From the University of Colorado Denver School of Medicine

Anti-NMDA Receptor Encephalitis: Diagnosis, Psychiatric Presentation, and Treatment

Meredith R. Chapman, M.D.

Holly E. Vause, D.N.P., P.M.H.N.P.-B.C.

A growing literature describes the clinical presentation, diagnosis, and pathophysiology of anti-NMDA (*N*-methyl-D-aspartic acid) receptor encephalitis. Once conceptualized as a condition primarily affecting adult women and frequently associated with tumors, anti-NMDA receptor encephalitis is increasingly recognized in males, in children, and in the absence of tumors. Despite the expanding knowledge base, much remains to be understood about effective treatments. The little available information on management focuses primarily on tumor management and immunotherapy to control the antibody response. Limited information is available on the management of psychiatric symptoms in these complex, often critically ill patients. Here we describe, through an illustrative case example, the clinical characteristics of anti-NMDA receptor encephalitis in an adolescent male. We also outline other disease processes to be considered in the differential diagnosis and describe currently used interventions, including psychotropic medications.

Case Presentation

A 16-year-old boy who had been in his usual state of good health until 4 days prior to admission presented with seizure-like episodes that included stiffening followed by rhythmic jerking of the entire body, right-sided facial twitching, and chewing without associated incontinence or postictal changes. Further inquiry into symptoms revealed nonspecific complaints of headache, low-grade fever, and malaise. On the day of admission, the patient had difficulty speaking, with pronounced word-finding difficulties. He was also experiencing periods of slurred speech, right arm numbness, and continued seizure-like episodes. ECG, EEG, head CT, and a basic metabolic panel were performed, and results were within normal limits. Urine screening for drugs of abuse was negative. The patient's past medical and psychiatric history was unremarkable.

Examination on the day of admission revealed an awake, alert, and interactive male with focal speech production difficulties, asymmetric facial grimace, hyperactive deep tendon reflexes, and normal sensation. EEG showed diffuse slowing as well as superimposed left hemisphere slowing. MRI of the brain with and without contrast revealed normal anatomy. Magnetic resonance angiography of the head and neck likewise showed normal vasculature of the great vessels of the neck. Lumbar puncture on the second day of hospitalization showed lymphocytic pleocytosis, with 11 nucleated cells per mm^3 with 93% lymphocytes and 4% monocytes. The patient's glucose level was normal, and his protein level was minimally elevated at 41 mg/dl (reference range=15–40 mg/dl). At this point the patient was empirically started on ceftriaxone and acyclovir, but these medications were discontinued when CSF culture and herpes simplex virus polymerase chain reaction results returned negative.

Over the next 5 days, the patient's condition worsened. He had frequent episodes of agitation, leading to physical restraint, as well as confusion, resulting in his wandering about the hospital, particularly at night. His ability to speak would wax and wane; at times he was able to produce speech with notable word finding difficulties, and at others he was mute. When able to communicate, he indicated that his sensations, including taste, smell, and touch, were abnormal. During this time the patient also showed significant mood lability, laughing uncontrollably at times, and at others being irritable, withdrawn, and sullen. He was observed by caregivers to be experiencing perceptual abnormalities, as evidenced by odd behaviors, including picking at his skin as though attempting to remove insects.

An exhaustive medical evaluation was undertaken given the broad differential diagnosis, which included infectious, inflammatory, autoimmune, and endocrine etiologies. The results of a complete metabolic panel were unremarkable, although the serum ammonia level was elevated at 47 μmol/liter (reference range=11–35 μmol/liter). A CBC showed 15,800 WBCs/ml with 84% neutrophils, 9% lymphocytes, and 7% monocytes. Inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein level, were not elevated. Screening tests for autoimmune disorders, including serum antineutrophil antibody profile, antineutrophil cytoplasmic antibodies, anticentromere antibody, rheumatoid factor, Sjögren's antibody group, and Smith antibody, were negative. Serum copper and ceruloplasmin studies were unrevealing. Thyroid function tests, vitamin B_{12} levels, and a porphyrin profile were likewise normal. Creatine kinase was well within the reference range of 35–232 U/liter at 123 U/liter.

