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Anti–*N*-Methyl-D-Aspartate Receptor Encephalitis:

A Patient With Refractory Illness After 25 Months of Intensive Immunotherapy

Alissa Thomas, MD, **Paula Rauschkolb, DO**, **Núria Gresa-Arribas, PhD**, **Alan Schned, MD**, **Josep O. Dalmau, MD, PhD**, and **Camilo E. Fadul, MD**
Department of Neurology, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire (Thomas, Schned, Fadul); Neurociences Institute, Intermountain Medical Center, Murray, Utah (Rauschkolb); IDIBAPS, Hospital Clinic, Barcelona, Spain (Gresa-Arribas); Service of Neurology, Hospital Clinic, Barcelona, Spain (Dalmau); Department of Medicine, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire (Fadul)

Abstract

IMPORTANCE—*N*-methyl-D-aspartate receptor (NMDAR) antibody encephalitis is an autoimmune encephalitis that can be paraneoplastic and usually responds to treatment. It is quickly becoming the most common paraneoplastic encephalitis.

OBSERVATIONS—We present a case of a woman in her late 30s who developed psychiatric symptoms that progressed to encephalopathy, seizures, autonomic instability, and hyperkinetic movements. The patient was found to have an ovarian teratoma and serum and cerebrospinal fluid NMDAR antibodies. Despite resection of the teratoma and treatment with immunosuppressive therapy, the patient progressed to a minimally conscious state. She was supported medically in our institution for 25 months. During her hospitalization, she was treated with multiple immunosuppressive agents. With each treatment, we analyzed the serum and cerebrospinal fluid for NMDAR antibodies. While there was some initial reduction in the serum antibodies, the spinal fluid antibodies remained persistently elevated. The patient did not have any clinical improvement and eventually died after the family decided to withdraw care.

CONCLUSIONS AND RELEVANCE—As far as we know, this case represents the longest active treatment without improvement of a patient with anti-NMDAR encephalitis. The patient had persistently high cerebrospinal fluid and serum antibody titers, which may be of prognostic significance.

Corresponding Author: Camilo E. Fadul, MD, Norris Cotton Cancer Center/Dartmouth Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, camilo.e.fadul@hitchcock.org.

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Study concept and design: Thomas, Fadul.
Acquisition of data: Rauschkolb, Gresa-Arribas, Schned.
Analysis and interpretation of data: Schned, Dalmau, Fadul.
Drafting of the manuscript: Thomas, Gresa-Arribas, Fadul.
Critical revision of the manuscript for important intellectual content: Rauschkolb, Schned, Dalmau, Fadul.
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In 2005, case reports of young women with a syndrome of memory loss, psychiatric symptoms, altered consciousness, and hypoventilation emerged.[1] Two years later, antibodies to the *N*-methyl-D-aspartate receptor (NMDAR) were identified.[2] The syndrome is now well described, with more than 550 patients in a recent case series,[3] and the pathogenic effects of the antibodies have been shown in cultures of neurons and after injection to rat brain.[4] The characteristic symptoms begin with a prodrome of headache, fever, vomiting, and malaise, followed by psychiatric symptoms and social withdrawal.[5] Patients can rapidly deteriorate, with loss of language function, decreased responsiveness, hyperkinetic movements, autonomic instability, and seizures. The frequency of an underlying tumor, almost always a teratoma, varies according to sex, age, and ethnicity[3,5]; approximately 50% of women older than 12 years have an ovarian teratoma.

The diagnosis of anti-NMDAR encephalitis requires high clinical suspicion. *N*-methyl-D-aspartate receptor antibodies are usually found in serum and cerebrospinal fluid (CSF), and most patients have intrathecal synthesis of antibodies. About 80% of patients with anti-NMDAR encephalitis fully recover or have only minor sequelae, while the rest have substantial deficits and approximately 7% die.[5]

Report of a Case

Patient MF was a woman in her late 30s admitted to our facility with new-onset psychosis. The patient presented with confusion and headaches, followed by disorientation to place and time. She had a normal head computed tomography scan and a lumbar puncture that was notable for 237 nucleated cells. Antibiotic therapy for meningoencephalitis was initiated and she was transferred to our facility.

The patient became unresponsive and developed respiratory distress leading to intubation 6 days after admission. She developed persistent fever and autonomic instability. Serum and CSF samples were tested for an extensive list of infectious agents, all of which had negative results. A paraneoplastic antibody panel, sent approximately 4 weeks after admission, revealed the presence of NMDAR antibodies. Transvaginal ultrasonography was performed and showed an echogenic mass in the right ovary. The mass was resected and the pathology revealed an ovarian teratoma. Lumbar puncture performed at the time of the teratoma resection showed a high titer of anti-NMDAR antibodies in the CSF (Table).

The patient's condition declined. She remained minimally responsive, in a state akin to a dissociative coma with resistance to eye opening. She developed a hyperkinetic movement disorder with episodes of flailing limbs, oddly contoured facial expression, and thrusting of her pelvis, which compromised her safety. Numerous medications were tried, but none controlled the movements. Ultimately, a combination of phenobarbital, fentanyl citrate, haloperidol, and lorazepam was sufficient to keep the patient in bed, reducing most self-injurious activity.

The patient started receiving immunomodulatory medications at the time of the teratoma resection. She was treated first with a 5-day course of intravenous immunoglobulin (IVIg) followed by a course of methylprednisolone. She was then treated with 6 doses of rituximab.

Her CSF was reanalyzed 4 months after presentation (Table). The patient was treated with 3 monthly cycles of cyclophosphamide followed by 4 more doses of rituximab, without any change in her clinical status. Out of concern that she might still be harboring a malignancy, she underwent a complete left salpingo-oophorectomy; however, the pathology results were negative. A positron emission tomography scan was also normal, showing no evidence of malignancy. The CSF and serum analyses performed 10 months after hospital admission, following complete oophorectomy and treatment with IVIg, steroids, 4 cycles of cyclophosphamide, and 10 doses of rituximab, showed a moderate and transient decrease of serum and CSF anti-NMDAR antibody concentrations.

