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Case Report Open Access

Four-Year Course of Serum and Cerebrospinal Fluid Antibody Titers in a Patient with Anti-NMDAR Encephalitis

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Abstract

The natural long-term course of antibody titers in patients with anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis remains uncertain. We measured anti-NMDAR antibodies in a patient with anti-NMDAR encephalitis who had a severe disease course for 5 years. The antibody titers in the first serum and cerebrospinal fluid (CSF) samples were 1:1600 and 1:320, respectively. During gradual recovery, the serum and CSF titers initially decreased, but remained unchanged during the last 2 years. Four years after the onset of disease, the serum and CSF antibody titers were 1:200 and 1:80, respectively. Anti-NMDAR antibodies can persist for prolonged periods in patients with a poor clinical course.

Keywords: Paraneoplastic encephalitis; NMDAR; Autoimmune encephalitis; Cerebrospinal fluid; Antibody

Introduction

Paraneoplastic encephalitis is a rare neurological disorder associated with small cell lung carcinomas, lymphomas, thymomas, and testicular tumors. The disappearance of psychiatric features after removal of an ovarian teratoma in an acutely confused woman was reported in 1997 [1], and several similar cases have been documented subsequently. In 2007, a specific autoantibody to the N-methyl-D-aspartate receptor (NMDAR) related to the paraneoplastic encephalitis associated with ovarian teratoma was identified [2]. Clinically, this condition is characterized by acute behavioral changes, prominent psychiatric symptoms, seizures, involuntary movements, autonomic instability, and central hypoventilation [2]. The binding epitope of the antibody is part of the NR1-subunit of the NMDAR on postsynaptic dendrites in the forebrain and hippocampus. This disorder is referred to as "anti-NMDA receptor encephalitis." The immune response underlying this disorder is triggered systemically by a tumor or other unknown causes and is reactivated and expanded intrathecally [3]. Many patients respond to immune treatment, such as steroids, plasmapheresis, and intravenous immunoglobulin (IVIG), and approximately 80% of this disorder fully recover or have minor sequelae [2-4]. A recent large cohort study of this disorder reported that the underling tumor is almost always an ovarian teratoma, while other tumors were present in some patients, such as testicular, lung, or breast tumors [4]. Male patients with anti-NMDA receptor encephalitis or patients with anti-NMDA receptor encephalitis who had no tumor have also been identified [4]. Recently, the 2-year outcomes of 577 patients with anti-NMDAR encephalitis were reported, and second-line immune treatment such as rituximab or cyclophosphamide was recommended for patient's refractory to first-line therapy [4].

In a patient with anti-NMDAR encephalitis who received immune treatments, the cerebrospinal fluid (CSF) levels of antibodies correlated with clinical outcomes during 10 months [5], and the levels of anti-NMDAR antibodies were apparently related to clinical severity. However, a more recent case report indicated that anti-NMDAR antibodies do not necessarily reflect disease activity on prolonged follow-up [6]. After long-term follow-up of more than 2 years, patients who had anti-NMDAR encephalitis without recurrence were limited, and to the best our knowledge anti-NMDAR antibodies titers were evaluated in 3 patients as shown in Table 1 [6-8]. Two of these 3 patients with anti-NMDAR encephalitis received first-line (steroids, plasmapheresis, or IVIG) or second-line immune treatments (immunosuppressants) [7,8]. In the other patient, signs and symptoms of anti-NMDAR encephalitis spontaneously, gradually, and completely resolved over the course of 15 years without immune treatment [6]. The long-term course of antibody titers in response to first-line treatment in patients with anti-NMDAR encephalitis remains to be fully defined. We measured serum and CSF antibodies over the course of 4 years in a patient with anti-NMDAR encephalitis who received first-line immune treatment and had a poor clinical course for 5 years.

	patient 1 [6]	patient 2 [7]	patient 3 [8]	present patient
age/sex	15 / F	late 30s / F	42 / F	45 / F
initial symptoms	phychosis	phychosis	phychosis	phychosis
other clinical features				

involuntary movements	+	+	+	+
autonomic instability	+	+	-	+
seizures	-	-	-	+
ventilatory support	+	+	+	+
tumor	-	ovary teratoma	ovary teratoma	-
cranial MRI	normal	progressive atrophy	normal	normal
therapies				
first-line immune treatments	-	ST, IVIG, PE	ST, IVIG	ST, IVIG, PE
second-line immune treatments	-	rituximab, cyclophosphamide	-	-
tumor resection	-	+	+	-
first hospital stay	5 yr	25 mo	25 mo	4 yr
disease condition at first hospital discharge	learning impairments	dead	cognitive impairments	GCS 9
anti-NMDAR antibodies titers				
first examination				
serum	1: 1000*a	1: 102400	+*b	1: 1600
CSF	1: 320*a	1: 10240	+*b	1: 320
CSF cells	29 /mm3*a	237	NA*b	13 /mm3
final follow-up examination	15 yr	16 mo	4 yr	4 yr
disease conditions	no symptoms	comatose with hyperkinetic movements	mild cognitive impairments	GCS 9
serum	1: 320	1: 25600	+	1: 200
CSF	1: 32	1: 5120	ND	1: 80
CSF cells	1 /mm3	NA	NA	0 /mm3

