

N-methyl-D-aspartate Receptor Autoimmune Encephalitis Presenting With Opsoclonus-Myoclonus

Treatment Response to Plasmapheresis

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Objectives: To report the clinical, laboratory, and radiographic features and the response to plasmapheresis in a patient with encephalopathy, opsoclonus, and myoclonus whose cerebrospinal fluid was positive for N-methyl-D-aspartate receptor-IgG.

Design: Case report.

Setting: St Marys Hospital, Rochester, Minnesota.

Patient: A 27-year-old woman with a history of episodic migraine developed subacute progressive myoclonus, opsoclonus, and encephalopathy.

Results: Magnetic resonance imaging demonstrated nodular leptomeningeal enhancement in the superior cerebellar folia and subsequent T2 hyperintensities in the periventricular regions and amygdala. A positron emission tomographic scan of the head demonstrated predominantly frontotemporoparietal cortical hypometabolism with sparing of the primary sensory and motor cortices. Cerebrospinal fluid examination revealed a lymphocytic pleocytosis, mildly elevated protein level, el-

evated IgG index, and positive oligoclonal banding. Autoimmune cerebrospinal fluid screening revealed a neural-specific IgG that bound to synapse-rich regions of mouse hippocampus and cerebellar granular layer; the neural-specific IgG was confirmed to be N-methyl-D-aspartate receptor specific. No neoplasm was detected by physical examination or by whole-body computed tomography and positron emission tomography. A 5-day course of high-dose intravenous methylprednisolone sodium succinate yielded limited improvement, and the patient subsequently required intensive care unit admission following a pulseless electrical activity arrest associated with pulmonary embolism. The encephalopathy improved dramatically after plasmapheresis.

Conclusions: This case highlights opsoclonus and myoclonus as manifestations of autoimmune N-methyl-D-aspartate receptor encephalitis in the setting of a novel appearance on positron emission tomography, and it shows a remarkable clinical response to plasmapheresis.

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THE SYNDROME OF N-METHYL-D-aspartate receptor (NMDAR) autoimmune encephalitis is characterized by behavioral changes, hallucinations, seizures, amnesia, movement disorders, and/or dysautonomia and



Video available online at
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detection of NMDAR-IgG in serum or cerebrospinal fluid.^{1,2} Dalmau et al¹ reported 100 cases, of which 91% were female and more than half had an associated ovarian tumor. However, in a recently published European series of 34 adult patients, 32.4% were male and tumors were found in only 26.5%.²

Neuroimaging from the European patient series revealed that magnetic resonance imaging (MRI) findings were normal in 89% at the initial study and remained normal in 77% at follow-up. When detected, MRI abnormalities were localized to the hippocampi or white matter tracts.² Contrast enhancement in the meninges, cortex, and basal ganglia may be seen in rare cases.¹ Cerebrospinal fluid often reveals a lymphocytic pleocytosis, which may be accompanied by oligoclonal banding later in the disease course.

While the clinical and paraclinical features of this newly described disorder are being more completely defined, there is no standardized approach to treatment, except for removing any identified tumor.¹⁻³ We herein describe a patient who presented with the rare manifestation of

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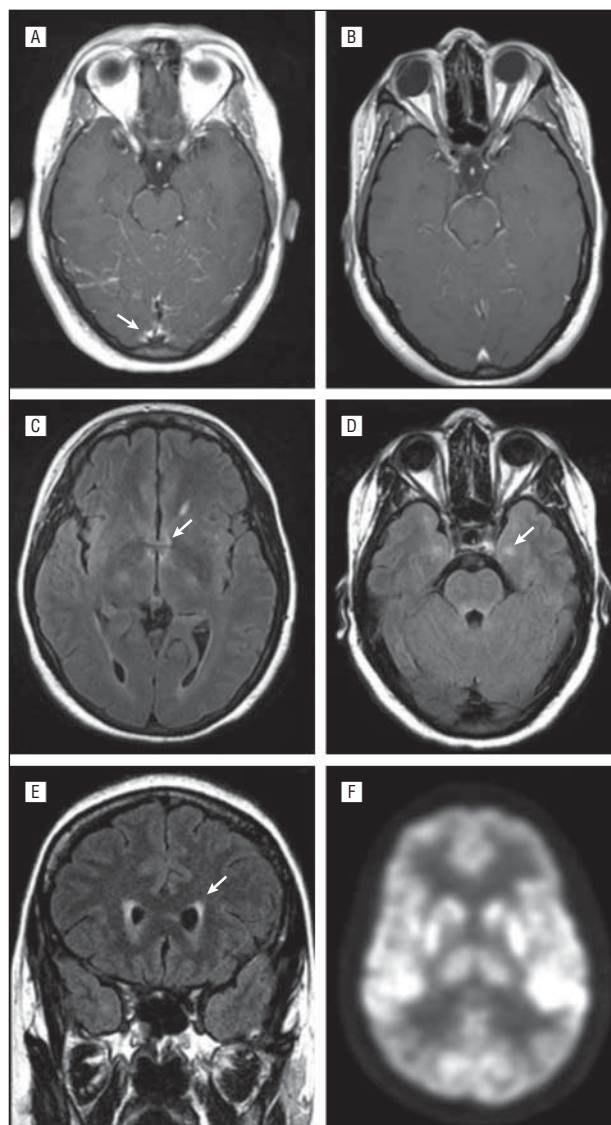


