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BRIEF COMMUNICATION

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis: an etiology worth considering in the differential diagnosis of delirium

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Background. Medical toxicologists are frequently consulted when young patients present with delirium attributed to suspected poisoning. Medical toxicologists should be aware of non-toxicological mimics of delirium. We describe two patients ultimately diagnosed with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis for which a toxicological consultation was requested to evaluate for neuroleptic malignant syndrome (NMS). *Case 1.* A 21 year old male was sent from a psychiatric facility for new, worsening psychotic symptoms. He had autonomic instability, confusion, and hyper-reflexia. He was treated for NMS without improvement, and after an extensive workup was unrevealing, he was discharged home with significant cognitive dysfunction. Stored CSF later tested positive for anti-NMDAR antibodies. *Case 2.* A 27 year old female was sent from a psychiatric facility for a seizure and new psychiatric symptoms. She was agitated and had violent, alternating extremity flexion and extension along with autonomic instability. She was treated for NMS, rhabdomyolysis, and rabies before analysis of CSF demonstrated anti-NMDAR antibodies. Treatment included surgical resection of a suspicious ovarian cyst, steroids and IVIG, with moderate improvement. *Discussion.* Autoimmune syndromes of the central nervous system result from receptor dysfunction after an antibody response to extracellular or intracellular antigens, such as subunits of the NMDA receptor. The NMDA subunits NR2b and NR2a, in addition to the N-terminal region of the glycine binding NR1 subunit, have been implicated. Typical features such as memory loss, movement disorders, and hallucinations reflect the density and distribution of neuronal NDMA receptors. As young people, particularly young women, are predominantly affected, initial symptoms may be attributed to encephalopathy from drug abuse or schizophrenia. Toxicologists may be consulted as many features mimic NMS. Serum and cerebrospinal fluid can be checked for anti-NMDAR antibodies as part of a paraneoplastic or meningioencephalitis panel. Effective treatments have been described and include surgical resection and immunosuppressive medications.

Keywords Delirium; Encephalitis; Neurology; Autoimmune; Toxicology; Neuroleptic malignant syndrome; n-methyl-d-aspartate receptor

Background

Medical toxicologists are frequently consulted when previously healthy young patients present with acute alterations in attention and cognition attributed to suspected poisoning. These suspicions may arise out of concern for illicit drug use, unusual adverse drug reactions or interaction, or some other occult environmental exposure. If the initial evaluation is unrevealing, and resolution of encephalopathic signs and symptoms does not occur, further workup for more exotic metabolic, infectious, and autoimmune etiologies is often undertaken. Medical toxicologists should be aware of non-toxicological mimics of delirium initially attributed to a toxidrome.

Significant advancement has occurred in the identification of encephalitides that occur in association with central nervous system (CNS) antigen and receptor autoantibodies. One such autoimmune syndrome that appears to be more common than previously recognized is anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.[1] The syndrome was first identified in 2005[2] and is attributed to NMDAR autoantibodies. Estimates of the prevalence of this disorder range from 1% to 41% of patients with idiopathic encephalitis, depending on the patient population being studied.[1,3] Since the syndrome is well-described, and laboratory testing options for NMDAR autoantibodies are available, proper diagnosis and treatment is possible if the diagnosis is considered. In order to increase awareness of the syndrome among medical toxicologists, we report on two patients ultimately diagnosed with anti-NMDAR encephalitis for which an initial toxicological

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Table 1. Selected results of CSF analysis.

	Case 1	Case 2
Protein	24 (15–45 mg/dL)	18 (15–45 mg/dL)
Glucose	**80** (50–75 mg/dL)	**81** (40–70 mg/dL)
CSF RBC	0 (0 cells/uL)	**10** (0/mcL)
CSF WBC	**24** (1–10 cells/uL)	9 (< 11/mcL)
Differential	96% lymphocytes	88% lymphocytes

Bolded values are outside of reference range.

consultation was requested to evaluate for neuroleptic malignant syndrome (NMS).

