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Case Report

The efficacy of adrenocorticotropic hormone in a girl with anti-N-methyl-D-aspartate receptor encephalitis

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Abstract

Background: Immunomodulatory therapy has shown some therapeutic benefits in patients with anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. In this report, we describe the use of adrenocorticotropic hormone (ACTH) immunotherapy with good outcome in a patient with anti-NMDAR encephalitis.

Subject and Methods: A 4-year-old girl developed convulsions in her right arm and leg without impaired consciousness. These convulsions occurred frequently in clusters of 10–20 events of 10–20 s duration. She was admitted to our hospital on the 6th day following her initial series of convulsions. Flaccid paralysis of the right hand and leg was also found. Interictal electroencephalography showed high-amplitude slow waves. No abnormal findings were shown on MRI. ^{99m}Tc-ECD brain SPECT on the 14th day showed hyperperfusion in the left hemisphere, including the left basal ganglia. The convulsions ceased following the oral administration of valproic acid on the 10th day; however, paralysis associated with choreic dyskinesia of the right arm and leg remained. ACTH immunotherapy was then performed on the 15th day. We identified the presence of N-methyl-D-aspartate receptor antibody in CSF samples taken on the 6th day. After ACTH therapy, the patient fully recovered from the paralysis associated with choreic dyskinesia of the right arm and leg. She has not had a relapse and has not required medication for over a year.

Conclusion: ACTH immunotherapy may be a useful treatment option for patients with anti-NMDAR encephalitis, although further evaluation is required.

Keywords: Anti-N-methyl-D-aspartate receptor encephalitis; ACTH therapy; Treatment; Autoimmune focal encephalitis

1. Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a well-recognized clinicoimmunological syndrome that presents with neuropsychiatric symptoms, cognitive decline, movement disorder and seizures [1]. Immunotherapy (steroids, intravenous immunoglobulin, plasma exchange and immunosuppressants) is recommended and appears to be associated with improved outcome [1].

Although most patients with anti-NMDAR encephalitis make a full recovery, 15% of patients recover with some deficits [1], and 20–25% of patients

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relapse [2]. Consequently, there is a strong need for more effective treatment.

In this report, we describe the use of adrenocorticotropic hormone (ACTH) immunomodulatory therapy in a patient with anti-NMDAR encephalitis, with good outcome.

2. Case report

A 4-year-old girl who was the elder sister of diamniotic-dichorionic twins was born at 36 weeks gestation with a birth weight of 3205 g, and had no previous health or developmental problems. There was no family history of neurologic disease. Convulsions in her right arm and leg, without impaired consciousness, occurred frequently in clusters of 10–20 events of 10–20 s duration. She was admitted to a hospital on the day of the initial convulsions. Midazolam (MDZ) and fosphenytoin were injected intravenously, under a diagnosis of epileptic seizure cluster. However, the seizures continued despite the use of these drugs. She was then transferred to our hospital on the 6th day. Flaccid paralysis of the right hand and leg was found. She could sit without support, but could not stand or walk, and had impaired use of her right hand. Consciousness was not impaired, and neuropsychiatric symptoms and cognitive decline were not found. Interictal electroencephalography (EEG) showed high-amplitude slow waves arising predominantly from the left hemisphere (Fig. 1). Epileptic discharges could not be found in ictal EEG, in our hospital. Routine hematological studies, blood gas analysis, all biochemical studies and cerebral spinal fluid examinations were normal. There were no abnormal findings on MRI. ^{99m}Tc-ECD brain SPECT on the 14th day following the initial convulsions showed an area of hyperperfusion in the left hemisphere, including the left basal ganglia (Fig. 2).