Figure. Neuroimaging in *N*-methyl-D-aspartate receptor autoimmune encephalitis. Axial T1-weighted magnetic resonance imaging with gadolinium contrast at presentation showed nodular leptomeningeal enhancement at the superior cerebellar folia (arrow) (A), which resolved following steroid administration (B); axial T2-weighted fluid-attenuated inversion recovery sequences showed interval development of hyperintensities in the periventricular regions (arrows) (C and E) and at the amygdala (arrow) (D); and positron emission tomography demonstrated cortical hypoperfusion with sparing of the primary sensorimotor cortices (F).

opsoclonus-myoclonus and exhibited a dramatic therapeutic response to plasmapheresis.

REPORT OF A CASE

A 27-year-old obese woman with a history of episodic migraine was admitted with a 1-month history of gradually progressive behavioral changes and jerking movements of the arms and eyes. The onset was preceded by an upper respiratory tract infection, orthostasis, and gait instability. The family had noted fluctuations in the patient's level of alertness and aggressive-disinhibited behavior (she was described as formerly being a very gentle and quiet person). On admission, the patient was noted

to have brief, unprovoked episodes of tachypnea without oxygen desaturation. She was encephalopathic, did not follow commands, and required mechanical restraint for agitation. She had multidirectional saccadic eye movements and spontaneous and startle-induced myoclonus of the arms, consistent with an opsoclonus-myoclonus syndrome (video 1, <http://www.archneurology.com>).

Magnetic resonance imaging of the head with and without gadolinium contrast revealed nodular leptomeningeal enhancement in the superior cerebellar folia (Figure, A). Cerebrospinal fluid examination demonstrated 56 nucleated cells with 98% lymphocytes, a mildly elevated protein level (0.036 g/dL; reference range, 0.000–0.035 g/dL; to convert to grams per liter, multiply by 10), and a normal glucose level. The IgG index was 1.31 (reference range, <0.85), and 8 oligoclonal bands were detected (reference range, <4). Electroencephalography showed mild nonspecific background slowing, without an electrographic correlate for the myoclonus. An extensive laboratory evaluation for infectious, inflammatory, autoimmune, and paraneoplastic causes revealed an elevated C-reactive protein level (54.8 mg/L; reference range, <8 mg/L; to convert to nanomoles per liter, multiply by 9.524), a normal erythrocyte sedimentation rate, and a neural-specific IgG in cerebrospinal fluid that bound to synapse-rich regions of mouse hippocampus and cerebellar granular layer. The neural-specific IgG was confirmed to be NMDAR specific by reflex testing on a substrate of transfected mammalian kidney cells (Euroimmun Biochip Assay; Euroimmun AG, Lübeck, Germany).

After a 5-day course of intravenous methylprednisolone sodium succinate (1 g/d), the opsoclonus and myoclonus improved mildly and the nodular leptomeningeal enhancement resolved (Figure, B). However, encephalopathy persisted and there was interval development of symmetric bilateral T2 hyperintensities involving the periventricular regions along the frontal horns of the lateral ventricles and around the fornices behind the anterior commissure, in addition to increased signal in the amygdala (Figure, C–E).

A comprehensive evaluation for neoplasia was unrevealing, including mammography, computed tomography of the chest, abdomen, and pelvis, ultrasonography of the pelvis, and positron emission tomography of the body. Positron emission tomography of the brain revealed marked frontotemporoparietal cortical hypometabolism with sparing of the sensory and motor strips (Figure, F).

Six days after completing the course of steroid therapy, the patient became acutely tachypneic and diaphoretic and was transferred to the medical intensive care unit, where she developed pulseless electrical activity. She received immediate hemodynamic resuscitation and intubation, and cardiopulmonary resuscitation was required for more than 1 hour. She was treated empirically with alteplase for presumed pulmonary embolus, following which she improved clinically. A lower-extremity deep vein thrombosis was found, despite mechanical and chemical prophylaxis throughout the hospitalization (subcutaneous heparin, 5000 U 3 times daily). The resuscitation was complicated by a traumatic liver laceration with

hemoperitoneum and an abdominal compartment syndrome requiring laparotomy and surgical repair. The open abdominal wound allowed gross surgical inspection for ovarian and extraovarian abdominal tumors; none were found. Because of her age and nulliparous status, her ovaries were left intact.

