Anti-NMDA Receptor Encephalitis: A Case Study of Recovery Through Art

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Anti-NMDA receptor encephalitis, rehabilitation, art therapy, psychosis, encephalopathy, immunotherapy

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CASE PRESENTATION

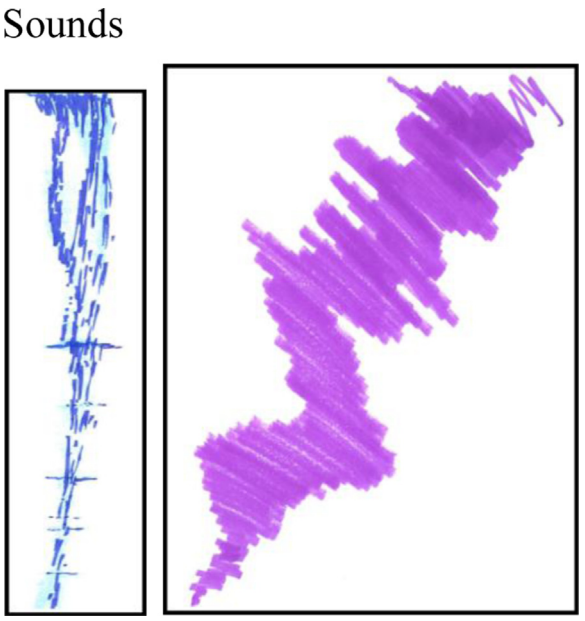
On the eve of her high school graduation, a healthy, 18-year-old female adolescent experienced new-onset seizures, and less than 2 weeks later, she was in a pediatric intensive care unit (PICU) in a catatonic state. After an extensive workup, she was diagnosed with anti–N-methyl D-aspartate (NMDA) receptor encephalitis, which marked the start of a 4-month hospitalization, including 2 months on an inpatient rehabilitation unit. Her long recovery was not always clinically apparent, but it was revealed slowly through her artwork (Figures 1-3).* Her drawings became her principal method of expression and communication, and they improved in both subject and sophistication as she slowly emerged from the fog of encephalitis.

Anti-NMDA receptor encephalitis is a neuroautoimmune disorder that was first described in 2005 and further classified by Dalmau and his colleagues at the University of Pennsylvania in 2007 (Dalmau et al., 2007). It is characterized by inflammation in the brain, particularly in the hippocampus, amygdala, and cortex, as a result of antibodies that attack the NR1 and NR2 subunits of NMDA receptors (Dalmau et al., 2007). Because of the location of these receptors, patients may present with neurologic, psychiatric, or behavioral changes. In children, these changes can

> Because behavior and activity changes can be subtle, the early signs of anti-NMDA receptor encephalitis are often missed.

* Consent to use the patient's medical information and artwork was given by the patient's mother at the time of discharge from the hospital.

FIGURE 1. The patient drew "sounds" that she heard.



appear subtle and may manifest as hyperactivity, irritability, temper tantrums, or mood swings. For weeks prior to her seizures, our patient experienced frequent and abrupt mood swings, alternating between acting excited about graduation and lashing out at her family; her parents attributed these mood swings to the transition of graduating high school. Because behavior and activity changes can be subtle, the early signs of anti-NMDA receptor encephalitis are often missed.

Research regarding this recently identified cause of encephalitis is ongoing, but it is important for pediatric nurse practitioners (PNPs) to be aware of this potentially lethal disorder. Prompt recognition and diagnosis of this disease is important to facilitate treatment and

FIGURE 2. Throughout her rehabilitation course, the patient's drawings improved in both subject and sophistication.

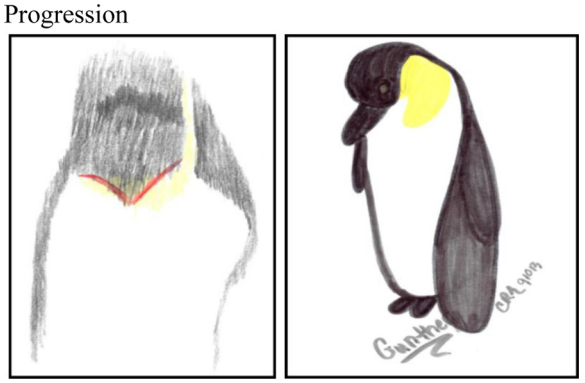


FIGURE 3. The patient repeated themes throughout her drawings.

prevent long-term sequelae. Because of the protracted course of anti-NMDA receptor encephalitis, NPs need to be familiar with the transition from inpatient care to outpatient follow-up. As this case study demonstrates, inpatient rehabilitation is an essential component of the recovery process, and patients often require continued comprehensive therapies after discharge. In particular, creative therapies, such as art therapy, can facilitate recovery and reveal clinical improvement.