Convulsions ceased following oral administration of valproic acid on the 10th day; however, paralysis associated with choreic dyskinesia of the right arm and leg remained. Epileptic encephalopathy was suspected from her clinical course. ACTH immunotherapy was initiated on the 15th day. After informed consent was obtained, ACTH therapy (synthetic ACTH, zinc hydroxide suspension of tetracosactide acetate [Cortrosyn-Z]) was initiated as daily intramuscular injections (0.0125 mg/kg) for 2 weeks, which was then gradually tapered off over one week. After ACTH therapy, the patient fully recovered from paralysis associated with choreic dyskinesia of the right arm and leg. She could walk without support, and there was no impairment of her right hand or leg. Interictal EEG on the 29th day (Fig. 1) and ^{99m}Tc-ECD brain SPECT on the 35th day after the initial convulsions (Fig. 2) were normal. After discharge, CSF samples from the 6th day following the start of seizures were positive for NMDAR antibody, as detected by immunocytochemistry (Fig. 3). From her clinical features and detection of autoimmune antibody, she was diagnosed with anti-NMDAR encephalitis. Ovarian tumor was not identified by ultrasonography.

After discharge, her developmental quotient was 101 using the Kyoto Scale of Psychological Development, a developmental quotient scale commonly used in Japan. She has not had a relapse and has not required medication for over 1 year.

3. Discussion

Steroids and intravenous immunoglobulin have been reported to benefit patients with anti-NMDAR encephalitis [1]. ACTH therapy was effective for our patient, and she has not had a relapse for over a year. To our knowledge, this is the first report of a patient with anti-NMDAR encephalitis administered ACTH therapy.

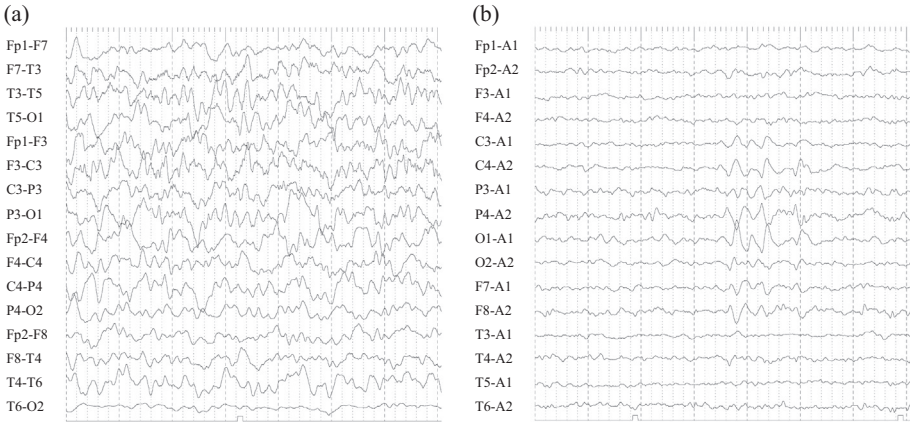

Fig. 1. (a) Interictal EEG on the 6th day following the initial convulsions showed high-amplitude slow waves arising predominantly from the left hemisphere. (b) Repeated interictal EEG performed after ACTH therapy on the 29th day showed near complete normalization.

