항-NDMA 수용체 뇌염: 난소 기형종과 항체의 관계

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Anti-N-methyl-D-aspartate Receptor (NMDAR) Encephalitis: Neuronal Burden of a Comorbid Ovarian Teratoma

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a disease that is characterized by acute psychiatric symptoms, seizures, and central hypoventilation. Patients with anti-NMDAR encephalitis exhibit speech alterations, insomnia, seizures, and movement disorders. We describe a previously healthy 6-year-old girl who presented with seizures, disorientation, and fever. Over the five weeks of treatment, the patient exhibited progressive neurologic symptoms, including a change in mental status. Her serum and cerebrospinal fluid contained high titers of antibodies against the NMDAR, and she was diagnosed with anti-NMDAR encephalitis. She was treated with plasmapheresis, steroid pulse therapy, intravenous immunoglobulins, and repeated doses of rituximab. After the patient was diagnosed with a concomitant ovarian teratoma, a unilateral salpingo-oophorectomy was performed. A histopathologic examination revealed that neuronal elements accounted for 60% of the resected ovarian teratoma. The patient's clinical symptoms and antibody titers improved after the surgical treatment and rituximab therapy. These observations suggested that patients with high titers of anti-NMDAR antibodies should be examined for the presence and quantity of neuronal components in concurrent ovarian teratomas.

Key Words: Anti-N-Methyl-D-Aspartate Receptor Encephalitis, Epilepsy, Children, Teratoma

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Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a unique clinical entity that results in a progressive presentation of symptoms, including speech alterations, insomnia, seizures, and movement disorders, in children. The disease is a major cause of autoimmune encephalitis in children and adolescents¹⁾. A large cohort study revealed that 81% of the patients with anti-NMDAR encephalitis were girls and that 38% had primary tumors, which were exclusively ovarian teratomas¹⁾. Several patients without primary tumors exhibited other types of immunologic disorders, such as a viral prodrome with febrile episodes.

Recently, dysplastic neuronal elements in ovarian teratomas have been identified as being closely related to predominant central nervous system infiltration. The interactions of the abnormal neurons in the immature teratomas with normal

tissues and the increase in the inflammatory infiltrates result in the antibodies that are observed in patients with teratoma-associated anti-NMDAR encephalitis²⁾.

We encountered a pediatric patient with anti-NMDAR encephalitis and large amounts of neuronal elements in an ovarian teratoma without dysplasia. In this report, we describe the association of high titers of antibodies in serum and excessive neuronal tissue in a resected ovarian teratoma in a patient with anti-NMDAR encephalitis.

Case report

A girl who was 6 years and 11 months old presented to the emergency room with fever, seizures, and disorientation. The patient was previously healthy and developmentally normal. She had experienced a fever for 10 days and vomiting for 3 days. Subsequently, she became lethargic and exhibited various symptoms, including mutism and dysphagia. She exhibited isocoric pupils with adequate light reflexes, normal motor and sensory function, and normal deep tendon reflexes. There was no evidence of neck stiffness or Kernig's or Brudzinski's signs.

The day after admission, the patient developed a prolonged seizure attack that consisted of a focal seizure involving twitching of the left side of her face and jerking of her left arm for seven minutes. She demonstrated generalized bizarre and jerking movements and frequent alterations in her mental status. She was preliminarily diagnosed with an encephalitis and treated with the empirical antibiotics and antiviral agents: vancomycin, cefotaxime, and acyclovir and intravenous immunoglobulin (400 mg/kg/dose). In addition, the antiepileptic drugs phenobarbital, fosphenytoin, and levetiracetam were administered intravenously.

Laboratory analyses, including a complete blood count, serum chemistry, erythrocyte sedimentation rate, and C-reactive protein levels, were normal. A cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis with normal protein and glucose levels. A bacterial culture and virus test were negative. Magnetic resonance diffusion images of the brain were normal. A continuous electroencephalogram (EEG) recording showed irregular delta activities on whole backgrounds without epileptiform discharges. Her serum and CSF were positive for antibodies against NMDAR, and an immunofluorescence assay of the anti-NMDAR subunit revealed the high titer of 1:320. She was finally diagnosed with anti-NMDAR encephalitis.

After she was diagnosed, she was evaluated for any comorbid conditions with abdominal computed tomography. Her abdominal scans revealed a right ovarian teratoma that consisted of

calcifications, fluid, and adipose tissue (Fig. 1).

She underwent a unilateral salpingo-oophorectomy to remove the focus that was contributing to the production of the antibodies. Light microscopic examinations of tissue stained with hematoxylin and eosin revealed that neuroglial elements accounted for 60% of the teratoma and an absence of dysplasia (Fig. 2). The teratoma tissue was positively stained for the neuron-specific protein, NeuN (1:200, EMD Millipore Corporation, Billerica, MA, USA) and the glial fibrillary acidic protein (1:2,000, Agilent Technologies Japan, Ltd., Tokyo, Japan). It was confirmed that the tissue was a mature teratoma with excessive neuroglial elements.

After surgical removal of the teratoma, plasmapheresis was performed seven times for two weeks to remove the antibodies that had already formed. Then, in order to suppress any residual

Fig. 1. Computed tomography image of a mass containing a mixture of a high density of calcification and a low density of fluid and adipose tissue in the right ovary and adnexa (arrow). The patient was diagnosed with a unilateral ovarian teratoma.