Case 1

A previously healthy 21-year-old Hispanic male construction worker began to have headaches and insomnia. According to friends and family, the patient developed worsening irritability and confusion, and finally presented to an outside emergency department with psychomotor agitation and audiovisual hallucinations. As he had no previous history of psychiatric disease or drug misuse, a medical workup including computed tomography (CT) of the head, magnetic resonance imaging (MRI)/magnetic resonance angiogram (MRA) of the brain, and electroencephalogram (EEG) was performed. The only abnormality was a mild pleocytosis seen on cerebrospinal fluid (CSF) analysis (see Table 1), but as the radiographic imaging and basic bacterial and viral testing were negative, the patient was transferred to an inpatient psychiatric facility for treatment of psychosis. After administration of multiple doses of olanzapine, ziprasidone, diazepam, and haloperidol he "stopped eating" and was sent to our facility for further evaluation. On arrival, he was noted to be hyperthermic (temperature, 38.1°C), and had confused speech, increased muscle tone in all four extremities, and brisk reflexes throughout. Inpatient evaluation was unremarkable except for an elevated creatine phosphokinase (CPK) that peaked at 5420 (reference range 49–397 U/L) and a commercial enzyme-linked immunoassay urine drug screen positive for benzodiazepines. Treatment was initiated for suspected NMS with bromocriptine, dantrolene, and lorazepam without improvement; he was also treated with acyclovir. Repeat workup including brain MRI/MRA, EEG, and testing for infectious and autoimmune etiologies (including serum NMDAR antibody testing by cell-based indirect immunofluorescence assay, or IFA) was unrevealing (see Table 2). A PEG tube was placed for feeding, and eventually the patient was discharged home with 24-h nursing care. Six months after discharge, additional testing on previously stored frozen CSF by cell-based IFA was positive for anti-NMDAR antibodies.

Case 2

A previously healthy 27-year-old African-American female bartender was transferred from an inpatient psychiatric facility for evaluation after having a single, tonic–clonic seizure. The medical toxicology service was consulted out of a concern for NMS. Three weeks prior, the patient had begun to experience headaches, irritability, odd behavior, and difficulty in finding words to express herself. She was admitted to an inpatient psychiatric facility for 7 days, where she was treated with haloperidol, thorazine, benzotropine, and lorazepam. A history provided by the family revealed that the patient had no past psychiatric disease but frequently abused cocaine. On evaluation by the medical toxicology service, the patient was severely agitated, delirious, and had clinical findings of autonomic nervous system instability with heart rate ranging from the 40s to 140s. She was also experiencing violent, alternating extremity flexion and extension. Bromocriptine, dantrolene, physostigmine (1 mg, initiated by the primary care team), multiple anti-convulsants, high doses of lorazepam, and treatment for presumptive tetanus did not result in improvement and she eventually required endotracheal intubation. Basic laboratory workup was remarkable only for an elevated CPK of 9729 (38–234U/L), urine drug screen positive for marijuana and benzodiazepines, and mildly elevated liver enzymes which peaked at AST 116 (10–42U/L) and ALT 58 (14–54U/L). Diagnostic evaluation, including MRI/MRA of the brain EEG, and extensive serum and CSF testing for toxic, paraneoplastic, and infectious etiologies was unrevealing (see Tables 1 and 2), with the exception of positive anti-NMDAR antibody detection in CSF by cell-based indirect IFA. Pelvic ultrasound, MRI, and PET imaging in search of an underlying gynecological neoplasm revealed only bilateral physiologic appearing cysts. A salpingo-oophorectomy of the larger cyst was performed out of concern for the presence of microscopic neoplastic tissue; gross ovarian histology showed only benign cystic tissue. The patient was treated with intravenous immunoglobulin (IVIG) and corticosteroids. After 6 weeks she was discharged

Table 2. Non-toxicological testing with normal results.

	Infectious	Paraneoplastic/Autoimmune	Hormonal	Other
Serum	Serum HIV1/2 Ab, HIV RNA, RPR, acute hepatitis panel, toxoplasma Ab, Ehrlichia DNA, Cryptococcal Ag, Histoplasma Ag, Lyme disease panel	ANA, anti-GM Ab, AFP, CEA	Urinary metanephrines, prolactin, TSH, HCG	Serum B12, folate, complete blood count, metabolic profile
CSF	VDRL, Cryptococcal Ag, Toxoplasma Ab, gram stain, AFB, India Ink, DNA PCR for HSV1/2 PCR, CMV, JCV; HSV and viral cultures	Commercial meningoencephalitis panel or paraneoplastic panel (IgG or IgM with reflex titer levels)		

RPR = rapid plasma reagin; CEA = carcinoembryonic antigen; Ab = Antibody; AFP = alpha-fetoprotein; TSH = thyroid stimulating hormone; HCG = human chorionic gonadotrophin; anti-GM = anti-glomerular basement membrane; VDRL = venereal disease research laboratory.

with improvement in her agitation and orientation, but her memory and cognition remained significantly impaired.

