has direct clinical implications and could inform future studies addressing management of patients with large pleural effusions.

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References

1. Brown NE, Zamel N, Aberman A. Changes in pulmonary mechanics and gas exchange following thoracocentesis. *Chest*. 1978;74(5):540-542.
2. Perpiñá M, Benlloch E, Marco V, Abad F, Nauffal D. Effect of thoracentesis on pulmonary gas exchange. *Thorax*. 1983; 38(10):747-750.
3. Karetzky MS, Kothari GA, Fourre JA, Khan AU. Effect of thoracentesis on arterial oxygen tension. *Respiration*. 1978; 36(2):96-103.
4. Estenne M, Yernault JC, De Troyer A. Mechanism of relief of dyspnea after thoracocentesis in patients with large pleural effusions. *Am J Med*. 1983;74(5):813-819.
5. Wang JS, Tseng CH. Changes in pulmonary mechanics and gas exchange after thoracentesis on patients with inversion of a hemidiaphragm secondary to large pleural effusion. *Chest*. 1995;107(6):1610-1614.
6. Wang LM, Cherng JM, Wang JS. Improved lung function after thoracocentesis in patients with paradoxical movement of a hemidiaphragm secondary to a large pleural effusion. *Respirology*. 2007;12(5):719-723.
7. Campbell EJ, Freedman S, Smith PS, Taylor ME. The ability of man to detect added elastic loads to breathing. *Clin Sci*. 1961;20:223-231.
8. Bennett D, Jayson M, Rubenstein D. The perception of dyspnea. *Dis Chest*. 1963;43:411-417.
9. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA*. 2012;307(22): 2383-2389.
10. Tremblay A, Michaud G. Single-center experience with 250 tunnelled pleural catheter insertions for malignant pleural effusion. *Chest*. 2006;129(2):362-368.

Challenges in Providing Critical Care for Patients With Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis

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Anti-*N*-methyl-D-aspartate receptor encephalitis (NMDARE) is characterized by a constellation of psychiatric, neurologic, autonomic, and cardiopulmonary manifestations. Although patients typically recover with appropriate treatment, they commonly require weeks to months of inpatient care, including prolonged stays in critical care units. This case series not only advocates for consideration of the disease in the appropriate context but also specifically highlights the distinct challenges intensivists encounter caring for patients with NMDARE. With a greater knowledge of the nuances and sequelae of NMDARE, critical care specialists will be better equipped to anticipate and manage the potentially life-threatening complications of the disease.

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Abbreviations: AED = antiepileptic drug; CSF = cerebrospinal fluid; ETT = endotracheal tube; IVIG = IV immunoglobulin; LOS = length of stay; NMDARE = anti-*N*-methyl-D-aspartate receptor encephalitis

Patients with anti-*N*-methyl-D-aspartate receptor encephalitis (NMDARE) experience dramatic neuropsychiatric and cardiopulmonary changes often requiring extensive critical care management.[1,2] They are typically young and female (80%), and many have ovarian teratomas.[3,4] Among women, teratomas are typically found in older, black patients.[5] Other types of tumors have been reported, but their direct association with NMDARE has not been confirmed. Symptoms often start with nonspecific respiratory and GI symptoms, followed approximately 2 weeks later by neuropsychiatric symptoms, including agitation, hallucinations, delusions, and amnesia.[6,7] Other early neuropsychiatric manifestations include grandiosity, mania, paranoia, mutism, and echolalia. Dramatic, unusual movement disorders uniquely characterize this disorder, including oral-lingual-facial and limb dyskinesias and opisthotonic postures. Seizures are also common.[8] Dysautonomias, such as hyperthermia, tachycardia, bradycardia, hypertension, hypotension, hypersalivation, and hypoventilation, further complicate management, especially with concurrent waxing and waning levels of consciousness and dissociative states. Occasionally, these patients require long-term mechanical ventilation and sedation, the weaning of which may trigger status epilepticus.[2]

A definitive diagnosis of NMDARE requires detection of anti-NMDAR antibodies in the cerebrospinal fluid (CSF); serum antibodies are often also present.[9] (Although teratomas may often be identified, particularly in many female patients, their identification is not part of the diagnostic process.) CSF study results are often normal but may demonstrate a nonspecific lymphocytic pleocytosis, elevated protein level, or oligoclonal bands. Brain MRI imaging is

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often unremarkable but may have nonspecific hyperintensities on T2 FLAIR sequences. EEG may show nonspecific slowing, disorganized activity, or seizure activity. Brain biopsies are nondiagnostic.