Repeat lumbar puncture obtained during the second week of hospitalization revealed clear, colorless CSF with 1 red blood cell per mm^3 and 5 nucleated cells per mm^3 with 83% lymphocytes and 8% monocytes. The CSF glu-

cose level was 62 mg/dl, and the protein level remained mildly elevated at 44 mg/dl. Additional CSF studies excluded viral causes, including adenovirus, Epstein-Barr virus, enterovirus, human immunodeficiency virus, varicella zoster virus, and West Nile virus. Oligoclonal bands, a marker of inflammation, were not present in the sample. Rapid plasma reagin titer was nonreactive. CSF samples were sent to reference laboratories to be screened for the known classic paraneoplastic antigens as well as the more recently characterized cell membrane antigens implicated in limbic encephalitis, specifically those targeting the NMDA receptor and its subunits. No informative paraneoplastic autoantibodies were detected in this evaluation. Likewise, antibodies to voltage-gated potassium channels and P/Q and N type calcium channels were not detected.

Throughout the remainder of the patient's medical hospitalization, which lasted 3 weeks, no diagnostic clarity was achieved, and the patient continued to exhibit a number of fluctuating neuropsychiatric symptoms, including agitation, confusion, irritability, cogwheel rigidity, dystonic posturing, and bradykinesia. In an attempt to manage the myriad of problematic behavioral symptoms, the patient was started on aripiprazole, at 2.5 mg/day, as well as lorazepam, diphenhydramine, and benztropine on an as-needed basis. As no major improvements were noted with these medications, haloperidol was initiated at 2 mg b.i.d. With this change, the patient exhibited increased levels of rigidity and bradykinesia. Simultaneously he was noted to engage in purposeless, repetitive activities; had autonomic instability with tachycardia, hypertension, and hyperhidrosis; and was described as having periods of catatonia with waxy flexibility. On hospital day 16, intravenous methylprednisolone was initiated, at 1,000 mg/day for 3 days, to address the presumptive diagnosis of autoimmune encephalitis, without clinical improvement. Enalapril was prescribed to manage hypertension; the patient had consistent systolic readings in the 150–170 mm Hg range and diastolic readings in the 80–90 mm Hg range. At the conclusion of hospital week 3, the patient was transferred to an inpatient psychiatric unit to decrease the need for physical restraint and 1:1 supervision.

Shortly after transfer, 30 days after admission, confirmation of anti-NMDA receptor encephalitis was obtained. Recently reported methods (1, 2) were utilized to identify antibodies to the NR1/NR2 subunits of the NMDA receptor in the patient's serum and CSF. With this diagnosis, the patient underwent a number of tests to identify potential tumor associations. Testicular and renal ultrasonography were unremarkable, and full-body positron emission tomography (PET) showed no evidence of abnormal uptake or mass to suggest neoplasm.

By this time, the patient spent his days lying in bed in a fixed, stiff position with his arms and legs outstretched. He would not open his eyes in response to verbal instruction and had bilateral palmar grasp and groping reflexes. Overall his sensorium continued to wax and wane; at times he was withdrawn, refusing to walk or swallow liquids, and at others he was overtly aggressive and agitated. He had significant insomnia and developed hypersensitivity to clothing. Intravenous immune globulin (IVIg) was administered at a dose of 2 g/kg body weight over a period of 5 days, beginning on hospital day 32. During this first round of IVIg treatment, the patient continued to have periods of vital sign instability and developed a new cough, with decreased ability to protect his airway. Attempts to manage the ongoing neuropsychiatric symptoms of anti-NMDA receptor encephalitis, including suspected auditory and visual hallucinations, mutism, fluctuating catatonia, agitation, and insomnia, were largely unsuccessful. Administration of antipsychotic medications, both conventional (haloperidol) and atypical (aripiprazole), led to increased symptoms, including facial masking, bradykinesia, drooling, and decreased blink rate. A low dosage of risperidone (0.5 mg b.i.d.) was well tolerated, however, and resulted in improvements in the patient's irritability and an apparently decreased response to internal stimuli. Lorazepam, at a maximum dosage of 1 mg t.i.d., decreased the patient's level of agitation and somewhat improved his sleep. Initially benztropine, titrated to a dose of 0.5 mg t.i.d., was beneficial in decreasing jaw dystonia and rigidity, but as the patient's condition worsened, he became unable to swallow medications in pill form. Benztropine was discontinued and replaced with trihexyphenidyl liquid. This anticholinergic medication was beneficial despite its reported low-potency antagonistic effect on the NMDA receptor (3).

