

Clinical Vignettes

Anti-NMDA-Receptor Encephalitis: Case Report and Literature Review of an Under-Recognized Condition

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Anti-N-methyl-D-aspartate receptor (anti-NMDA-R) encephalitis is an immune-mediated syndrome that remains under-recognized despite a growing body of literature. This syndrome has been predominantly described in young females with a constellation of symptoms, including personality changes, autonomic dysfunction and neurologic decompensation. It is commonly associated with mature ovarian teratomas. We describe the classic presentation of anti-NMDA-R encephalitis in three dramatically different patients: Case A, a young woman with ovarian teratoma; Case B, the eldest case reported to date; and Case C, a young male with no identifiable tumor. We review the literature summarizing the differential diagnosis, investigative approach, treatment options and challenges inherent to this disorder. We advocate good supportive care, involvement of multiple health disciplines and use of immune-modulating therapies in patient management. These cases underscore the need for increased awareness and high diagnostic suspicion when approaching the patient with suspected viral encephalitis.

KEY WORDS: encephalitis; NMDA-receptor; teratoma; autoimmune.

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INTRODUCTION

The classic presentation of anti-NMDA-R encephalitis involves a confluence of psychiatric, neurologic and autonomic symptoms, often with a viral prodrome. Psychosis, hallucinations, memory loss and personality changes are the earliest symptoms; for this reason psychiatry is often consulted. Dyskinesias (especially orofacial), ataxia, seizures and decreased level of consciousness may follow, prompting referral to an internist. Days to weeks later, autonomic instability may occur, manifesting as cardiac arrhythmia, hypotension and hypoventilation, requiring supportive care in the intensive care unit (ICU).

Results of conventional investigations including examination of cerebrospinal fluid (CSF), brain imaging and electroencephalogram (EEG) are non-specific. Lymphocytic pleocytosis, oligoclonal banding, increased CSF protein, hyperintensity on T2 magnetic resonance imaging (MRI), decreased uptake in hippocampal structures on functional MRI and epileptiform activity on EEG have been described¹⁻³. The lack of specific laboratory and radiologic findings explain why this syndrome was not described until 2007, with the majority of previous cases likely diagnosed as viral encephalitis.

This case series describes the classic presentation of anti-NMDA-R encephalitis in three diverse patients. Putative pathophysiology, diagnosis and management of this under-recognized syndrome are discussed through literature review. Having read these vignettes the clinician should recognize when to consider anti-NMDA-R encephalitis in the differential diagnosis of a patient with suspected viral encephalitis.

Case A

A 21-year-old previously healthy woman was brought to a community hospital with confusion, agitation, auditory hallucinations and suicidal ideation. She was febrile without focal neurologic deficits or meningeal signs (Mini-Mental Status Examination⁴ [MMSE]>26/30; Modified Rankin Scale⁵ [MRS]=2). Laboratory parameters were normal. She was diagnosed with brief psychotic disorder and discharged home.

Symptoms progressed, requiring admission to a psychiatric hospital. On admission, hyperventilation was observed. Days later, the patient became apneic, had a witnessed generalized tonic-clonic seizure, and was transferred to our tertiary care center. Brain computerized tomography (CT) and MRI were normal. CSF showed mildly elevated lymphocytes and protein. Treatment with acyclovir was started for presumed viral encephalitis. Four days later, she experienced another generalized seizure with decreased level of consciousness. She was intubated and transferred to the ICU.

In the ICU, orofacial dyskinesias and involuntary movements of the upper extremities were observed. Continuous EEG demonstrated non-convulsive status epilepticus, requiring high doses of anticonvulsants and general anaesthesia. Repeat serum and CSF investigations were unchanged. A paraneoplastic antibody panel was sent given the constellation of personality changes, autonomic instability (requiring mechanical ventilation), orofacial dyskinesia and seizures. Anti-NMDA-R antibodies were detected in serum and CSF. Search for a primary tumor revealed a 2.9-centimeter right ovarian cyst. Laparoscopic right oophorectomy was per-

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formed; pathology confirmed mature cystic teratoma. The patient was treated with plasma exchange (PLEX) followed by intravenous immunoglobulin (IVIg, 2 g/kg divided over 5 days) without improvement in neurological status.

The patient's prolonged ICU course was complicated by diabetes insipidus, *Staphylococcus aureus* pneumonia, *Clostridium difficile* colitis and bacteremia. Three months following initial presentation, she developed third-degree heart block with hypotension. Instability persisted despite transvenous pacemaker insertion. Fourteen and one-half weeks following admission, she suffered a cardiac arrest and died despite aggressive resuscitation attempts.