First-line treatments include teratoma resection, high-dose IV corticosteroids, plasma exchange, and IV immunoglobulin (IVIG). Second-line therapies such as rituximab and cyclophosphamide are often required for patients with delayed diagnoses, protracted courses, or those without teratomas.[10,11] Despite the prolonged length of stay (LOS) in the ICU, approximately three-fourths of patients make complete or near-complete recoveries. Others may develop significant disabilities or die. Relapses occur in about one-fourth of patients and can occur months to years after initial resolution.[3]

The critical care literature on NMDARE has focused on general descriptions of this entity.[12,13] In contrast, this report focuses on the particular challenges critical care physicians confront when managing patients with NMDARE in the ICU. This report describes the authors' recent experience providing care for five patients with CSF-confirmed NMDARE admitted to the medical ICU at Ben Taub General Hospital in Houston, Texas, from 2010 to 2013. The narrative and accompanying table highlight the diagnostic and management difficulties encountered while caring for patients with NMDARE, thereby helping other ICU teams anticipate these patients' complex critical care needs.

Case Reports

Case Vignette

A young female patient in her mid-20s was admitted to an inpatient psychiatric hospital for 2 weeks of acute psychosis. Her bizarre behavior included audiovisual hallucinations (talking to cartoon characters) and violent threats to herself and close family members. Ten days into her hospitalization she was referred to the ED for seizures and developed severe lethargy and mutism. After undergoing initial diagnostics and receiving empirical therapy for seizures, her persistent lethargy resulted in ICU admission and intubation for airway protection. In the ICU, the patient manifested dramatic orofacial dystonic movements as well as marked dysautonomia with hypertension and hypotension, fever, and tachycardia and bradycardia. She bit her endotracheal tube (ETT) forcibly for prolonged periods of time, triggering dysautonomias. Her violent neck movements put her at risk for tracheostomy dislodgment and development of tracheal damage and fistula. On hospital day 29, the ICU team received confirmation that her CSF tested positive for anti-NMDAR antibodies. While waiting for CSF confirmation of NMDARE, she had received empirical therapies with steroids, plasma exchange, and IVIG. Soon after confirmed diagnosis, the patient underwent left salpingo-oophorectomy for teratoma resection, based on a cystic lesion found on pelvic CT scan. This patient remained in the ICU for 43 days. At 6 months after initial diagnosis, she regained baseline physical and mental function. At 12-month follow-up she had not relapsed.

Initial Presentations and Prior Psychiatric Treatments

The information in Table 1 provides data related to each patient's clinical characteristics, evaluation, and management. The patients ranged in age from 18 to 40 years, and three were women. All presented with acute psychiatric symptoms, including bizarre behavior (suicide attempts, undressing at work, hyperreligiosity) and audiovisual hallucinations. They had received diagnoses and treatments for psychiatric illnesses such as bipolar disorder, acute psychosis, and major depression. Symptoms typically began 2 to 4 weeks prior to hospital and ICU admission. Consistently, it was the recurrent or initial seizure-like activity that prompted inpatient medical evaluation. All patients had received empirical antiepileptic drugs (AEDs) either prior to or upon admission to the ICU. Most patients had received medical care (including ED assessments and admissions to inpatient psychiatric facilities) at least once prior to hospital and ICU admission. Most presentations occurred within the context of either recent stresses (death of family members) or substance abuse (alcohol and marijuana). CSF-confirmed diagnosis occurred between 11 and 29 days after admission. Treatment included combinations of short-term high-dose IV corticosteroids, plasma exchange, IVIG, rituximab, and cyclophosphamide (Table 1).

Referral to Critical Care and General Sequelae

Patients were referred to the ICU for persistent somnolence, altered mental status, seizures, or seizure-like movements, with eventual need for intubation for airway protection. ICU LOS and days of mechanical ventilation ranged from 4 to 78 days and from 0 to 63 days, respectively. Total hospital LOS ranged from 31 to 159 days. Most patients required tracheostomies for chronic respiratory failure and gastric tubes for enteral nutrition. There were no deaths among the patients, and only one patient was found to have a teratoma, prompting surgical resection.

Diagnosis

All patients had diagnosis confirmed with anti-NMDAR antibodies in the CSF. All patients had normal or nonspecific abnormalities on CSF studies and brain MRI. One patient had EEG-confirmed seizures.