"Psychiatrists may encounter patients with anti-NMDA receptor encephalitis in any number of settings, including emergency departments, inpatient units, consultation-liaison services, and outpatient offices."

The patient began to show signs of improvement 5 to 7 days after completion of IVIg treatment, including increased responsiveness, attentiveness, and ability to communicate verbally using one-word responses spoken in a whisper. Because the trihexyphenidyl was titrated to 4 mg b.i.d. concurrently with the IVIg infusion, it was unclear what contribution it made to the patient's improvement.

Because of a plateau in symptom improvement, the decision was made 1 month after the first IVIg treatment to repeat the infusion at a dose of 2 g/kg of body weight over 2 days. The patient had communicated that he was experiencing auditory and visual hallucinations, and risperidone had been successfully titrated to 1 mg b.i.d. Lorazepam taper was well under way, and sleep initiation and continuity difficulties had been ameliorated using trazodone, at 100 mg h.s. After the second IVIg infusion, the patient continued to make slow progress in his ability to perform activities of daily living and to communicate. Although he was able to name his relatives in photographs, he had persistent deficits in short-term memory. His speech remained almost a whisper but was intelligible, and he was using three- to four-word sentences. Although oriented to person, he remained disoriented to date, time, and place.

Three months after admission, the patient remained hospitalized on an inpatient psychiatric unit with persis-

tent short-term memory impairment and executive function deficits necessitating 24-hour supervision for safety. His social functioning remained significantly disrupted, with limited capacity to form appropriate, stable, or lasting relationships. He could not attend or maintain focus in group activities and required ongoing 1:1 staff support. At times he exhibited inappropriate and bizarre behaviors under the stress of socializing with others, such as disrobing or becoming physically agitated. He remained socially isolated, apathetic, and emotionally withdrawn from family and peers. He exhibited marked poverty of speech, poverty of content of speech, illogical thinking, intermittent incoherence, and loosening of associations. His affect fluctuated between flat, agitated, and appropriately calm. Rituximab, given in two doses of 1,000 mg 2 weeks apart, was initiated in the 14th week of hospitalization to address the aforementioned symptoms and in the hope of preventing relapse.

At the time of discharge, 16 weeks after initial presentation, the patient went home in the care of his parents. He continued to demonstrate difficulties in cognition, short-term memory, and social use of language, but to a degree that was significantly less impairing than at any point during the illness course. He had successfully discontinued all psychotropic medications with the exception of trazodone, which was still prescribed for sleep difficulties. He had returned to baseline levels of gross motor functioning. Enalapril was continued for blood pressure control. He and his parents denied ongoing mood lability, irritability, or psychotic symptoms. He returned to a public high school in a modified classroom setting. At follow-up 3 months after discharge, the patient and his parents reported that he had returned to baseline levels of academic, social, and family functioning. His recall of the illness course was significantly limited, which was not surprising as persistent amnesia has been reported to be a characteristic feature in patients who recover from anti-NMDA receptor encephalitis (2).

Differential Diagnosis

Paraneoplastic limbic encephalitis as a distinct clinical entity with pathognomonic clinical and pathological features has been described since the 1960s (4, 5). Likewise, anti-NMDA receptor encephalitis is increasingly recognized as a unique syndrome with characteristic clinicopathological findings (2). The differential diagnosis of anti-NMDA receptor encephalitis includes viral and autoimmune causes, the latter involving classic paraneoplastic antigens or cell membrane antigens. The most commonly encountered viral causes include herpes simplex virus and human herpes virus-6 (HHV-6). Although varicella zoster virus and cytomegalovirus screening is frequently included in CSF testing, these viruses are rarely responsible for viral encephalitis. Immunocompromised individuals, particularly those having undergone bone marrow or stem cell transplantation, are more susceptible to infection with HHV-6. Arboviral encephalitis and rabies should also be considered (6).