Over the next 6 months, the patient was treated with 6 cycles of plasmapheresis and 5 cycles of high-dose intravenous methotrexate. The CSF and serum anti-NMDAR antibodies remained unchanged. There was no clinical improvement. She remained comatose with hyperkinetic movements and resistance to eye opening.

Twenty months after initial presentation and after consultation with one of us (J.O.D.), it was decided to proceed with more treatment. The patient received 2 more cycles of IVIg and cyclophosphamide. The cyclophosphamide treatment was complicated by neutropenia. After her white blood cells recovered, the patient developed high fevers, hypotension, and tachycardia. She displayed septic shock physiology and blood and urine cultures grew *Escherichia coli*. The patient was treated and recovered from the infection but remained in a coma. The family decided to stop treatment at that time, and the goals of care were changed to comfort measures. She died after a 25-month inpatient hospitalization.

The patient had serial lumbar punctures throughout her hospitalization. Initially, the spinal fluid was abnormal with 237 white blood cells, lymphocytic predominance of 87%, and a high protein level at 65 mg/dL. With time, the spinal fluid normalized. In the first month, the white blood cell count dropped from 237 to 114 to 24. Thereafter, the fluid was normal or nearly normal with 0 to 6 white blood cells with each of the 7 subsequent lumbar punctures.

Antibodies to the NMDAR were followed up in both serum and spinal fluid after completion of each new course of treatment (Table). Initially, both serum and CSF antibody titers were quite high. After the first round of treatment with steroids, IVIg, and rituximab, both the serum and CSF antibody titers fell. With additional immunomodulatory treatment, the antibody levels were unchanged.

The patient had 11 magnetic resonance imaging scans of the brain during her hospitalization. With time, there was progressive atrophy, with parenchymal loss and ventricular dilation.

Discussion

To our knowledge, this case represents the longest active treatment without improvement of a patient with anti-NMDAR encephalitis. In other cases and case series, most patients had either improved or recovered but about 20% had substantial deficits or died. In the cases in which patients improved, the CSF antibody titers decreased, usually accompanied by a decrease of serum titers, although the antibodies may remain detectable (usually at lower

titers) after a patient's recovery. In a large case series, the most important prognostic factors include prompt initiation of immunotherapy or tumor removal and lack of critical care admission.[3]

In the case of our patient, treatment seemingly had minimal effect on CSF and serum antibody titers. Further, the treatment had no effect on the patient's clinical condition. The patient received most types of immunotherapies used for this disease, including steroids, IVIg, plasmapheresis, rituximab, and cyclophosphamide. Because of the lack of response to these treatments, high-dose methotrexate was also used, without any effect.

We are left with the question of why extensive treatment had no effect on the disease in this patient. Several studies have demonstrated that the antibodies in NMDAR encephalitis are synthesized systemically but also intrathecally by plasma cells present within the central nervous system.[6–8] Our patient appeared to have a strong immune response against NMDAR, refractory systemically and intrathecally to all the immuno-therapies used. We also questioned whether we may have been missing a secondary source of immunological activation and antibody production. The patient had a teratoma removed from her right ovary and the contralateral ovary that was also excised was normal. The possibility remains there may have been another undetected teratoma at a distant site.

Anti-NMDAR encephalitis is a relatively new disease characterized by mental status changes, seizures, autonomic instability, and hyperkinesis. Most patients do well with treatment and often make a near complete recovery, but a small proportion of patients do not improve. Since the antibody alters the levels of NMDAR synaptic receptors,[4] the persistent high levels of antibodies in our patient correlate with her lack of improvement, but it is unclear why she was refractory to all immunotherapies used. It is not known whether treatments such as bortezomib, which eliminates plasma cells, or alemtuzumab would have helped our patient; however, these drugs do not cross the blood-brain barrier, suggesting important limitations for the effects on plasma cells and inflammatory infiltrates in the brain.[9] Improvement in the prognosis of patients unresponsive to treatment would require use of early biomarkers to identify those requiring a more aggressive approach to reboot the immune system.

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Table

Antibody Titers Measured Using Serial Dilutions of Serum or Cerebrospinal Fluid and Cell-Based Assay

Time After Hospital Admission, mo	Summary of All Treatment Modalities and Antibody Titers	Serum Antibody[a]	CSF Antibody[a]
1	Diagnostic lumbar puncture	1:102 400	1:10 240
1.5	Teratoma resection and oophorectomy		
2	IVIg		
2	Methylprednisolone		
2–3	Rituximab		
4	Diagnostic lumbar puncture	1:51 200	1:5120
6, 7, and 8	Cyclophosphamide		
8–9	Rituximab		
10	Diagnostic lumbar puncture	1:25 600	1:2560
11	Cyclophosphamide		
12	Plasmapheresis		
12	Diagnostic lumbar puncture	1:51 200	1:5120
13–16	Intravenous high-dose methotrexate		
16	Rituximab		
16	Diagnostic lumbar puncture	1:25 600	1:5120
18	Electroconvulsive shock		
20	Cyclophosphamide		
20	IVIg		
22	Cyclophosphamide		
22	IVIg		

Abbreviations: CSF, cerebrospinal fluid; IVIg, intravenous immunoglobulin.

[a] Antibody titers were determined using serial dilutions of serum and CSF on rat brain tissue and human embryonic kidney cells expressing NR1 subunits of the *N*-methyl-D-aspartate receptor. The titer reflects the highest dilution at which reactivity was visible.