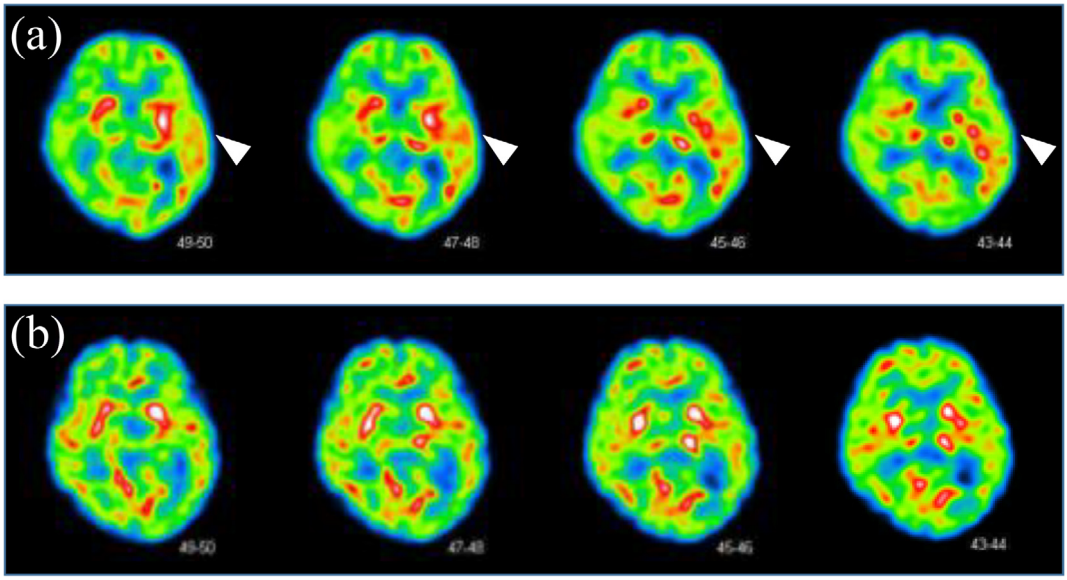

Fig. 2. (a) ^{99m}Tc-ECD brain SPECT on the 14th day following the initial convulsions showed hyperperfusion in the left cortical area and basal ganglia (arrow head). (b) Repeated ^{99m}Tc-ECD brain SPECT performed after ACTH therapy on the 35th day showed near complete normalization.

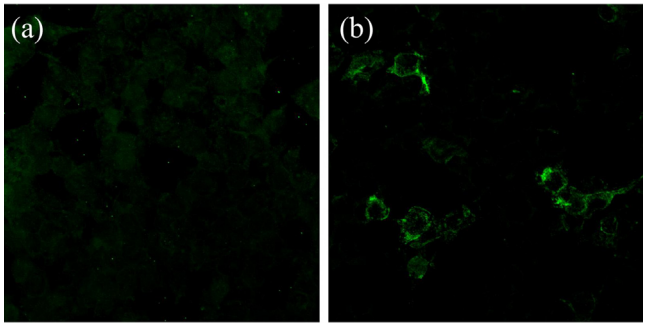

Fig. 3. Detection of NMDAR antibody using indirect immunofluorescence assay. Control (a) and patient (b) sera (undiluted) were reacted with HEK293 cells transfected with human NMDAR according to the manufacturer's instructions (Autoimmune Encephalitis Mosaic, EUROIMMUN, Lübeck Germany).

Behavioral or psychiatric change, a typical symptom in most cases of anti-NMDAR encephalitis, was not observed in our case [1]. Predominantly unilateral involuntary movements and flaccid paralysis were present and contralateral abnormal cortico-basal hyperperfusion and slowing by ^{99m}Tc-ECD brain SPECT and EEG indicated anti-NMDAR encephalitis. Neurological symptoms and neuroradiological and electrophysiological changes in our case were applicable to that of focal encephalitis [3]. Atypical symptoms such as cerebellar ataxia or hemiparesis were reported in patients with anti-NMDAR encephalitis, especially in children than in adults [4]. Clinical features of childhood onset autoimmune focal encephalitis are not well recognized. Therefore, our case might increase our understanding of autoimmune focal encephalitis.

Previous studies reported EEG features in the early phase (when behavioral change and/or movement disorders are commonly recognized clinical features) of anti-NMDAR encephalitis, indicating the variable presence of intermittent or subcontinuous, medium-to-high amplitude, non-reactive, sometimes monomorphic, unilateral and/or bilateral slow waves (1–3 Hz), which were most evident in the frontotemporal regions of the scalp [5]. EEG findings in our case corresponded with the past report [5].

Our case was administered ACTH therapy on the 15th day after the initial convulsions. The factors associated with good outcome included early treatment and no requirement for admission to an intensive care unit [4]. Early recognition and diagnosis of anti-NMDAR encephalitis might lead to favorable outcomes. Patients with rapidly progressive alterations of neurological symptoms should undergo differential diagnosis for anti-NMDAR encephalitis.