Recent studies have led to the characterization of autoimmune encephalitis into two broad categories: those associated with antibodies to intracellular neuronal antigens and those associated with antibodies to cell membrane antigens in the neuropil of the hippocampus and cerebellum (7, 8). The more frequently encountered intracellular autoantigens are Hu and Ma2, with CV2/CRMP5 and amphiphysin present less often. Immune-mediated encephalitis with intracellular neuronal antigens is more frequently associated with neoplasm, having cytotoxic T cell-mediated pathogenesis. These encephalitides often show limited response to treatment. Conversely, autoimmune limbic encephalitis with antibodies to cell membrane antigens, including NMDA receptors (2), voltage-gated potassium channels (5), AMPA receptors (9), and other yet to be characterized cell membrane antigens, is less frequently associated with cancer, has an antibody-mediated pathogenesis, and is amenable to immunotherapy.

Other autoimmune disorders that warrant consideration include systemic lupus erythematosus cerebritis, antiphospholipid antibody syndrome, Sjögren's syndrome, encephalopathy associated with Hashimoto's thyroiditis, and angitis, either primary or systemic. Toxic ingestion (over-the-counter or illicit drugs as well as carbon monoxide, methanol, and cyanide), porphyria, mitochondrial disorders, and disorders of amino or organic acid metabolism should also be excluded.

Given that anti-NMDA receptor encephalitis differs significantly from other paraneoplastic encephalitides in the nature and prominence of presenting psychiatric problems, this differential is vast. Diagnoses of primary psychotic disorders, including psychotic disorder not otherwise specified, schizophreniform disorder, and even schizophrenia, are often considered. Similarly, mood dysregulation disorders, disorders of impulse control, and sleep disorders may be identified. Careful consideration should be given to the syndromes presenting with the constellation of autonomic dysregulation, muscle rigidity, and psychiatric symptoms. These include neuroleptic malignant and serotonin syndromes. Exclusion may be challenging, particularly in the setting of concurrent administration of neuroleptic or antidepressant medications. Mild to moderate elevations in creatine kinase levels have been reported in both male and female patients with anti-NMDA receptor encephalitis (6). In a report of eight patients with anti-NMDA receptor encephalitis, Florance et al. (10) discussed five patients with transient elevations in creatine kinase ranging from 415 to 18,000 U/liter, with a median of 1,500 U/liter.

Key Clinical Concepts

NMDA receptors are ligand-gated cation channels that play a role in synaptic transmission and plasticity. These receptors, which are highly expressed in the forebrain, limbic system, and hypothalamus, are made up of two subunits: the NR1 subunit, which binds glycine, and the NR2 subunit, which binds glutamate. Overactivity of the

receptor with resulting excitotoxicity is the underlying process implicated in acute ischemic stroke and traumatic brain injury (11), while underactivity is hypothesized to produce symptoms of schizophrenia (12). In anti-NMDA receptor encephalitis, antibodies decrease the number of cell-surface NMDA receptors and NMDA receptor clusters in postsynaptic dendrites. Multiple studies have shown that this effect can be reversed with the removal of the offending antibodies. Dalmau and colleagues (1) coined the term anti-NMDA receptor encephalitis and characterized a neuropsychiatric syndrome first recognized to occur in young women with ovarian teratomas. Anti-NMDA receptor encephalitis is increasingly recognized in males and in children, as well as in the absence of tumor.

