical cortical and sub-cortical cystic encephalomalcia in the frontal lobes	IVIG, steroids, acyclovir, Rtx	None	Mild motor and speech delay and hyperactivity
Alexopoulos *et al.* [7]	6	9/F	F, agitation, Sz, Choreoathetotic-dystonic movements	Haemorrhagic lesion in the left temporal lobe	IVIG, MP, acyclovir, Rtx	HSV-1 PCR (+) in CSF	Significant neurodevelopmental delay, epilepsy
Alexopoulos *et al.* [7]	7	10/F	F, agitation, Sz, hypotonia, Choreoathetotic-dystonic movements	Increased T2-MRI signal diffusely at the left temporal and occipital lobes	IVIG, MP acyclovir	HSV-1 PCR (+) in CSF	Gradual clinical and psychomotor improvement
García-Moreno *et al.* [8]	8	11/M	F, CAM, AMS	Unavailable	IVIG, MP, Rtx, acyclovir, Csp	HSV-1 PCR (+) in CSF	Global developmental delay
Wang *et al.* [9]	9	4/M	F, Sz, involuntary movement, mental regression, including not chasing light or objects, no eye contact, and no communication	No specific change but enlargement of the extracerebral gap.	IVIG, MP, Rtx, Csp azathioprine, methotrexate, dexamethasone	HSV-1 PCR (+) in CSF	mRS of 4
DeSena *et al.* [10]	10	3/M	AMS, CAM, developmental regression, orofacial dyskinesias	An extensive right temporal lobe lesion.	IVIG, plasma exchange	HSV-2 PCR (+) in CSF	Gradual clinical improvement
Bravo-Oro *et al.* [11]	11	10/M	F, Sz, AMS, orofacial dyskinesias, movement disorder	Mesial temporal sclerosis	IVIG, MP methotrexate, Csp	None	Epilepsy
Mohammad *et al.* [12]	12	8/F	F, Sz, encephalopathy pyramidal signs	Unilateral parietal cortical, and white matter, basal ganglia and thalamic lesions	IVIG, MP acyclovir	Intrathecal HSV1 IgG synthesis, IgM positive	Refractory epilepsy, dystonic CP, intellectual disability
Hacohen *et al.* [13]	13	10/F	Encephalopath,orofacial dyskinesia, CAM, cognitive regression	Extensive area of left temporal, parietal, and occipital cortical destruction	IVIG, acyclovir	HSV-1 PCR (+) in CSF	Residual motor and cognitive deficit

Abbreviations: M: Male; F: Female; F: Fever; Sz: Seizure; AMS: altered mental status; CAM: choreoathetoid movements; MP: methylprednisolone; Rtx: rituximab; Csp: Cyclophosphamide; mRS, modified Rankin Scale; CP: Cerebral palsy.

indicates abnormalities except for cases 2 and 8. In our patient, brain MRI showed T2 and FLAIR signal hyperintensity and atrophy, predominantly in the right temporo-occipital lobes, with cortex and adjacent white matter involvement.

Prompt immunotherapy is proposed to improve patient outcomes in anti-NMDAR encephalitis [1, 14]. First-line therapy consists of steroids and IVIG or plasma exchange, alone or combined. Second-line therapy most commonly includes rituximab and cyclophosphamide, separately or combined [14]. In the infants with anti-NMDAR encephalitis, 7 (53%) received first-line therapy. Varying degrees of motor and cognitive deficit and/or epilepsy were reported in long-term outcomes; however, our study patient achieved full recovery with first-line therapy. We emphasize that prompt and appropriate immunotherapy is effective, as with our patient.

Conclusion

In literature, the infants with anti-NMDAR encephalitis were a small number of cases. However, it cannot be suggested that NMDA encephalitis has a good prognosis in infancy except in the present case. Although we cannot show whether recovery was associated with HSV, a favorable clinical response was obtained with prompt treatment. Studies to clarify the etiopathogenesis of anti-NMDAR encephalitis in infants are required for improved treatment approaches and outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Disclosure statement

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ORCID

Dilek Cavusoglu http://orcid.org/0000-0003-4924-5300
Cigdem Ozer Gokaslan http://orcid.org/0000-0001-5345-1735
Nihal Olgac Dundar http://orcid.org/0000-0002-5902-3501

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