Case B

A high-functioning 84-year-old Italian woman presented to our tertiary care hospital with a six-day history of disorientation, agitation and visual hallucinations. Physical examination demonstrated impaired cognition with decreased attention (MMSE=22/30, MRS=3). Blood tests, toxicology and brain CT were normal. Urinalysis was positive for leukocytes and nitrites, and urine culture confirmed *Escherichia coli* sensitive to fluoroquinolones. Urinary tract infection was treated with ciprofloxacin.

While in hospital the patient experienced insomnia, anxiety and delusions that her food was being poisoned. Given concern for non-resolving delirium, a lumbar puncture was performed; CSF showed high-normal protein and lymphocytic pleocytosis. Six weeks after admission, she developed orofacial dyskinesias, unilateral dystonic posturing of the limbs and hyperventilation, followed by hypoxic respiratory failure requiring intubation and ICU admission. Brain MRI was normal. EEG showed diffuse slowing. Diagnosis of viral encephalitis was presumed. Seven weeks later, phenytoin was started after EEG demonstrated periodic lateralized epileptiform discharges—a non-specific pattern seen in patients with seizures, brain infections, tumors and intracranial hemorrhage, amongst other causes. A second lumbar puncture was performed with anti-NMDA-R antibodies detected in the CSF. Imaging of the thorax, abdomen and pelvis failed to detect malignancy. Empiric treatment with IVIg was started (2 g/kg divided over 5 days). No response was observed within two weeks. PLEX was performed without improvement. Fourteen weeks into admission, the patient remained unresponsive with complications, including ventilator-associated pneumonia and *Pseudomonas* bacteremia. In consultation with family and health-team members (including palliative care specialists) the decision was made to withdraw ventilatory support. The patient died from respiratory failure within 24 hours.

Case C

A 38-year-old healthy Caucasian male complained of a six-month history of intermittent nausea, vomiting, vertigo and imbalance. Neurologic examination was normal. Three months following assessment he experienced a generalized tonic-clonic seizure and was admitted to hospital (MMSE=30/30, MRS=1). Over the following week, he developed progressive confusion, short-term memory dysfunction, prosopagnosia, agitation, orofacial dyskinesias, partial complex seizures and broad-based gait. Brain CT and MRI were normal. CT and positron emission tomography (PET) of the chest, abdomen and pelvis failed to reveal a

malignancy. Serial CSF samples showed a non-specific lymphocytic pleocytosis and oligoclonal banding, suggestive of immune upregulation with intrathecal antibody production. CSF was sent for anti-NMDA-R antibodies. Empiric high-dose corticosteroids and acyclovir were started to treat possible steroid-responsive encephalopathy and viral encephalopathy, respectively. Acyclovir was discontinued when herpes simplex virus was not identified by polymerase chain reaction (CSF). A course of IVIg (2 g/kg divided over 5 days) was completed with no response. Three weeks into admission, the patient developed global aphasia and flaccid quadriplegia with opsoclonus. He was urgently transferred to our tertiary care center.

Within 24 hours of transfer the patient experienced a generalized tonic-clonic seizure with respiratory compromise requiring intubation and ICU admission. Repeat brain imaging was normal. EEG showed generalized non-specific slowing. His course was complicated by treatment-resistant status epilepticus, ventilator-associated pneumonia and Stevens-Johnson syndrome (presumed secondary to anticonvulsants, including carbamazepine). Within two weeks of transfer, anti-NMDA-R antibodies were confirmed in the CSF. A five-day course of PLEX was administered without improvement. He continued to deteriorate and developed bradycardia, prolonged QT interval and apnea. Rituximab was administered (375 mg/m² to be given weekly, six cycles). Six days following the first dose he developed sepsis with hemodynamic failure. Consistent with advanced directives, cardiopulmonary resuscitation was not provided and he died.

Anti-NMDA-Receptor Encephalitis

The syndrome of anti-NMDA-R encephalitis was first characterized in 2007⁶. Over 120 cases have been reported in the literature (Table 1). Initially described as a paraneoplastic syndrome affecting young women with ovarian teratomas, anti-NMDA-R encephalitis is associated with mediastinal teratomas, sex-cord stromal tumors, small-cell lung cancer and testicular teratomas¹. In the largest case series published to date¹, the syndrome of anti-NMDA-R encephalitis was described in 91 females and 9 males. Ovarian teratomas were diagnosed in 56 females (62%; 56/91); small-cell cancer and testicular teratoma were diagnosed in two males (22%; 2/9). Microscopic analysis of ovarian teratomas confirmed the presence of central nervous system tissue, with NMDA-receptors expressed in 25 tumors further analyzed. An immune-mediated mechanism likely underlies this syndrome: antibodies formed against neoplastic cells cross-react with native NMDA-receptors leading to destruction or down-regulation¹.