The disease itself evolves through several stages, ultimately resulting in recovery (limited to full) or death. In the prodromal phase, affected individuals have a flu-like illness with fever, malaise, headache, and fatigue. A psychotic phase follows in which many patients present to psychiatrists or are admitted to psychiatric units with a diagnosis of acute psychosis or schizophrenia. Described psychiatric symptoms have included anxiety, mood dysregulation, or depression progressing to severe behavioral and personality disturbance, delusional or disorganized thinking, paranoid ideation, and hallucinations. Unresponsiveness with hypoventilation, autonomic instability, and dyskinesias generally follow. In the unresponsive state, affected individuals have their eyes open but are unresponsive to visual threats. These patients are often mute, or they only mumble unintelligible words. Muscle tone is often increased, and a catatonic state with dystonic and/or cataleptic postures may be encountered. Dyskinesias almost always start in the face and/or mouth and manifest as clenching of the teeth or jaw dystonia. Despite association with rhythmic abdominal contractions or complex movements of the extremities, these orofacial dyskinesias do not have epileptic correlates on EEG. Hypoventilation of a central origin may be missed until extubation is attempted, often after prolonged mechanical ventilation. Autonomic instability, evidenced by blood pressure and temperature fluctuations, tachycardia, bradycardia, and even cardiac pauses, is not uncommon.

In a recent seminal article, Dalmau and colleagues (2) eloquently summarized both the clinical and immunological characteristics of anti-NMDA receptor encephalitis. Primary emphasis has been placed on eradication of associated malignancy or suppression of the immune reaction. These interventions, when instituted promptly on diagnosis, have been shown to decrease morbidity and mortality and reduce the risk of irreversible neuronal damage (13, 14). Described immunotherapies have included corticosteroids, IVIg, plasmapheresis, rituximab, cyclophosphamide, and azathioprine (15). If anti-NMDA receptor encephalitis is suspected, antibody testing should be undertaken promptly. When the diagnosis is confirmed, a comprehensive search for neoplasm should be conducted concurrently with the initiation of immunotherapy. The neurological literature suggests a first-line approach using corticosteroids, IVIg, or plasmapheresis. In the case of treatment failure, second-line agents such as rituximab and cyclophosphamide may be used. Psychiatric symptoms often show gradual but continuous improvement, leading to full recovery without targeted intervention.

Treatment

Given that anti-NMDA receptor encephalitis routinely first presents with psychiatric manifestations, with symptoms that persist and evolve throughout the illness course, often giving rise to clinical management conundrums, very little has been presented in the literature on targeted management of psychiatric symptoms caused by limbic encephalitis (paraneoplastic or otherwise). There is a dearth of information regarding management of psychiatric and behavioral symptoms, including agitation, anxiety, mood dysregulation, depression, disorganized thinking, paranoid ideation, and hallucinations. Whereas the best treatment approach for anti-NMDA receptor encephalitis as outlined by Sansing et al. (6) encompasses a combination of tumor resection, immunotherapy, intensive care, and rehabilitation including physical therapy, discussions regarding the optimal approach to behavioral management are lacking (6). What information can be gleaned from the available literature is often mentioned in passing as part of the case description. Little attention has been given to the response to treatment, except when it has been unexpected or negative. There are several documented cases of neuroleptic administration actually exacerbating neuropsychiatric symptoms and movement abnormalities, as occurred in the case presented here (6, 10). Some attention has been given to the use of ECT as a means of targeting catatonic presentations in patients with autoimmune encephalitis (16–18). Known effective treatments for catatonia in psychotic and mood disorders include neuroleptics, benzodiazepines, and ECT, but much less is known about the therapeutic usefulness of these agents in catatonia associated with general medical and neurological illnesses.

Because resolution of psychiatric and behavioral symptoms tends to follow suppression of the immune response in anti-NMDA receptor encephalitis, amelioration of problematic symptoms within these domains should be the focus of management. Once antibodies to the NMDA receptor are positively identified, the presence of an underlying neoplasm should be excluded. In female patients, ovarian teratomas are the most frequently encountered, with rates of occurrence decreasing with age. Males and young children are less likely to have identifiable tumors but should nonetheless be appropriately screened. Immunotherapy should start with corticosteroids, IVIg, or plasma exchange. Subsequent therapies, if indicated as a result of inadequate response, deterioration, or relapse, may include rituximab, azathioprine, or cyclophosphamide.