Neuropsychiatric Symptoms in the ICU

Patients commonly exhibited prolonged dissociative behaviors, such as opening eyes and making eye contact without withdrawing to painful stimuli, and persistent inarousability alternating with extreme agitation, including violent opisthotonic posturing. One patient's movements were so violent that he vaulted himself out of his bed. To treat these episodes, most patients received prolonged multidrug AED regimens, typical and atypical antipsychotics, continuous-infusion and intermittent sedatives, and neuromuscular blocking agents. Two patients who had received antipsychotic medications while on an inpatient psychiatry service developed elevated creatinine kinase levels with fever and rigidity and were treated for presumed neuroleptic malignant syndrome.

Table 1—*Characteristics of Patients With NMDARE Admitted to the Medical ICU, Ben Taub General Hospital, Houston, Texas, 2010-2013*

Patient	Time From Onset to Admission, Admission to Diagnosis	ICU LOS, d	Days of MV	Teratoma	NMDARE Specific Complications	Hospital-Related Complications	MRI/EEG/CSF	Medical Therapies/Treatment	Trach/PEG Tube
Patient 1: female, mid-20s	3 wk, 15 d	35	33	No	Constantly biting ETT, pulling out IV lines, verbally abusive with staff, incessant screaming, and was intermittently catatonic. Severe dysautonomia with hyper/hypotension, fever, tachy/bradycardia, severe agitation despite heavy sedatives.	HCAP, UTI, line sepsis	Negative/negative/ WBC count 3 (first lumbar puncture), 14 (second lumbar puncture)	Steroids: yes PLEX: yes IVIG: yes Rituximab: yes	Yes/Yes
Patient 2: female, late 20s	1 wk, 14 d	45	42	No	Treated empirically for NMS. Severe dysautonomia with hyper/hypotension, fever, tachy/bradycardia. Severe agitation despite heavy sedatives. Despite negative EEG, required up to 4 concurrent AEDs. Multiple episodes of severe clenching of teeth, leading to bradycardia, perforation of ETT, and tongue entrapment and significant bleeding.	HCAP, sepsis, UTI	Negative/negative/ WBC count 13	Steroids: yes PLEX: no IVIG: yes Rituximab: yes	Yes/Yes
Patient 3: male, late teens	3 wk, 11 d	78	63	No	Severe agitation resulting in falling out of bed twice despite restraints. Severe dysautonomia with hyper/hypotension, fever, and tachy/bradycardia. Persistently somnolent and nonverbal in a dissociative state. Required paralytics for tonic-clonic episodes approximately 30 times.	HCAP, reintubation, empyema requiring 2 chest tubes, subdiaphragmatic abscess with laparoscopic drainage, persistent seizures, DVT, CDiff, PEG dysfunction/dislodgement	Negative/seizures/ WBC count 61	Steroids: yes PLEX: yes IVIG: yes Rituximab: yes Cytoxan: yes	Yes/Yes

(Continued)

Table 1—*Continued*

Patient	Time From Onset to Admission, Admission to Diagnosis	ICU LOS, d	Days of MV	Teratoma	NMDARE Specific Complications	Hospital-Related Complications	MRI/EEG/CSF	Medical Therapies/Treatment	Trach/PEG Tube
Patient 4: female, mid-20s	2 wk, 29 d	43	40	Yes	Severe orofacial dystonic movements. Severe dysautonomia with hyper/hypotension, fever, tachy/bradycardia. Significant bradycardia due to airway obstruction caused by biting the ETT. Presence of ovarian tumor required resection for treatment.	HCAP, UTI, PEG tube malfunction	Negative/negative/ WBC count 16	Steroids: yes PLEX: yes IVIG: yes Rituximab: no	Yes/Yes
Patient 5: male, early 40s	4 wk, 27 d	4	0	No	Significant agitation and psychiatric manifestations, such as anger and agitation, making it difficult to provide care, obtain laboratory studies, and give medications.	None	Negative/negative/ WBC count 0 (first lumbar puncture), 5 (second lumbar puncture)	Steroids: no PLEX: yes IVIG: no Rituximab: no	No/No

AED = antiepileptic drug; CDiff = *Clostridium difficile* colitis; CSF = cerebrospinal fluid; ETT = endotracheal tube; HCAP = health care-associated pneumonia; IVIG = IV immunoglobulin; LOS = length of stay; MV = mechanical ventilation; NMDARE = anti-*N*-methyl-D-aspartate receptor encephalitis; NMS = neuroleptic malignant syndrome; PEG = percutaneous endoscopic gastrostomy; PLEX = plasma exchange; Trach = tracheostomy; UTI = urinary tract infection.