HISTORY OF PRESENT ILLNESS

Our patient was a healthy 18-year old female adolescent who had recently accepted an art scholarship to college. She had no significant medical issues until early summer 2013, when she presented to her local emergency department (ED) with new-onset seizure activity. She was discharged home, but over the next week, she experienced continued seizures and extreme fluctuations in behavior and emotion. At home, she alternated between displaying erratic behavior, such as wandering around the house saying that "everyone was going to die," and having moments of clarity with a good memory. She began to have facial twitches and slurred speech that would come and go, and her emotions fluctuated between extreme happiness with uncontrolled laughter and agitation with aggression and hostility. She presented to the ED twice for seizure activity before she was admitted to the hospital, 7 days after her first seizure.

After she was admitted to her local hospital, her workup included a computerized tomography (CT) scan, magnetic resonance imaging (MRI), magnetic resonance venography of the brain, a lumbar puncture (LP), abdominal ultrasound, and long-term electroencephalography (EEG) monitoring at the referring hospital. Despite treatment with three antiepileptic medications and good clinical control of her seizures, her EEG revealed a seizure focus in the right temporal lobe. Because of the subclinical seizures and concern for worsening neurologic deterioration without a known cause, she was transferred to a large, free-standing pediatric hospital on day 10 with presumed encephalitis. Upon presentation to the PICU, she was maintaining her own airway but had a Glasgow Coma

Scale score of 9 and exhibited symptoms that raised concern for worsening mental status, including repetitive left upper extremity movement, vocal tics, grimacing, and facial dystonia.

MEDICAL, SOCIAL, AND FAMILY HISTORY

Prior to this hospitalization, our patient was healthy without any previous hospitalizations or surgeries. She had not traveled recently outside of the United States. Her immunizations were up to date, and her only medication included oral contraceptives, because she was sexually active with one steady partner. She had no history of alcohol or drug use, and her toxicology screens were negative. Her mother had a history of chronic pain with positive antinuclear antibodies, her father had a history of low back pain and transient ischemic attack, and her maternal grandfather had a history of diabetes. She lived at home with her mother, stepfather, and younger brother. She was developmentally appropriate and a high-achieving student.

DIFFERENTIAL DIAGNOSES

At the time of transfer to the pediatric hospital, the differential diagnosis included encephalitis related to an infectious process, encephalopathy, and seizures of unknown cause. She had previously been started on a regimen of intravenous (IV) acyclovir for the possibility of herpes simplex virus (HSV) encephalitis. Given her age and status as sexually active, this working diagnosis was reasonable; however, both HSV polymerase chain reaction testing and HSV antibodies from cerebral spinal fluid (CSF) came back negative. After transfer to the freestanding pediatric institution, she underwent a head CT scan, which confirmed the absence of acute intracranial processes. Initial antiepileptic medications included a regimen of levetiracetam and fosphenytoin, and video EEG monitoring was ongoing in the PICU to evaluate for status epilepticus. Neurology and Infectious Disease services were consulted to determine the cause of her encephalitis and to suggest further workup.

DIAGNOSIS

The LP performed on day 14 of her illness revealed the presence of anti-NMDA antibodies in the CSF, providing a diagnosis of anti-NMDA receptor encephalitis. This diagnosis is made by the presence of the anti-NMDA receptor antibodies in CSF or serum, which can only be identified in designated laboratories. Anti-NMDA receptor encephalitis can be easily missed because the results of many standard tests, including MRI, CT, EEG, and viral studies, are often normal. Since its classification, the prevalence of anti-NMDA receptor encephalitis has risen sharply. With increasing awareness and diagnostic testing, anti-NMDA receptor encephalitis is now the most common cause of autoimmune encephalitis after acute demyelinating encephalomyelitis. This disorder predominately affects women (80%), although anti-NMDA encephalitis has been reported across the life span, from 8 months to 85 years (Titulaer et al., 2013).