The patient stabilized hemodynamically, but weaning from the ventilator was complicated by continued agitation and need for sedation. Tracheotomy was performed, and the patient was weaned from the ventilator with addition of quetiapine fumarate and clonazepam. Remarkably, despite prolonged resuscitation, no neurologic status changes developed to suggest hypoxic-ischemic injury. With return to baseline encephalopathy, opsoclonus and myoclonus were minimal. Large-volume plasmapheresis was continued every other day for 7 treatments. Improvement was dramatic by the third treatment: the encephalopathy had resolved, the patient was following commands, and myoclonus was diminished, but opsoclonus continued (video 2). The patient was dismissed from the hospital to complete the 7 plasma exchanges and to have once weekly treatments locally. At 1-month hospital follow-up, encephalopathy, myoclonus, and opsoclonus had resolved completely and the patient had retrograde amnesia for the events of the hospitalization (video 3). The head MRI abnormalities resolved completely (images not shown). We discontinued the plasmapheresis and began long-term treatment with azathioprine, 2.5 mg/kg, with a 6-month steroid taper starting at 1 mg/kg. Six months after the initial hospitalization, the patient has returned to work and no relapses have been reported. She is receiving maintenance treatment with azathioprine alone.

COMMENT

Treatment of NMDAR autoimmune encephalitis involves early removal of the tumor in paraneoplastic cases and immunotherapy in paraneoplastic and idiopathic cases. Recovery is reported to be more favorable if a tumor is found (usually a teratoma), but relapses may occur and the clinical course may be protracted, especially in nonparaneoplastic cases. In refractory cases, exploratory laparotomy for microscopic teratoma is indicated.¹ Patients in whom a tumor is not identified appear not to respond as well to immunotherapy.¹⁻³ Recent data by Irani et al² suggest that the best treatment strategy is early (within 40 days) combination therapy with glucocorticoids and an additional agent. Our patient's course would be consistent with these observations and specifically demonstrates that dramatic improvement can be achieved with plasmapheresis despite an inadequate response to steroids. A profound clinical response to plasmapheresis has been previously reported in a 12-year-old girl with NMDAR autoimmune encephalitis who also did not respond well to steroids.⁴

Opsoclonus-myoclonus syndrome has been reported only in a single previous case of NMDAR autoimmune encephalitis.⁵ The patient in that case was a 23-year-old woman whose clinical presentation followed a presumed viral gastrointestinal illness. No tumor was iden-

tified. Interestingly, a pulmonary embolus was identified in that patient also. The patient exhibited an incomplete response to treatment with steroids and intravenous immunoglobulin. The mechanism of opsoclonus in our case is not clear, although the symptom improved with immunotherapy, suggesting a pathogenic role for the NMDAR antibody.⁵ Several other autoantibodies have been reported in association with opsoclonus-myoclonus syndrome.⁶ The autoantigens implicated in cases of opsoclonus-myoclonus syndrome, including adenomatous polyposis coli protein and zinc finger proteins, are often linked by an association with the postsynaptic density, where they may interact in a complex with NMDAR.⁶ While functional MRI has suggested a role for bilateral disinhibition of the fastigial nucleus in the pathophysiology of idiopathic opsoclonus, the positron emission tomographic study in our case did not reveal cerebellar hypermetabolism.⁷

Our patient's lack of morbidity following cardiopulmonary arrest and prolonged resuscitation may be attributable to fortuitous protection against hypoxia-induced excitotoxic effects by NMDAR-IgG. This hypothesis is supported by experimental observation that an oral vaccine against NMDAR1 had a strong neuroprotective effect in rats following experimental stroke.⁸

Several preclinical findings in our case are consistent with previously reported observations on MRI and cerebrospinal fluid abnormalities in NMDAR autoimmune encephalitis.^{1-3,9} Transient leptomeningeal enhancement has been reported in rare circumstances, without further characterization.^{1,2,9} Our finding of a nodular quality may be unique in the literature. The MRI abnormality in the amygdala is consistent with higher levels of NR2A and NR2B antigens in this nucleus.⁹ In our case, positron emission tomography demonstrated a pattern of diffuse frontotemporoparietal hypometabolism with sparing of the primary sensorimotor cortices. In a previously reported case with positron emission tomographic findings, relative hypermetabolism was noted in the bilateral frontal, temporal, and parietal lobes, with relative hypometabolism in the bilateral occipital lobes and cerebellum.¹⁰ This discrepancy of findings likely represents the varied presentations among individual patients.

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