Psychiatric symptoms as described throughout the neurological literature can be roughly divided into the following categories: agitated aggression; anxious avoidance, which encompasses more generalized anxiety states, phobic preoccupations, and obsessive-compulsive behaviors; withdrawn depression; psychosis, including auditory and visual hallucinations, paranoid ideations, and delusions; sleep disruption, either hypersomnia or insomnia; catatonia; and dysregulated mood with lability, disinhibition, and/or hypersexuality. A number of psychotropic medications have been utilized in an attempt to modify or control these symptoms or symptom clusters. For example, agitated aggression, a commonly cited symptom of anti-NMDA receptor encephalitis, has been treated throughout the literature with conventional antipsychotics (haloperidol, chlorpromazine), with atypical antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone), and in the extreme with medically induced coma using pentobarbital and fentanyl (10). Treatment response has been limited at best, with examples of each agent decreasing symptom burden but also potentially worsening dystonia and other abnormalities of movement. Atypical antipsychotics have also been used to target psychotic symptoms, with marginal success. Insomnia has been described as similarly managed with pharmacotherapy, using melatonin, clonidine, trazodone, benzodiazepines (lorazepam, clonazepam, diazepam), and gabapentin. Of these agents, the benzodiazepines, clonidine, and trazodone proved the most useful in addressing difficulties in sleep initiation and continuity. In the case presented here, trazodone was particularly helpful in achieving regulated sleep-wake cycles after the use of escalating dosages of benzodiazepines and atypical antipsychotics had failed to do so. For any of these agents, recommended or effective dosage ranges have not been established.

Mood dysregulation symptoms, particularly in patients under 18 years of age, have been detailed in only a few cases; whether this is because they are less frequently encountered or less frequently reported is unclear. Valproic acid and lithium have both been prescribed, although no significant change in the target symptoms has been reported. The use of antidepressants to manage anxious or depressed states has not been described. In one case, a 6-year-old boy was successfully treated with a psychostimulant to target hyperactivity and impulsivity (10).

Medications frequently prescribed by psychiatrists to address the extrapyramidal side effects of antipsychotics, such as benztropine and trihexyphenidyl, have not been routinely used as primary therapies to address movement abnormalities in anti-NMDA receptor encephalitis. Orofacial dyskinesia, dystonia, and rigidity, when treated, have been managed with benzodiazepines or anticonvulsants. For the young man in our case, the aripiprazole and haloperidol that were initiated to target agitation and hallucinations led to increased rigidity and dystonic posturing. Benztropine, and eventually trihexyphenidyl, proved beneficial in reducing the patient's rigidity, jaw dystonia, and parkinsonism. As these medications were used after immunotherapy with corticosteroids and IVIg, their efficacy remains unclear. However, in this case the anticholinergics provided observable relief not only to the patient but also to frustrated and discouraged staff.

Given the complex presentations of individuals affected by anti-NMDA receptor encephalitis, nonpharmacological and multidisciplinary interventions also deserve discussion. As recovery times can vary considerably (with reports ranging from 8 to 50 weeks [2]) and hospitalizations can be lengthy, treatment approaches need to be individualized. Generalized physical deconditioning and inadequacies in the ability to independently complete activities of daily living can best be addressed by the combination of physical and occupational therapies. Speech-language pathologists benefit patients who experience speech disruption as a primary symptom of anti-NMDA receptor encephalitis or who secondarily develop swallowing or feeding difficulties after prolonged mechanical ventilation. Targeted strategies to address short-term memory impairments should be developed and applied during and after hospitalization. Even in instances of full recovery or mild persistent deficits, more than 85% of patients are reported to have significant psychiatric symptoms at the time of discharge (19). In addition to deficits in memory, patients may experience a number of impairments in executive function, including inattention, disorganization, poor planning, disinhibition, and lack of impulse control. With time, these symptoms may abate or remain stable. Surveillance for occult neoplasm should occur in conjunction with observation for recurrence or deterioration of psychiatric symptoms, which may signal relapse of encephalitis.