ACTH exerts anti-inflammatory and immune-modulating effects in the central nervous system via increasing endogenous corticosteroid production and binding the melanocortin receptors [6]. Recently, it was shown that the pathophysiology of anti-NMDAR encephalitis might involve neuroinflammation and dysregulated B cell activity. Chemokine (C-X-C motif) ligand 13 (CXCL13), a B cell attractant, was elevated in the CSF of 70% of patients with anti-NMDAR encephalitis [7]. In children with opsoclonus-myoclonus syndrome, B cell chemoattractant, B cell frequency, and oligoclonal bands necessary for B cell recruitment, activation, and survival might promote neuroinflammation [8]. High concentrations of B cell

chemoattractant CXCL13 in CSF was associated with clinical treatment response and outcome in anti-NMDAR encephalitis [7]. Treatment of opsoclonus-myoclonus syndrome by peripherally administered ACTH and corticosteroids directly reduced CSF CXCL13 [8–10]. Targeting B cells may prevent their function as antigen-presenting cells and the loss of T cell tolerance [9]. Therefore, the therapeutic effectiveness of ACTH in anti-NMDAR encephalitis might be mediated by a reduction in CSF CXCL13 levels. Further investigation of CXCL13 concentrations in the CSF of patients with anti-NMDAR encephalitis administered ACTH therapy is required.

No serious adverse effects of ACTH therapy occurred in our case. ACTH is used as an immunomodulatory therapy in patients with opsoclonus-myoclonus syndrome. The rate of adverse events associated with ACTH therapy can be high, as for infantile spasms, yet tolerability is usually good because most events are transient or reversible [10]. Serious adverse events during ACTH therapy are rare [10]. Continuous ACTH therapy for multiple years should be avoided.

In summary, we found that ACTH therapy stopped abnormal movement and flaccid paralysis in our case, who has not had a relapse for over 1 year. ACTH therapy may be a useful treatment option for anti-NMDAR encephalitis, although further evaluation is required.

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References

[1] Armangue T, Titulaer MJ, Málaga I, Bataller L, Gabilondo I, Graus F, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. J Pediatr 2013;162:850–6.

[2] Peery HE, Day GS, Dunn S, Fritzler MJ, Prüss H, De Souza C, et al. Anti-NMDA receptor encephalitis. The disorder, the diagnosis and the immunobiology. Autoimmun Rev 2012;11:863–72.

[3] Sekigawa M, Okumura A, Niijima S, Hayashi M, Tanaka K, Shimizu T. Autoimmune focal encephalitis shows marked hypermetabolism on positron emission tomography. J Pediatr 2010;156:158–60.

[4] Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157–65.

[5] Nosadini M, Boniver C, Zuliani L, de Palma L, Cainelli E, Battistella PA, et al. Longitudinal electroencephalographic (EEG) findings in pediatric anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis: the Padua experience. J Child Neurol 2015;30:238–45.

[6] Ross AP, Ben-Zacharia A, Harris C, Smrtka J. Multiple sclerosis, relapses, and the mechanism of action of adrenocorticotropic hormone. Front Neurol 2013;4:21.

[7] Leypoldt F, Höftberger R, Titulaer MJ, Armangue T, Gresa-Arribas N, Jahn H, Rostásy K, et al. Investigations on CXCL13 in anti-N-methyl-D-aspartate receptor encephalitis: a potential biomarker of treatment response. JAMA Neurol 2015;72:180–6.

[8] Pranzatelli MR, Tate ED, McGee NR, Travelstead AL, Colliver JA, Ness JM, et al. BAFF/APRIL system in pediatric OMS: relation to severity, neuroinflammation, and immunotherapy. J Neuroinflam 2013;10:10.

[9] Pranzatelli MR, Tate ED. Trends and tenets in relapsing and progressive opsoclonus-myoclonus syndrome. Brain Dev 2016;38:439–48.

[10] Tate ED, Pranzatelli MR. Response to correspondence on "active comparator-controlled, rater-blinded study of corticotropin-based immunotherapies for opsoclonus-myoclonus syndrome". J Child Neurol 2013;28:417–8.