In the normal state, NMDA-receptors are found throughout the central nervous system, mediating a critical role in synaptic transmission and plasticity. NR1 and NR2 subtypes bind glycine and glutamate, respectively, and together form heteromers with distinct pharmacologic properties, abilities to interact with intracellular messengers and localizations⁷. In patients with anti-NMDA-R encephalitis, antibodies directed towards the NR1 and NR2 heteromers of NMDA-receptors circulate within CSF. NR1 and NR2 heteromers predominate within the hippocampus, with less intense reactivity described in the forebrain, basal ganglia, spinal cord and cerebellum^{1,8}. Thus, antibodies may preferentially affect areas responsible for memory, personality, movement and autonomic control, accounting for the unique confluence of personality changes, impairments in cognition,

Table 1. Selected Summary of Cases, Patient Presentation*

	Number of Cases, Median Age (Range)		Viral Prodrome	MRI FLAIR [†] / T2 Hyperintensity (focal findings)	CSF Lymphocytic Pleocytosis [‡]	Presence of Neoplasm	
	Women	Men				Women	Men
Dalmau et al. 2007 ⁶	12	0	83% (10/12)	75%, 9/12 (67%, 6/9)	100% (12/12)	100% (12/12)	–
Dalmau et al. 2008 ¹	27 (14–44) years	9	86% (86/100)	55%, 55/100 (35%, 19/55)	91% (91/100)	62% (56/91)	22% (2/9)
Iizuka et al. 2008 ¹²	23 (5–76) years	4	100% (4/4)	25%, 1/4 (0)	100% (4/4)	75% (3/4)	–
Ishihara et al. 2008 ²	4 25.8 (17–33) years	0	100% (1/1)	MRI Normal	100% (1/1)	0	–
Gable et al. 2009 ³	1 42 years	4	“Most patients”	40%, 4/10 (25%, 1/4)	90% (9/10)	33% (2/6)	0
Davies et al. 2010 ⁹	6 18.5 (11–31) years	2	Not specified	17%, 1/6 (0)	100% (6/6)	50% (2/4)	0
Prüss et al. 2010 ¹⁰	4 27 (21–41) years	0	83% (5/6)	67% (4/6) (0)	100% (6/6)	33% (2/6)	–
Day et al. 2011	6 22.5 (18–31) years	1	100% (3/3)	0	100% (3/3)	50% (1/2)	0
	2 38 (21–84) years						

* Cases were compiled through MEDLINE search of English-language publications (2007–2010) using keyword “anti-NMDA-receptor encephalitis.” Case reviews featuring multiple cases were included. Cases cited in manuscript text were included regardless of number of cases to provide outcome information

[†] Fluid-attenuated inversion recovery

[‡] Absolute white blood cell count >5/μL, lymphocytic predominance

motor derangements, bradyarrhythmias and disturbances in respiratory drive that define the syndrome.

Antibody titres are higher in patients with confirmed malignancies and highest in those with the most severe symptoms¹. Antibodies are also detected within the CSF of patients presenting with the typical syndrome without tumor (similar to Cases B and C). It is therefore likely that other immunologic triggers contribute to the production of autoantibodies. One such trigger may be viral infection, as viral prodrome is reported in the majority of cases (Table 1). Similar associations with neoplasm and viral prodromes are described in other antibody-mediated syndromes including limbic encephalitis, dermatomyositis-polymyositis, myasthenia gravis and Lambert-Eaton myasthenic syndrome.

Diagnosis and Management

The identification of NMDA-receptor antibodies has established a laboratory diagnosis for the characteristic clinical syndrome. Case A exemplifies the most common presentation of anti-NMDA-R encephalitis: a young female of reproductive age with an ovarian teratoma. Case B describes the syndrome in an 84-year-old woman—the eldest case reported to date. Finally, Case C provides an example of anti-NMDA-R encephalitis in a young male without evidence of tumor. Although patients' ages vary widely, symptoms, signs and courses are similar (Table 2).