Discussion

Until as recently as 5 years ago, limbic encephalitis was thought primarily to be a paraneoplastic phenomenon, frequently encountered with cancer of the lungs or testes, with associated antibodies to intracellular neuronal antigens (20). This conceptualization has since expanded to include conditions in which antibodies to cell membrane antigens in the neuropil of the hippocampus and cerebellum are present. These encephalitides include those associated with antibodies to voltage-gated potassium channels, NMDA receptors, AMPA receptors, and other yet to be characterized neuronal surface antigens. The clinical presentation of anti-NMDA receptor encephalitis varies, with a myriad of neurological and psychiatric symptoms reported. There are also appreciable differences in clinical presentations between affected adults and youths. Neoplasm is less frequently encountered in children and adolescents, and autonomic disruption, particularly hypoventilation, is less severe in this group (10). While a preponderance of reported adult cases initially presented to psychiatric providers with symptoms suggestive of mood,

anxiety, and/or psychotic disorders, children more often exhibit subtle behavioral and neurological changes.

When faced with a patient like the one we present here, there are data to guide the clinical decision-making process; what remains unclear is the targeted management of psychiatric symptoms. Psychiatric treatments described in the literature on autoimmune encephalitis focus primarily on the management of catatonia with ECT. The use of multiple classes of psychotropic medications, including conventional and atypical antipsychotics, mood stabilizers, and benzodiazepines, is detailed in a number of case reports, but concurrent use with other therapeutic modalities makes clinical outcomes difficult to assess. As in this case, the most profound improvements in psychiatric and behavioral symptoms occur when the antibody response is suppressed or reversed. One particularly challenging aspect of this case involves the initial evaluation and subsequent surveillance for neoplasm. The available information is limited, but somewhat more robust for affected females, particularly those with ovarian teratomas (21). Periodic surveillance for at least 2 years using MRI and ultrasound of the abdomen and pelvis has been recommended in females of all ages diagnosed with anti-NMDA receptor encephalitis (10). Guidelines on tumor surveillance in males are not available. The patient presented here is scheduled to undergo testicular ultrasound and full-body PET at 6-month intervals.

Patients with complex neuropsychiatric disorders present management dilemmas on a number of fronts in addition to those regarding appropriate diagnosis and medication management. Traditional medical floors are often ill equipped to meet the behavioral and psychiatric needs of such challenging patients. Requirements for 1:1 staffing, constant supervision, alternative methods of communication, and secure physical surroundings are but a few of the considerations involved. Lack of appropriate resources in this case led to numerous uses of physical restraint and the frequent administration of emergency medications for agitation. These management techniques were no longer used once the patient was transferred to the psychiatric unit, where alternative interventions were readily available. Psychiatric units, on the other hand, far too often have limited ability to conduct indicated medical interventions, lacking appropriately trained staff and well-equipped facilities. Maintaining open and clear lines of communication among multiple providers—including pediatric subspecialists, psychiatrists, psychologists, social workers, and speech/language, occupational, and physical therapists—and the family also proved a challenge. Lack of clear consensus recommendations regarding treatment as well as the number of providers involved likely led to less-than-aggressive management in this case. Furthermore, it was difficult to obtain authorization for payment of services rendered with the novel diagnosis, coded as a medical condition (anti-NMDA receptor encephalitis) causing psychiatric symptoms at the time of discharge.

Psychiatrists may encounter patients with anti-NMDA receptor encephalitis in any number of settings, including emergency departments, inpatient units, consultation-liaison services, and outpatient offices, and thus should have a basic understanding of the clinical characteristics, differential diagnosis, currently available treatment interventions, and unique management dilemmas of this condition.

Received Feb. 6, 2010; revision received April 3, 2010; accepted April 12, 2010 (doi: 10.1176/appi.ajp.2010.10020181). From the Department of Psychiatry, University of Colorado Denver School of Medicine; and the Department of Psychiatry and Behavioral Sciences, Children's Hospital, Aurora, Colo. Address correspondence and reprint requests to Dr. Chapman, Department of Psychiatry and Behavioral Sciences, Children's Hospital, 13123 E. 16th Ave., B-130, Aurora, CO 80045; chapman.meredith@tchden.org (e-mail).

The authors report no financial relationships with commercial interests.