Table 1: Long-term follow-up (>2 years) of anti-N-methyl-D-aspartate receptor (NMDAR) antibody titers in previous patients with anti-NMDAR encephalitis who did not have recurrence

MRI: magnetic resonance images, anti-NMDAR : anti-N-methyl-D-aspartate receptor, CSF: cerebrospinal fluid, ST: steroids, IVIG: intravenous immunoglobulin, PE: plasmapheresis, GCS: Glasgow coma scale scores, M: male, F: female, NA: not available, ND: not done, mo: months, yr: years, *a: one month after the disease onset, *b: nine months after the disease onset.

Case Presentation

In March 2008, a 45-year-old previously healthy Japanese woman had distortion of visual perception. She would say, for example, "Your face looks like it is stretched out". After several days, she noticed unusual behavior, such as walking around in her underwear or wearing her clothes inside out. In April, generalized seizures and delusional thinking developed, and she was admitted to our hospital. She presented with a confusional state. She had low-grade pyrexia (37.3℃). Meningismus was absent. The results of brain magnetic resonance imaging (MRI) were normal. Lumbar puncture showed 13 lymphocytes per cubic millimeter and a protein concentration of 39 mg/dl. Intravenous dexamethasone (8 mg/day, 14 days), and intravenous acyclovir (500 mg three times daily) were started for a presumptive diagnosis of herpes simplex encephalitis. Twelve days after admission, she presented with involuntary chewing movements in the orolingual region, and subsequently frequent seizures developed. She became comatose and required ventilatory support and sedative drugs. IVIG (5 g/day, 3 days) was started for suspected autoimmune encephalitis. She was treated in neurological intensive-care units.

Disease course

Initially, intravenous phenytoin (500 mg/day) and carbamazepine (400 mg/day) were begun. After that, she was given valproate sodium, diazepam, zonisamide, or topiramate in addition to these antiepileptic drugs. Anti-NMDAR encephalitis was diagnosed in October 2008. The patient was given intravenous steroids (500 mg/day, 3 days, 2 times) and double-filtration plasmapheresis (4 times, alternating days) in October 2008 and IVIG (0.4 g/kg/day, 5 days) in April 2009. She had seizures, autonomic instability, and involuntary chewing or twitching movements in the orolingual region as well as arm ballistic involuntary

movements. These involuntary movements and seizures persisted and did not respond to antiepileptic drugs. Treatment with intravenous propofol and midazolam was therefore begun. If the dosage of the intravenous sedative medications was reduced, the magnitude or frequency of seizures and involuntary movements increased. Thus, prolonged treatment with high doses of intravenous propofol (4 mg/kg/hr) and midazolam (3.75 mg/kg/hr) was needed. Ventilator support was needed because of sedation, and she received prolonged mechanical ventilation from April 2008 through February 2011. She received a tracheostomy because of long-term ventilation. Gallium scintigraphy (7 times), pelvic computed tomography (CT) (8 times), MRI (3 times), ultrasound examinations (5 times) including transvaginalsonography (2 times), chest CT (6 times), abdominal CT (9 times), gastrofiberscopy (1 time), and colonoscopy (1 time) were performed every 3 or 6 months, but there was no evidence of a teratoma or other type of tumor. The second and third lumbar punctures, performed in June 2008 and September 2009, showed 3 and 0 lymphocytes per cubic millimeter and a protein concentration of 64 and 68 mg/dl, respectively. CSF cultures were negative for microorganisms. The CSF titers of herpes simplex, cytomegalovirus, varicella zoster, influenza, and Epstein-Barr viruses were not increased. Slow wave abnormalities on the electroencephalogram were present, but epileptiform potentials and periodic complexes were absent on the initial and subsequent recordings. She received nine brain MRI examinations. These examinations showed no hypoxic cerebral damage or abnormal signal intensity. Mild temporal and frontal brain atrophy was evident on the last follow-up brain MRI (Figure 1).

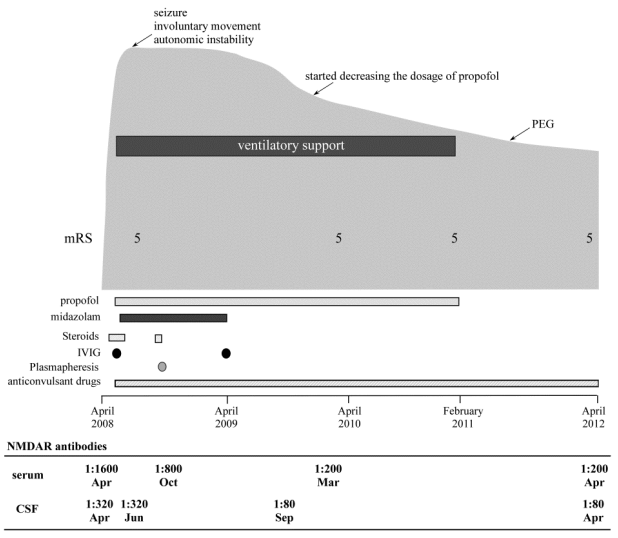

Figure 1: Clinical course in our patient with anti-N-methyl-D-aspartate receptor encephalitis