Discussion

The patients described in this case series exemplify many common aspects of clinical presentation, misdiagnosis, diagnosis, and typical clinical course in patients with NMDA encephalitis. They serve to illustrate several points for medical toxicologists who are either not familiar with the disease or who may need to consider the diagnosis when a putative toxicological etiology for delirium has been ruled out.

Autoimmune syndromes of the CNS are the result of an antibody response to extracellular antigens, such as those associated with a neoplasm, and to intracellular antigens, such as voltage-gated potassium channels, AMPA, $GABA_B$ receptors, and the NMDA receptor.[4] Disease occurs as antibody binding alters receptor function. The terms "limbic encephalitis" and "paraneoplastic encephalitis" are often used to describe these disorders. N-methyl-D-aspartate receptor encephalitis is increasingly being recognized as a cause of encephalitis after other commonly encountered encephalitides are excluded. In patients less than 30 years of age with idiopathic encephalitis, NMDAR encephalitis was noted to be four times more common than the 2nd most frequent etiology, herpes simplex virus (HSV)-1.[1] We present the young male in Case 1 to reinforce that, although reproductive-aged females appear to be overrepresented, the disease also occurs in children, males, and the elderly.[5,6] In one typical case series the mean age of patients was 23 years, but the range was 5–76 years.[7]

The autoimmune response may be due to molecular mimicry to neoplastic tissue (ovarian teratomas have been noted to have high rates of tissue positivity for the expression of NMDA receptors[4]) or a preceding viral or bacterial illness that triggers an autoantibody response to antigenic epitopes located on the external surface of neuronal membranes. Binding of autoantibodies to NMDA receptor sites causes cross-linking and internalization of NMDA receptors, leading to decreased surface cluster densities.[5,8] Immunolabeling studies using CSF from affected patients have identified unique antibody-binding patterns to specific heteromer combinations of several NMDA receptor subunits: the glutamate binding NR2 subunits 2b and 2a, and the glycine binding NR1 subunit.[3,4] Newer work has suggested that the extracellular N-terminal region of the NR1 subunit is the key binding region.[3,7] While these subunits are expressed throughout the nervous system, they are concentrated in the limbic system, particularly the hippocampus. Thus, patients often develop features typical of limbic encephalitis such as irritability, sleep disturbances, memory loss, and hallucinations.[9] Dysfunction of the NMDA receptor not associated with NMDA autoantibody disease has been implicated in schizophrenia, Alzheimer's disease, and epilepsy.[10] NMDAR antagonists such as phencyclidine and ketamine have been noted to induce similar features to both schizophrenia and NMDAR encephalitis.[7,8]

The symptoms that preceded overt illness in both cases reported here were typical, as up to 25% of patients have an unremarkable prodrome of respiratory infection or headache.[6] Initial symptoms of NMDAR encephalitis are most commonly speech disorders, memory deficits, and behavioral changes.[6,7] As seen in both of our patients, these symptoms may be initially attributed to psychiatric disease or drug abuse, leading to a delay in diagnosis. While there is a range of severity of symptoms, there is often a striking progression of new and increasingly severe symptoms typically occurring over a 5–15-day period. Later symptoms include tachy or bradydysrythmias, dystonias, and a decreasing level of consciousness that may develop into catatonia. Both patients in this case series had very typical symptoms, and the level of dysfunction was such that both required placement of percutaneous feeding tubes. Progressive and rapidly worsening neuropsychiatric symptoms should be a clue to clinicians, as this greatly narrows the differential diagnoses. In one study, the most common overall-reported neurological findings were aphasia (72%), movement disorders (63%), and autonomic instability (47%).[1] Central hypoventilation may necessitate mechanical ventilation. The incidence of seizures has been reported to be as high as 82%,[6] and status epilepticus has been reported.[4,6,7] Dyskinesias commonly involve the tongue and face, or manifest as seen in Case 2: choreoathetosis, with elaborate motions of arms and legs.[7] More rarely reported signs are ataxia and hemiparesis. The combination of dystonia and autonomic instability, when seen in patients who have received neuroleptics to control the behavioral and psychiatric symptoms of an undiagnosed NMDAR encephalitis, may prompt toxicology consultation out of concern for NMS.