References

1. Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR, Lynch DR: Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis associated with the ovarian teratoma. Ann Neurol 2007; 61:25–36
2. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld M, Balice-Gordon R, Lynch DR: Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008; 7:1091–1098
3. McDonough JH, Shih TM: A study of the *N*-methyl-D-aspartate antagonistic properties of anticholinergic drugs. Pharmacol Biochem Behav 1995; 51:249–253
4. Tüzün E, Dalmau J: Limbic encephalitis and variants: classification, diagnosis, and treatment. Neurologist 2007; 13:261–271
5. Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB, Dalmau J: Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings, and tumour association in 60 patients. Brain 2000; 123:1481–1494
6. Sansing LH, Tüzün E, Ko MW, Baccon J, Lynch DR, Dalmau J: A patient with the encephalitis associated with the NMDA receptor antibodies. Nat Clin Pract Neurol 2007; 3:291–296
7. Bataller L, Kleopa KA, Wu GF, Rossi JE, Rosenfeld MR, Dalmau J: Autoimmune limbic encephalitis in 39 patients: immunophenotypes and outcomes. J Neurol Neurosurg Psychiatry 2007; 78:381–385
8. Ances BM, Vitaliani R, Taylor RA, Liebeskind DS, Voloschin A, Houghton DJ, Galetta SL, Dichter M, Alavi A, Rosenfeld MR, Dalmau J: Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. Brain 2005; 128:1764–1777
9. Lai M, Hughes EG, Peng X, Zhou L, Gleichman AJ, Shu H, Matà S, Kremens D, Vitaliania R, Geschwind MD, Bataller L, Kalb RG, Davis R, Graus R, Lynch DR, Balice-Gordon R, Dalmau J: AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol 2009; 65:424–434
10. Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, Campen CJ, Moss H, Peter N, Gleichman AJ, Glaser CA, Lynch DR, Rosenfeld MR, Dalmau J: Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009; 66:11–18
11. Kalia LV, Kalia SV, Salter MW: NMDA receptors in clinical neurology: excitatory times ahead. Lancet Neurol 2008; 7:742–755

12. Goff DC, Coyle JT: The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. Am J Psychiatry 2001; 158:1367–1377
13. Munshi SK, Thanvi B, Chin SK, Hubbard I, Fletcher A, Vallance TR: Paraneoplastic limbic encephalitis: case report and review of literature. Age Ageing 2005; 34:190–193
14. Alamowitch S, Graus F, Uchuya M, Rene R, Bescansa E, Delattre JY: Limbic encephalitis and small-cell lung cancer: clinical and immunological features. Brain 1997; 120:923–928
15. Schimmel M, Bien CG, Vincent A, Schenk W, Penzien J: Successful treatment of anti-*N*-methyl-D-aspartate receptor encephalitis presenting with catatonia. Arch Dis Child 2009; 94:314–316
16. Kaestner F, Mostert C, Behnken A, Boeckermann I, Ternes F, Diedrich M, Zavorotnyy M, Arolt V, Weckesser M, Rothermundt M: Therapeutic strategies for catatonia in paraneoplastic encephalitis. World J Biol Psychiatry 2008; 9:236–240
17. Novillo-Lopez ME, Rossi JE, Dalmau J, Masjuan J: Treatment-responsive subacute limbic encephalitis and NMDA receptor antibodies in a man. Neurology 2008; 70:728–729
18. Lee A, Glick DB, Dinwiddie SH: Electroconvulsive therapy in a pediatric patient with malignant catatonia and paraneoplastic limbic encephalitis. J ECT 2006; 22:267–270
19. Kayser MS, Kohler CG, Dalmau J: Psychiatric manifestations of paraneoplastic disorders. Am J Psychiatry 2010; 167:1039–1050
20. Graus F, Saiz A: Limbic encephalitis an expanding concept. Neurology 2008; 70:500–501
21. Iizuka T, Sakai F, Ide T, Monzen T, Yoshii S, Iigaya M, Suzuki K, Lynch DR, Suzuki N, Hata T, Dalmau J: Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. Neurology 2008; 70:504–511