Outcomes

Decreasing frequencies of seizures and involuntary movements were noted as the initial signs of improvement in November 2009, and the dose of intravenous propofol was slowly tapered. In 2009, the patient's family requested that further immunotherapy (IVIG, plasmapheresis, steroids, and immunosuppressants) be withheld because of the patient's poor condition and economic reasons. Ventilatory support was withdrawn in February 2011 owing to the decreased magnitude or frequency of seizures, involuntary movements, and autonomic instability, such as tachycardia. She was transferred to another hospital in April 2012, and the score on modified ranking scale was 5. The final lumbar puncture in April 2012 showed 0 lymphocytes per cubic millimeter and a protein concentration of 53 mg/dl. At this time, she received valproate (1000 mg/day), diazepam (40 mg/day), and topiramate (200 mg/day). In April 2013, modified ranking scales were the same, and valproate (1000 mg/day), diazepam (10 mg/day) and topiramate (200 mg/day) were given.

Anti-NMDAR antibodies

Anti-NMDAR antibodies were detected on immunocytochemical studies, as described previously [2]. In brief, HEK 293 cells were transfected with NR1 and NR2 plasmids to express NR1/NR2 heteromers. Reactivity with CSF on cells expressing these heteromerswas strong in the present patient, whereas non-transfected cells did not show reactivity. The antibody titers (obtained by serial dilutions of paired samples) in the first serum and cerebrospinal fluid (CSF) samples were 1:1600 and 1:320, respectively. The serum and CSF titers initially decreased, but remained unchanged during the last 2 years. Four years after the onset of disease, the serum and CSF antibody titers were 1:200 and 1:80, respectively.

Discussion

In our patient, the serum and CSF anti-NMDAR antibody titers persisted during the prolonged disease course. Previously, the long-term time course of anti-NMDAR antibody titers was evaluated in 3 patients [6-8]. One woman (patient 3 in Table 1) with an ovarian tumor who received both first-line therapy and tumor resection showed signs of recovery during the first 2 years and mild cognitive impairment during the next 2 years [8]. This patient had persistent serum antibodies at the last follow-up, but CSF and serum antibody titers were not evaluated. In contrast to our patient, who had a poor outcome, one woman without a tumor recovered completely over the course of 15 years without immune therapy (patient 1 in Table 1) [6]. That patient had antibodies in serum (1:32) and CSF (1:32) at the last follow-up, and the authors speculated that the patient had chronic, mild, subclinical central nervous system autoimmune reactivations with antibody titers below threshold levels causing symptoms [6]. There are 2 possible reasons for the persistent antibodies. First, although the intrathecal inflammatory and plasma cell infiltrate disappeared in association with return to normal CSF findings, self-contained meningeal germinal centers with or without systemic antibody synthesis may have been retained [6]. Alternatively, some B cell clones that remained able to trigger an immune relapse might have persisted in the peripheral lymphoid tissue [8]. In another patient (patient 2 in Table 1), long-term first- and second-line treatments produced no improvement, and high levels of anti-NMDAR antibodies elicited by strong systemically and intrathecally immune reactions persisted [7]. These findings suggest that anti-NMDAR antibodies may persist for prolonged periods, similar to our patient.

Patients without a tumor had poorer responses to first-line immune treatments than those with a tumor [3]. A 2-year follow-up study reported that 43 of 55 patients with or without a tumor who failed to respond to first-line treatment received second-line treatment, and the use of second-line treatment was identified as an additional factor for good outcomes [4]. It is essential to continue monthly cycles of

steroids or IVIG for the effective management of chronic immune-mediated disorders, even if the initial response is not dramatic. Our patient also showed no decrease in antibodies titers during the last 2 years, suggesting that second-line treatment should be given to such patients.

Reportedly, the levels of serum antibodies [9] or CSF antibodies [5] correlate with clinical outcomes. Our patient had a poor disease course, and the serum and CSF anti-NMDAR antibody titers initially decreased with time. During the last 2 years, clinical improvement was limited and these antibodies remained unchanged. Recently, a large cohort study showed that the level of CSF and serum titers of anti-NMDAR antibodies were higher in patients with poor outcomes as defined by a score of 3 to 6 on the modified ranking scale than in patients with good outcomes [10]. The CSF anti-NMDAR antibody titer in patients with poor outcomes (1:340) was similar to that in our patient, whereas the serum titer (1:7370) was much higher [10]. The sensitivity for diagnosis of anti-NMDAR encephalitis thus appears to be higher for CSF anti-NMDAR antibody than for serum anti-NMDAR antibody [10]. A prolonged poor disease course such as that in our patient might be more strongly associated with the CSF antibody titer rather than the serum antibody titer.

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