Laboratory testing is available to aid in diagnosis, but typically must be performed at a reference laboratory. In clinical studies, a combination of immunofluorescence assays and immunocytochemistry typically involving labeling of rat hippocampal neurons is used for diagnosis. For clinical diagnosis, available cell-based IFAs that detect antibodies to the NR1 subunit can be found either as a single assay or as part of some reference laboratories' "paraneoplastic" and "meningioencephalitis" panels. In Case 1, samples of CSF and serum drawn concurrently were tested for anti-NMDAR (specifically, anti-NR1) antibodies by IFA with differing results. Patients who are improving or patients with milder symptoms will have lower serum autoantibody levels.[7] In addition, autoantibody titers are higher in CSF than serum, and serum autoantibodies can be below the level of detection or not present in patients with disease depending on when in the clinical course the samples are drawn .Thus, it is commonly recommended that patients with a high likelihood of disease who have undetectable serum autoantibodies should undergo CSF testing.[3,5] Brain MRI findings are normal in approximately 50% of patients,[1,7] thus the absence of white matter changes does not exclude the diagnosis. Electroencephalogram is normal in 10–15% of patients; the most common abnormality seen is generalized or frontotemporal slowing or disorganized activity, however similar findings are common in encephalitis due to HSV or West Nile Virus.[1,7] Analysis of CSF may demonstrate evidence of a mild lymphocytic pleocytosis. In one study, patients with anti-NMDAR encephalitis had a slightly elevated mean

white cell count of 23 cells/mm^3 as compared with the higher mean white cell count of 78 cells/mm^3 seen in patients with HSV-1 encephalitis,[1] however there is a large overlap in the range (0–252 and 3–540, respectively) rendering this finding minimally useful in discriminating between different encephalitides.

As up to 40% of patients with NMDAR encephalitis do not have a concurrent neoplasm,[5] the condition should not be exclusively considered a paraneoplastic syndrome. However, due to the high association between the two, when NMDAR encephalitis is diagnosed a thorough search for neoplasm is often performed. The most commonly associated cancers are small cell lung cancer, thymoma, and breast, ovarian, or testicular cancer.[5]

Not all patients with detectable NMDAR autoantibodies have NMDAR encephalitis; incidental development of NMDAR antibody positivity has been reported in other disease states. A retrospective analysis of patients with HSV encephalitis found NMDAR autoantibodies in 30% of patients, with some developing the antibodies during the course of hospitalization.[11] The role of these antibodies in the development of clinical symptoms and disease progression is unclear. A study of people with newly diagnosed schizophrenia found a high (9.9%) prevalence of NMDAR autoantibodies compared with disease-free controls (0.4%)[12]; the study authors hypothesize that while a few of these patients are likely NMDAR encephalitis misdiagnosed as schizophrenia, the majority probably represent a subset of schizophrenics with a component of autoimmune neuronal reactivity. The relationship between NMDA autoantibodies and NMDA receptor dysfunction in psychiatric disease, epilepsy, and viral encephalitis is not well understood and represents an area of intense interest for researchers. Therefore, testing for autoantibodies should be done only in patients with a suspicion for the disease based on available clinical and laboratory data.

Initial therapies used with success include high-dose steroids, IVIG and plasma exchange, with immunosuppressants such as cyclophosphamide and rituximab used as second-line agents.[7,13] Early institution of immunosuppressive therapy and resection of any underlying neoplasm are associated with good clinical outcomes.[1,3] A good clinical response to therapy is typically associated with declining CSF autoantibody titers.[3] One group in a referral center noted complete or near-complete resolution in 75% of aggressively treated patients,[6] but as seen with this case series, many patients have only a partial response or are discharged after lengthy hospitalizations with significant residual cognitive deficits. Mortality ranges from 4% to 6%[7,13] and a 2-year relapse rate of 12% was reported in a population with a 33% prevalence of neoplasm.[13]

Conclusion

Medical toxicologists should consider anti-NMDAR encephalitis in the differential diagnosis of patients with new-onset signs and symptoms of encephalopathy. As some patients may initially be diagnosed with a primary psychiatric disease and treated with neuroleptics, concern for NMS may prompt the initial toxicological consultation, as was the case with our two patients. Common clinical features have been well described and can aid in selecting appropriate patients for laboratory testing of serum or CSF; testing can be done in conjunction with the treatment and exclusion of suspected toxicological, infectious, psychiatric, and metabolic causes. A high rate of resolution of clinical symptoms has been reported in multiple case series using immunosuppressive agents. Research into NMDA receptor function and dysfunction is ongoing, and may yield important insights into the development and treatment of psychiatric, infectious, and autoimmune diseases.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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