STAGES OF ANTI-NMDA RECEPTOR ENCEPHALITIS

The acute course of anti-NMDA receptor encephalitis has been described in four stages (Garcia & Houtrow, 2013). In the initial (prodromal) stage, patients typically present with nonspecific symptoms, such as headache, fever, malaise, or upper respiratory symptoms. Within a few days to 2 weeks, patients exhibit psychiatric or behavioral symptoms as they enter the second (psychotic and/or seizure) stage. In the case of our patient, it was the new-onset seizure activity that prompted her parents to bring her to the hospital for evaluation. Adults may appear depressed, anxious, paranoid, or disoriented, but children often present with more subtle psychiatric symptoms, such as hyperactivity, irritability, or an increase in temper tantrums (Dalmau, Lancaster, Martinez-Hernandez, Rosenfield, & Balice-Gordon, 2011). Subtle changes in behavior or mental status are difficult to assess and quantify, and thus the first symptoms to be recognized are often neurologic, such as seizures, dystonia, speech disturbances, or abnormal movements (Garcia & Houtrow, 2013).

Our patient presented to the PICU in the third (unresponsive) stage as her clinical status deteriorated. She exhibited oral-lingual-facial dyskinesias and choreoathetoid movements commonly seen in persons with anti-NMDA encephalitis, and these abnormal movements prompted testing for anti-NMDA antibodies. This phase may overlap with the fourth (hyperkinetic) stage, when it is common for patients to experience autonomic instability (Garcia & Houtrow, 2013). Cardiac arrhythmias, blood pressure changes, hypoventilation, and hyperthermia are all common (Garcia & Houtrow, 2013), and seizure activity during this phase can be refractory to medications. Because of the autonomic instability and potential for further respiratory and cardiac deterioration, patients often require prolonged stays in an intensive care environment. Our patient spent just over 5 weeks in the PICU before she was deemed stable for transfer to the neurologic floor.

HOSPITAL COURSE

Upon arrival at the PICU in the unresponsive stage, our patient received a 5-day course of intravenous immunoglobulin (IVIG), followed by high-dose steroids (methylprednisolone). Her IV methylprednisolone was slowly tapered over the following month, during which time she also received apheresis for 5 days. Because anti-NMDA receptor encephalitis can be associated with ovarian teratomas (Dalmau et al., 2011), our patient underwent an extensive workup to rule out tumors of her pelvis, chest, and abdomen using a positron emission tomography scan. Both the initial abdominal ultrasound

performed at her local hospital and subsequent tests performed at the pediatric institution were negative for teratomas. The presence of an underlying neoplasm exists approximately 40% of cases, with an ovarian tumor occurring in 94% of the cases in which an underlying neoplasm has been identified (Titulaer et al., 2013). The presence of a tumor is much more likely in women between 12 and 45 years of age (Titulaer et al., 2013), and the younger the patient, the less likely a tumor will be detected (Dalmau et al., 2011). An underlying neoplasm was not found in our patient, and the exact cause of her encephalitis remains unknown.

As she transitioned into the hyperkinetic stage, our patient experienced sporadic episodes of tachycardia, hypertension, and hypotension, none of which required medical intervention. She also experienced bradycardic and apneic events, which occasionally required positive pressure ventilation, and desaturation events related to breath-holding spells, which resolved with stimulation. Although our patient did not require mechanical ventilation for her autonomic instability, as some patients do, she did have refractory seizures. With Neurology input, trials of multiple antiepileptic medications were initiated with our patient, and lacosamide and oxcarbazepine eventually led to her stabilization. Doses of her antiepileptic medications were adjusted to achieve therapeutic levels.

As her mental status waxed and waned, she alternated between periods of catatonia and agitation. Her manic and agitated episodes occurred mostly in the evenings, and managing them posed a great challenge. A regimen of olanzapine and clonidine was used at night, and lorazepam was available for agitation. Benzodiazepines were reserved only for use as rescue medications because of their short-term effect and potential for rebound agitation; antipsychotic medications provided better long-term control of agitation. Because these episodes affected her ability to sleep, she also received melatonin nightly and had zolpidem available as needed.

