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Case Reports

Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis: Early Treatment is Beneficial

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Anti-*N*-methyl-D-aspartate receptor antibody has been associated with a severe stereotypic form of subacute encephalitis, often found in women with ovarian teratoma. Reported here is the diagnosis of anti-*N*-methyl-D-aspartate receptor encephalitis in a 5-year-old girl who presented with subacute encephalopathy and movement disorder without evidence of malignancy. Early diagnosis and treatment with immune globulin and steroids resulted in near-complete recovery.

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Introduction

Anti-*N*-methyl-D-aspartate (NMDA) receptor antibody has been associated with a severe stereotypic form of subacute encephalitis [1]. A majority of reported patients have been young women found to have ovarian teratoma, but in some cases no tumor was identified [1-3]. In the case reported here, anti-*N*-methyl-D-aspartate receptor encephalitis was diagnosed in a 5-year-old girl who presented with subacute encephalopathy and movement disorder without evidence of malignancy. Anti-*N*-methyl-D-aspartate receptor antibody detection in cerebrospinal fluid allowed early diagnosis. Recovery was almost complete.

Case Report

A previously healthy 5-year-old girl of European origin presented in January 2009 for evaluation of abnormal movements, loss of developmental milestones, and behavioral changes. Nine days earlier, she had complained of intermittent headaches and paresthesias of her left hand; she stopped using the left hand and exhibited episodic agitation, slurred speech, and abnormal left arm movements. Evaluation at another hospital showed normal findings on cranial computerized tomography and magnetic resonance imaging, as well as a normal video electroencephalogram. The parents were told the episodes were due to stress at home. The patient initially regained baseline function between episodes, but with increasing frequency and duration of episodes, she was unable to perform previous skills, such as bathing and dressing herself.

At admission, her physical examination was unremarkable. However, upon neurologic examination she was alert but mute; she refused to follow commands and had difficulty swallowing. Her left arm and hand showed 4/5 weakness, and she did not use this arm as much as her right. She was ataxic and could not walk unassisted. Basic blood and cerebrospinal fluid evaluations yielded normal results; both cranial magnetic resonance imaging, including fluid-attenuated inversion recovery imaging, and magnetic resonance spectroscopy were unremarkable. The patient quickly deteriorated, exhibiting severe episodes of agitation, choreoathetoid movements of extremities, urinary incontinence, mutism, rhythmic tongue thrusting, and loss of ability to swallow or make eye contact. As she lost oral motor control and the ability to swallow, nasogastric feeding was necessary to protect her airway, and there was concern that her progressive hypotonia would require intubation. Extensive evaluation for genetic, infectious, metabolic, autoimmune, toxic, and psychiatric etiologies was initiated.

On day 3, video electroencephalography indicated bihemispheric slowing (right greater than left). Epileptiform discharges arose independently from occipital regions, but no seizures were noted. On day 6, rapid clinical deterioration and concern for an autoimmune encephalitis prompted initiation of methylprednisolone (IV, 40 mg/kg per day), which was continued for 4 days. The third day after initiation of steroids, her initial clinical improvement quickly plateaued. Therefore, intravenous Octagam was empirically initiated (0.4 g/kg per day) for 5 days. Oral steroids were slowly tapered over 12 weeks; lorazepam was given for agitation and trazodone for sleep disturbance. The patient slowly improved. She was transferred to inpatient rehabilitation on day 13. At outpatient follow-up examination, approximately 5 weeks after onset of the illness, she was nearly back to baseline.

Immunohistochemical analysis (Mayo Clinic) of cerebrospinal fluid obtained at admission revealed antibodies compatible with anti-*N*-methyl-D-aspartate receptor specificity. This was confirmed molecularly

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at the University of Pennsylvania. The identity of the antigen was established using a highly specific (unambiguous) cell-based assay with HEK293 cells transfected to specifically express the anti-*N*-methyl-D-aspartate receptor. The technique used to establish this antigen has been described previously [1,2].

The known association of this antigen with ovarian teratoma prompted pelvic magnetic resonance imaging evaluation, but the results were unremarkable. Given the patient's clinical recovery, no further treatment was planned; however, however close surveillance for relapse and occult malignancy is indicated.

The Institutional Review Board of Indiana University School of Medicine has approved the use of data for this report (study no EX0903-50), and the parents have given permission to report this case.

Discussion

This child's presentation is consistent with that previously described in patients with anti-*N*-methyl-D-aspartate receptor autoimmunity [1]. The initial symptom was headache; behavioral or psychiatric changes, dyskinesias (choreoathetoid movements and orolingual), and muteness proceeded to encephalopathy. In addition to the dyskinesias, she quickly lost her ability to swallow and protect her airway. Electroencephalography revealed considerable and diffuse slowing; magnetic resonance imaging findings were normal. Early initiation of immunosuppressant therapy likely averted respiratory distress, a common event in this syndrome, and permitted near-complete recovery. The variation in clinical outcome observed in previously published cases appears to correspond to the rapidity of commencing appropriate treatment [1].

The recently recognized anti-*N*-methyl-D-aspartate receptor antibody was initially described in several young women found to have ovarian teratoma [3]. A subsequent case series reported that 59% of patients with anti-*N*-methyl-D-aspartate receptor encephalitis had a neoplasm [1]. A retrospective study from Japan identified a tumor 4-7 years after initial neurologic diagnosis, despite extensive screening at diagnosis, and the authors highlighted the importance of long-term tumor surveillance [4].

In the present case, the long-term follow-up plan includes annual pelvic magnetic resonance imaging to monitor for possible occult teratoma. It will also be important to evaluate for neoplasm should the symptoms return or worsen. If symptoms prove refractory to corticosteroids and immune globulin therapy, anti-B-cell monoclonal antibody therapy, as used in adult refractory patients, may be considered [5]. It would be ideal to monitor serum antibody titers, because clinical improvement has been correlated with reduced antibody titers [1,4].

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References

[1] **Dalmau** J, Gleichman AJ, Hughes EG, et al. Anti-NMDA receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091-8.

[2] **Dalmau** J, Tuzun E, Wu HY, et al. Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25-36.

[3] **Vitaliani** R, Mason W, Ances B, Zwerdling T, Jiang Z, Dalmau J. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. Ann Neurol 2005;58:594-604.

[4] **Iizuka** T, Sakai F, Ide T, et al. Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. Neurology 2008;70:504-11.

[5] **Ishiura** H, Matsuda S, Higashihara M, et al. Response of anti-NMDA receptor encephalitis without tumor to immunotherapy including rituximab. Neurology 2008;71:1921-3.