These cases highlight several important discussion points. Perhaps most important is that anti-NMDA-R encephalitis is an under-recognized syndrome. With the advent of antibody markers, this syndrome was confirmed in 20% of cases of encephalitis at one tertiary referral center⁹, and retrospectively diagnosed

in 86% (6/7) of patients managed in a single-center ICU with diagnosis “encephalitis of unknown origin” and compatible clinical features¹⁰. The diagnosis ought to be considered in the differential of all patients presenting with findings of “viral encephalitis”—regardless of age or sex (previous reports have emphasized the classic presentation in the “young female”)—especially when findings out-of-keeping with presumed diagnosis are detected, as noted in Case A, describing a patient with fever incompatible with diagnosis of brief psychotic disorder. Similarly, the presence of seizures early in the illness course should raise diagnostic suspicion. Complex and generalized seizures are reported in the majority of cases (76% [76/100] in the largest case series¹), distinguishing anti-NMDA-R encephalitis from most causes of viral encephalitis³ and suggesting that seizures are part of the natural history of this syndrome. Investigations should be requested with the intent of confirming the diagnosis while excluding mimics (Table 3). Particular attention should be directed toward organs of gametogenesis, as the presence and removal of ovarian or testicular teratomas is associated with more favorable outcomes¹. Confirmatory testing should be requested in all patients presenting with psychiatric, neurologic and autonomic symptoms / signs that are not better explained by another disease process. Although routine antibody testing is not yet available, techniques for isolating antibodies have been published¹ and validated—sensitivity and specificity is reported to be 100%¹¹. Results may be obtained through communication with academic centers investigating paraneoplastic syndromes.

Empiric treatment should be initiated concurrent with investigations, with close monitoring for response. No randomized controlled trials have evaluated anti-NMDA-R encephalitis treatment. Open-label observational studies of immune-modulating

Table 2. Patient Presentations, Investigations and Outcomes

Sex	Patient A	B	C
	Female	Female	Male
Age	21	84	38
Symptoms			
- Psychiatric	Confusion, agitation, auditory hallucinations and suicidal ideation	Disorientation, agitation, anxiety, visual hallucinations, persecutory delusions	Confusion, short-term memory dysfunction, prosopagnosia, agitation
- Dyskinesias	Lip-smacking, chewing movements, rotatory movements of upper extremities	Lip-smacking, chewing movements	Lip-smacking, chewing movements, opsoclonus
- Hypoventilation	Yes, with apnea	Yes	Yes, with apnea
- Arrhythmias	3° heart block	No	Bradycardia, prolonged QT interval
Investigations			
- CSF	Lymphocytic pleocytosis (107 WBC/HPF*, 99% lymphocytes), oligoclonal bands not requested	Lymphocytic pleocytosis (22 WBC/HPF, 98% lymphocytes), elevated protein (170 mg/ml†), oligoclonal bands not requested	Lymphocytic pleocytosis (84 WBC/HPF, 92% lymphocytes) elevated protein (250 mg/ml), oligoclonal bands
- CT Head	Normal	Microangiopathic changes	Normal
- MRI	Normal	Normal	Normal
- EEG	Early: normal. Late: non-convulsive status epilepticus	Early: diffuse non-epileptiform activity Late: periodic lateralized epileptiform discharges	Early: Generalized slowing Late: status epilepticus
- Anti-NMDA-R antibodies in CSF	Yes	Yes	Yes
Tumor	Ovarian teratoma	None	None
Treatment			
- Corticosteroids	No	Yes	Yes
- IVIG	Yes	Yes	Yes
- PLEX	Yes	Yes	Yes
- Rituximab	No	No	Yes
Time from presentation to diagnosis	8 weeks	10 weeks	5 weeks
Duration of symptoms (ICU admission)	14.5 weeks (14 weeks)	14 weeks (8 weeks)	36 weeks (9 weeks)
Outcome	Deceased	Deceased	Deceased

* White blood cells per high powered field

† Milligrams per milliliter

Table 3. Differential Diagnosis of Anti-NMDA-R Encephalitis

Etiology	Distinguishing Features		
	Physical Examination	Laboratory Markers	Imaging
Infectious (e.g., bacterial meningitis, HSV* encephalitis, other viral, prion disease)	- Fever - Nuchal rigidity - Palpable purpura (<i>Neisseria meningitidis</i>)	- Positive CSF / serum cultures - Specific antibody / antigen detection	- CT: Hydrocephalus - MRI: Temporal lobe hyperintensity / degeneration (HSV encephalitis), cortical ribbon / basal ganglia enhancement (Creutzfeldt-Jakob Disease)
Neoplastic (e.g., primary / secondary brain neoplasm, central nervous system lymphoma)	- Focal neurologic signs	- Specific markers (PSA†, CA-125‡, CEA§) - Monoclonal proliferation on flow cytometry, immunohistochemistry	- CT / MRI: Space-occupying lesion(s)
Metabolic (e.g., Wernicke's, Hashimoto's encephalopathy)	- Abnormal eye movements, ataxic gait (Wernicke's)	- Decreased thiamine - Anti-thyroid peroxidase / thyroglobulin antibodies	- Periventricular enhancement / hemorrhage (Wernicke's)
Autoimmune (e.g., vasculitis, systemic lupus erythematosus)	- Systemic findings	- Increased ESR / CRP¶ - Specific rheumatologic seromarkers	- Diffuse cortical changes, vessel wall narrowing (with vessel-wall imaging)