No standardized treatment plan is available for anti-NMDA receptor encephalitis. Dalmau and colleagues (2011) proposed a treatment algorithm that includes methylprednisolone plus IVIG or plasma exchange as first-line therapy. Second-line therapy should be considered if no response is seen in 10 days. In adults, second-line therapy consists of rituximab combined with cyclophosphamide, followed by monthly cycles of cyclophosphamide (Dalmau et al., 2011). However, in children, rituximab is often used alone to prevent potential medication interactions and long-term adverse effects.

For our patient, after first-line therapy with IVIG, methylprednisolone, and apheresis and only minimal improvement after 1 month in the PICU, the neuro-oncology team was consulted. They recommended instituting second-line therapy to intensify immunotherapy, and a treatment plan was developed for our patient to receive weekly rituximab infusions for 3 weeks. She did not show significant improvement after the first rituximab infusion, and thus in between the first and second rituximab doses, she was also given an additional dose of IVIG plus 3 days of pulse steroids with IV dexamethasone. Her steroids were then transitioned to hydrocortisone to allow her to gradually wean off steroids over a 10-week period.

Our patient's hospital course was further complicated by her inability to maintain adequate hydration and caloric needs, as she was not deemed able to eat safely by mouth because of her mostly catatonic state. She received enteral nasogastric feedings and eventually had a gastrostomy tube (G tube) placed. The G tube also helped with the challenge of medication administration. Over time, even as her swallowing and cognitive abilities improved, she would not reliably take her medications because of her frequent episodes of agitation. Although the G tube was beneficial, it became a frequent source of agitation as her medical condition improved. As she became more aware of her physical surroundings, she grew obsessed with having her body free of medical devices and frequently ripped her G tube button out of her stoma site. Perseveration over the G tube continued as she was transitioned to the inpatient rehabilitation service.

REHABILITATION COURSE

The description of the disease stages by Dalmau and colleagues (2011) does not include the lengthy process of rehabilitation. Inpatient rehabilitation is instrumental in the recovery of patients with anti-NMDA receptor encephalitis to address lingering physical and cognitive deficits. Our patient was transferred to the inpatient rehabilitation unit on day 58 of illness. She continued to receive ongoing medical management of her seizures, insomnia, agitation, and dysphagia, in addition to continued immunotherapy. Specialists from Neurology, Neuro-Oncology, Endocrinology, and Psychiatry continued to follow her progress and make adjustments to her medical plan, as needed. Her multidisciplinary rehabilitation team included physical, occupational, and speech therapies, along with psychology and child life services, music therapy, and art therapy.

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Given our patient's interest in art, it was not surprising that she used art as a means of communication and expression. She began by drawing "sounds" that she heard (Figure 1). She repeated themes throughout her

drawings, and her caption "flower of death" (Figure 2) in one picture provided insight into her thoughts and fears. Throughout her rehabilitation course, her drawings improved in both subject and sophistication (Figure 3). Even before her clinical presentation showed signs of improvement, her artwork revealed that the fog of encephalitis was lifting.

When she presented to the rehabilitation unit, our patient required constant supervision for alternating states of catatonia and mania with disorientation. As she became more alert, her agitation and aggressive behaviors increased. She became increasingly aware of her limitations, particularly in her inability to express herself, which frustrated her. Her therapists were often successful during sessions by setting clear goals, expectations, and limits. However, her family became the unfortunate objects of her aggressive displays. For example, before one therapy session, she was calm as her therapist escorted her onto the elevator, but then she suddenly rushed toward her mother and pinned her against the elevator wall. Other particularly concerning behaviors were her hypersexuality and fixation on food. Her therapists allowed gradually increasing amounts of independence while still maintaining clear boundaries, and they set consequences for pushing those boundaries. With time and increasing awareness of her behaviors, she acted more safely, but she still acted impulsively. Her diet was gradually advanced until she no longer required enteral feedings, but once she was cleared to eat regular foods, she developed a voracious appetite and gained just over 10 kg by the end of her hospitalization.

DISCHARGE PLANNING

Recovery happens irregularly and occurs in reverse order of symptom presentation (Garcia & Houtrow, 2013) over the course of several months to years. Gross motor skills are typically regained first, followed by fine motor skills, with cognitive skills (particularly executive function) among the last to return. This situation can present a challenge for determining readiness for home and school, particularly for patients who require constant supervision. Especially for younger patients, ensuring safety at home is crucial, and parents may need to use bed or door alarms and lock up dangerous objects, including medications. The inappropriate behaviors that our patient displayed during inpatient therapies, such as hypersexuality, impulsivity, and hyperphagia, prevented her return to school. Once these behaviors were better controlled, neuro-psychological testing was recommended to help facilitate a strategic plan for return to school with services in place.