Fig. 2. Microscopic section (40X, hematoxylin-eosin stain) of the resected ovarian teratoma. Extensive neuronal tissue, which is seen under the dotted line outlining the cutaneous tissue, accounted for 60% of the resected ovarian teratoma. Dysplastic features were not found.

immune responses and inhibit antibody formation, the following medical treatment was added as an alternative strategy: rituximab treatment ($375 \text{ mg/m}^2/\text{dose}$) once a week for five weeks and steroid pulse therapy (30 mg/kg/day) on three consecutive days other than the day of the rituximab treatment for five weeks. The antiepileptic drugs were then decreased to oral forms of phenytoin and levetiracetam.

At the end of treatment, the patient exhibited an alert mental status with adequate awareness and no abnormalities on a neurologic examination. A follow-up EEG study showed poorly developed alpha waves in the waking state and diffuse delta waves, thus implicating diffuse cortical dysfunction. The NMDAR antibody titers in the serum and CSF were decreased to 1:40. After a month of rehabilitation, her serum and CSF titers had decreased to 1:20. At the time of discharge, she was assessed with Korean-Wechsler Intelligence Scale for Children (K-WISC-III) to evaluate intellectual capacity. Her Full Scale Intelligence Quotient (FSIQ) was 54 in the range of mild mental retardation.

The patient has been regularly admitted and treated with rituximab ($500 \text{ mg/m}^2/\text{dose}$) once a month to prevent antibody formation. She is currently fully recovered and is able to read, write, speak fluently, and recall short- and long-term memory.

Six months after the patient's initial presentation, she had recovered her previous neurologic conditions without any deficits. A repeat EEG was normal. A CSF analysis was normal for white blood cells, protein, and glucose. Her serum and CSF were negative for anti-NMDAR antibodies 20 months after her first symptoms. One year after her initial presentation, her FSIQ was increased to 101 by K-WISC-III in the range of average. She exhibits adequate neurologic development for a 8-year-old girl on her periodic visits to the outpatient clinic.

Discussion

In 2005, four young women who developed acute psychiatric symptoms, seizures, and central hypoventilation were reported to have ovarian teratomas and CSF inflammatory abnormalities. Their neurological disorder was classified as a paraneoplastic syndrome, which suggested the presence of antibodies that were specific for neurons' surfaces³. After detection of antibodies to the expression of the NMDAR on the cell membranes of hippocampal neurons, the disease was called anti-NMDAR encephalitis^{4,5}.

This disease accounts for the major cause of autoimmune encephalitis in children and adolescents with 40% of the patients being younger than 181). In a single-center study in Korea, only

one of the 128 patients who were diagnosed with encephalitis was diagnosed with anti-NMDAR encephalitis for 13 years⁶. However, the incidence of this disease is thought to be more frequent because case reports of this disease have accumulated rapidly⁷.

A case of pediatric anti-NMDAR encephalitis was reported recently in Korea. The patient had a progressive course like our case with progression from continuous partial seizures to dyskinesia and cognitive impairment. However, the patient had no evidence of tumors, including ovarian teratomas⁸.

In contrast to adults, the presence of an underlying tumor is uncommon in children. A study of 81 patients with anti-NMDAR encephalitis reported that the frequency of ovarian teratomas is lower in young girls than it is in women⁹. Thus, they recommended screening patients for teratomas with safe techniques, such as ultrasound and magnetic resonance imaging of the abdomen and pelvis⁹.

Recently, the abnormal features of tumors within teratomas have been revealed to contribute to the immune response that causes antibody formation against the NMDAR². In that case-control study, the authors found that four of five patients with anti-NMDAR encephalitis had abnormal or proliferating features in their ovarian teratomas. They hypothesized that the abnormal dysplastic neurons in the teratomas trigger inflammatory reactions that result in the pathogenesis of the anti-NMDAR encephalitis. However, these abnormal features of neurons were also observed in normal neuronal differentiation².

In our case report, no dysplastic features were observed on the neuronal tissue in the teratoma. An excessive amount of neuronal tissue in the ovarian teratoma might be related to the formation of antibodies by excessive proliferation. We found that the titer of the antibodies against the NMDAR was high when the neuronal elements were observed in the ovarian teratoma. The titer then markedly reduced after multidisciplinary treatment, and it has been diminished in the serum and CSF one year after the patient's initial presentation. The excessive neuronal burden was assumed to be related to the antibody formation process and higher antibody titer, which resulted in the development of anti-NMDAR encephalitis. Further investigations are needed to define the relationship between the amount of neuronal tissue and the antibody titer.

요약

의식 변화 및 반복적인 경련을 주소로 내원한 6세 11개월의 여아를 항-NMDA 수용체 뇌염으로 진단하였다. 환자의 혈장과 뇌척수액에

서 높은 항체가를 확인하였다. 동시에 항-NMDA 수용체 뇌염과 동반될 수 있는 난소 기형종을 진단하였다. 항체 제거를 위하여 난소 기형종을 수술적 치료하였으며 항체 형성을 막기 위하여 혈장 교환술, 리투시맙과 스테로이드 충격요법을 시행하였다. 난소 기형종 병리 조직 소견에서 상당한 양의 신경 조직이 발견되었고 이는 뇌염 발생에 있어 주요한 역할을 하였을 것으로 생각하며 제거 및 rituximab 치료 후 항체가의 음전과 임상 증상의 호전으로 미루어 보아 질병의 진행을 관련성을 유추할 수 있다. 다학제적으로 접근한, 높은 항체가를 지닌 항-NMDA 수용체 뇌염 환아를 1례 경험하였기에 보고하는 바이다.

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