Iatrogenesis

Patients underwent multiple diagnostic and therapeutic interventions, including antipyretics; blood, urine, stool, and respiratory cultures; imaging studies; antibiotics; IV fluid boluses; and intubation and reintubation. Iatrogenic complications included health care-associated pneumonia, urinary tract infections, bacteremia/line sepsis, and DVT. One patient's gastric tube dislodged, leading to an intraabdominal abscess requiring surgery and prolonged percutaneous drainage. Concurrently, the patient developed an associated empyema, also requiring percutaneous drainage.

Eventual outcomes ranged from "50%" subjective recovery of overall function 30 days postdischarge, to full recovery at 6 months postdischarge, to incomplete recovery and readmissions for seizures and other complications (gastric tube or tracheostomy dislodgment) at 12 months postdischarge. Even with full recovery, the patients often required additional time before returning to school or work because of memory deficits, emotional lability, or concentration difficulties.

Discussion

With a comprehensive understanding of NMDARE, ICU teams can better anticipate the challenges awaiting them when treating this disease. Inpatient psychiatric care was the first point of medical contact for the majority of patients with this disorder. A thorough medical evaluation took place only when clinical seizures manifested, which delayed diagnosis, treatment, and recovery, and likely prolonged ICU LOS. Distinguishing between true seizures and non-seizure-like dyskinesias proved to be a challenge both at initial presentation and throughout the hospital course. All of the patients received AEDs despite only one patient having EEG-confirmed seizures. Persistent dysautonomias, fevers, and fluctuating mental status were additional difficult-to-manage confounders. Distinguishing primary disease from nosocomial complications was often impossible, resulting in patients' receiving prolonged courses of sedatives, neuromuscular blockers, empirical antibiotics, invasive diagnostic tests, and neuroactive and psychoactive medications. Patients' severe oral-lingual-facial dyskinesias and opisthotonic posturing resulted in the dislodging and malfunction of airway devices (ETT and tracheostomies), which significantly complicated airway management.

Because of our institution's experience with NMDARE, all patients were suspected of having this diagnosis within 1 week of ICU admission and, thus, received some form of empirical immune therapy within that period once infectious causes of limbic encephalitis were ruled out. Steroids and rituximab were occasionally deferred because of persistent fevers, and plasma exchange was used as the first-line therapy on such occasions. The patient with the longest LOS received both rituximab and cyclophosphamide. Longer ICU and inpatient LOS correlated with longer recovery periods and the need for continued therapies after discharge.

This case series highlights a number of important lessons for critical care physicians. A greater awareness of the disease among first-line medical providers will allow for earlier diagnosis and treatment without diversion to an inpatient psychiatric facility. Additionally, more knowledgeable ICU teams may manage these patients more effectively, because they can anticipate the complexities of this condition and should be able to avoid incorrect secondary diagnoses and unnecessary interventions and therapies.

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References

1. Vitaliani R, Mason W, Ances B, Zwerdling T, Jiang Z, Dalmau J. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. *Ann Neurol*. 2005;58(4):594-604.
2. Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol*. 2007;61(1):25-36.
3. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008;7(12):1091-1098.
4. Florance NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol*. 2009;66(1):11-18.
5. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011;10(1):63-74.
6. Iizuka T, Sakai F, Ide T, et al. Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. *Neurology*. 2008;70(7):504-511.
7. Sansing LH, Tüzün E, Ko MW, Baccon J, Lynch DR, Dalmau J. A patient with encephalitis associated with NMDA receptor antibodies. *Nat Clin Pract Neurol*. 2007;3(5):291-296.
8. Bayreuther C, Bourg V, Dellamonica J, Borg M, Bernardin G, Thomas P. Complex partial status epilepticus revealing anti-NMDA receptor encephalitis. *Epileptic Disord*. 2009;11(3):261-265.
9. Pruss H, Dalmau J, Harms L, et al. Retrospective analysis of NMDA receptor antibodies in patients with encephalitis of unknown origin. *Neurology*. 2010;75(19):1735-1739.
10. Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain*. 2010;133(pt 6):1655-1667.
11. Ishiura H, Matsuda S, Higashihara M, et al. Response of anti-NMDA receptor encephalitis without tumor to immunotherapy including rituximab. *Neurology*. 2008;71(23):1921-1923.
12. Varvat J, Lafond P, Page Y, Coudrot M, Reynaud-Salard M, Tardy B. Acute psychiatric syndrome leading young patients to ICU: consider anti-NMDA-receptor antibodies. *Anaesth Intensive Care*. 2010;38(4):748-750.
13. Davies G, Irani SR, Coltart C, et al. Anti-N-methyl-D-aspartate receptor antibodies: a potentially treatable cause of encephalitis in the intensive care unit. *Crit Care Med*. 2010;38(2):679-682.