* Herpes simplex virus

† Prostate specific antigen

‡ Cancer antigen 125

§ Carcinoembryonic antigen

|| Erythrocyte sedimentation rate

¶ C-reactive protein

Table 4. Selected Summary of Cases, Treatment and Responses

	Surgical Excision of Tumor	First Line Therapy: Corticosteroids	Second Line Therapy: IVIG, PLEX, both	Alternative Therapies Attempted	Outcomes* (FR, MR, PR, Death)
Dalmau et al. 2007 ⁶	75% (9/12)	83% (10/12)	IVIG=50% (6/12) PLEX=50% (6/12) Both=33% (4/12)	Cyclophosphamide =8% (1/12)	FR=33% (7/12) MR=8% (1/12) PR=8% (1/12) Death=25% (3/12)
Dalmau et al. 2008 ¹	51% (51/100)	76% (76/100)	IVIG=62% (62/100) PLEX=34% (34/100) Both=Not specified	Azathioprine=10% (10/100) Cyclophosphamide=9% (9/100) Rituximab=10% (10/100)	FR=47% (47/100) MR=28% (28/100) PR=18% (18/100) Death=7% (7/100)
Iizuka et al. 2008 ¹²	75% (3/4)	50% (2/4)	IVIG=50% (2/4) PLEX=0 Both=0	–	FR=75% (3/4) MR=25% (1/4) PR=0 Death=0
Ishihara et al. 2008 ²	0	100% (1/1)	IVIG=0 PLEX=100% (1/1) Both=0	Rituximab=100% (1/1)	FR=100% (1/1) MR=0 PR=0 Death=0
Davies et al. 2010 ⁹	33% (2/3)	100% (6/6)	IVIG=33% (2/6) PLEX=50% (3/6) Both=17% (1/6)	Cyclophosphamide=17% (1/6) Ketamine=17% (1/6) Rituximab=17% (1/6)	FR=33% (2/6) MR=33% (2/6) PR=17% (1/6) Death=17% (1/6)
Day et al. 2011	33% (1/3)	67% (2/3)	IVIG=100% (3/3) PLEX=100% (3/3) Both=100% (3/3)	Rituximab=33% (1/3)	FR=0 MR=0 PR=0 Death=100% (3/3)

* FR=full recovery (MRS=0); MR=moderate recovery (MRS=1-2); PR=poor recovery (MRS=3-5); Death (MRS=6)

therapies have shown mixed results^{1,2,6,9,12} (Table 4). One treatment protocol to consider is to use intravenous corticosteroids, progressing to PLEX, IVIG, or both. Monoclonal-antibodies targeting CD-20 lymphocytes (i.e., rituximab) may be considered when other therapies have failed, although efficacy is unproven^{1,2,9}. The association between malignancy and anti-NMDA-R encephalitis suggests that antibodies are formed against tumor cells expressing NMDA-receptors. Consistent with this, surgical excision of tumor “antigen” precedes a reduction in antibody titres¹ and offers the most clinical benefit in affected patients^{1,6}. Excision should be considered in all patients with suspected neoplasm to decrease potential antigen burden. Limited evidence from case reports suggests rituximab may be useful for patients without confirmed neoplasm².

Anti-NMDA-R encephalitis is a complex syndrome with characteristic symptomatology, variable response to treatment and a broad differential diagnosis. Diagnosis and management necessitates awareness and communication between various medical professionals including internists, neurologists, psychiatrists, intensivists, cardiologists, infectious disease specialists, radiologists, gynecologic and urologic surgeons, and pathologists. With care as described, prognosis remains good with 75% (92/123) of cases recovering with minimal deficits (MRS \leq 2, Table 4). Mortality of our cases (100%) is higher than described (0-25%, Table 4), with disease courses adversely affected by complications associated with prolonged ICU admission. This observation stresses the importance of prompt diagnosis and treatment, with emphasis on supportive care.

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