After a 4-month hospital stay, our patient was discharged home with her parents. She had regained her physical strength, continued to have a voracious appetite, and was medically stable; however, her mental status was far from baseline. Even though she displayed moments of clarity, she still experienced confusion and episodes of extreme agitation, so planning for safety at home was a discharge planning priority. A home health aide was secured to help her family maintain adequate supervision over the patient and to continue to reinforce the behavioral strategies that she learned while on the rehabilitation unit. Her family was counseled to lock cabinets with medicines or hazardous materials, keep doors locked with an alarm set at night, and prevent overstimulation by limiting visits by family and friends. Outwardly our patient appeared to be much improved, so it would be difficult for some of her friends and family to understand how impaired she truly was, and her parents needed to respect her limitations when interacting with others. She was discharged home with medications for agitation, insomnia, seizure management, and the final taper of steroids. Close outpatient follow-up was arranged with continued outpatient therapies and appointments in Neurology, Neuro-Oncology, and Rehabilitation clinics.

PATIENT OUTCOME

At the time of discharge, continued inpatient rehabilitation was recommended for our patient; however, her family was eager for her to continue her recovery at home, and so she was followed up closely on an outpatient basis. Several weeks after discharge, she experienced two seizures and required an increase in her antiepileptic medications. Despite continued outpatient speech therapy, she began having more difficulty with concentration and processing about 1 month later, and an additional infusion of rituximab was recommended. Afterward, her mental status initially improved, but after another 2 months, she was readmitted to the hospital after experiencing headaches and worsening confusion. She underwent a repeat LP, which revealed the continued presence of anti-NMDA receptor antibodies. She was thus given additional doses of rituximab, although this time she was well enough to be discharged from the hospital and received the infusions on an outpatient basis. As of 8 months after her initial presentation with anti-NMDA receptor encephalitis, our patient continued to be closely followed by the Neurology, Oncology, Adolescent Medicine, and Rehabilitation services. She also continued to receive outpatient occupational and speech therapies in order to prepare her for entry to community college the following fall to begin her studies in art therapy.

DISCUSSION

The underlying cause of anti-NMDA receptor encephalitis is unknown. It is important for pediatric providers to be aware of this disorder, because the incidence is highest in patients between 12 and 29 years of age (Titulaer et al., 2013). Prior to Dalmau's research, patients who presented with new-onset psychiatric or behavioral changes were classified as schizophrenic

or given nonspecific psychiatric diagnoses and had poor prognoses. This disorder should be included in the differential diagnosis when patients, particularly children, present with a combination of neurologic and behavioral changes, so that they can be properly diagnosed and treated appropriately. With proper management, approximately 75% of patients will have complete or near-complete recovery; however, with delayed or ineffective treatment, the mortality rate is high (Dalmau et al., 2011). Because the antibodies attack the NMDA receptors, patients exhibit psychiatric and behavioral symptoms in conjunction with their neurologic deficits. In younger patients, this type of encephalitis presents more often with subtle behavioral changes (Dalmau et al., 2011). However, because these symptoms are more subtle than neurologic changes, they are often missed or attributed to other causes, which can delay the diagnosis of anti-NMDA receptor encephalitis.

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Because recovery from anti-NMDA receptor encephalitis is prolonged, it is also important for PNPs to be familiar with management of this disorder after patients are discharged from the hospital. These patients will have close follow-up with several specialists and outpatient therapies, and NPs are instrumental in coordinating the care of these patients among the various specialists to ensure the best possible outcomes. Even after substantial clinical recovery occurs, Dalmau and colleagues (2011) recommend continuing some type of immunosuppression for at least 1 year after initial immunotherapies are discontinued because of the 20% to 25% chance of relapse. A PNP may be the first provider to notice the subtle changes that precipitate a relapse, so it is important to establish the patient's baseline after discharge from the hospital and monitor for changes. Finally, the emotional turmoil of these patients and their families cannot be minimized, and NPs are uniquely poised to provide the close and trusting relationship required to provide the support needed by these patients and their families.

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