REVIEW

Anti-NMDA receptor encephalitis: a case study and illness overview

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Abstract

Anti-N-methyl D-aspartate (NMDA) receptor (anti-NMDAR) encephalitis is among one of the most common autoimmune encephalitides. However, variations in clinical presentation and nonsequential multiphasic course often lead to delays in diagnosis. The mild encephalitis (ME) hypothesis suggests a pathogenetic mechanism of low-level neuroinflammation sharing symptom overlap between anti-NMDAR encephalitis and other psychiatric disorders including schizophrenia. Clinical symptoms of anti-NMDAR encephalitis may mimic schizophrenia and psychotic spectrum disorders or substance-induced psychosis. Although initially described in association with ovarian teratomas in women, anti-NMDAR encephalitis has been reported in individuals without paraneoplastic association, as well as in males. It can affect all age groups but is usually lower in prevalence in individuals greater than 50 years old, and it affects females more than males. Clinical evaluation is supported by laboratory workup, which includes cerebrospinal fluid (CSF) assays. The latter often reveals lymphocytic pleocytosis or oligoclonal bands with normal to elevated CSF protein. CSF testing for anti-NMDAR antibodies facilitates diagnostic confirmation. Serum anti-NMDAR antibody assays are not as sensitive as CSF assays. Management includes symptomatic treatment and immunotherapy.

Keywords: anti-NMDAR, autoimmune encephalitis, encephalitis, NMDA.

Introduction

Anti-N-methyl D-aspartate (NMDA) receptor (anti-NMDAR) encephalitis, caused by immunoreactivity against the NMDA receptor 1 (NR1) subunit of the NMDA receptor, is one of the most common autoimmune encephalitides, first described in 2007 by Dalmau and colleagues in which psychiatric and neurologic symptoms were found in women with ovarian teratomas.[1] The condition was later confirmed to be not exclusively paraneoplastic. Later studies reported patients afflicted without tumor involvement.[2,3] Although available data suggest the disease is more prevalent in adult women, and in the non-Caucasian population, the condition has been described in both genders, in multiple races, and throughout the lifespan.[4,5] However, increasing case reports of anti-NMDAR encephalitis in the psychiatric literature have demonstrated the significant overlap between neurologic and psychiatric pathology associated with autoimmune encephalitis.[6–10] The clinical progression of the encephalitis has also been more thoroughly defined, with a multiphase model currently in use.[11] The prodromal phase is suggestive of a viral flu-like illness, in which fever, malaise, and fatigue may be prominent. This phase varies in duration and may also involve upper respiratory or gastrointestinal symptoms. The condition is often clinically recognized in the ensuing psychotic phase, in which delusions, hallucinations, paranoia, and agitation may be exhibited. During this phase, anti-NMDAR encephalitis is often misdiagnosed as a primary psychotic or substance-induced disorder. Following these psychotic symptoms is often the progression to a state in which catatonia, impaired attention, dyskinesias, and seizures may develop. In addition, significant autonomic instability, with wide-ranging fluctuations in body temperature, blood pressure, respiratory rate, and cardiac rhythm, may occur.[12] It is important to note that anti-NMDAR cases may not follow a strict phasic progression as mentioned earlier and may not include all of the symptomatology mentioned earlier, thereby complicating diagnosis.

Indeed, as autoimmune etiologies of psychiatric symptoms continue to be better recognized as a whole, patient

presentations that should prompt further immunologic evaluation have been identified. Herken and Pruss[13] have described 'yellow flag' and 'red flag' symptoms that are particularly indicative of an autoimmune process. Decreased level of consciousness, abnormal postures/movements, autonomic instability, focal neurologic deficits, aphasia/dysarthria, and rapid progression of psychosis despite therapy, hyponatremia, catatonia, headache, and presence of other autoimmune disease were described as 'yellow flag' (i.e., raising suspicion) indicators of an autoimmune process. Cerebrospinal fluid (CSF) pleocytosis and oligoclonal bands without infection, generalized seizures, faciobrachial seizures, suspected neuroleptic malignant syndrome (NMS), magnetic resonance imaging (MRI) abnormalities (mesiotemporal hyperintensities, atrophy pattern), and electroencephalogram (EEG) abnormalities (slowing, epileptic activity or extreme delta brush) are of even higher ('red flag') concern indicators of potential autoantibody involvement. Identification of these characteristics is associated with earlier diagnosis, implementation of immunotherapy, and improved patient outcomes.

In the following case report, we discuss a patient who presented to the emergency department (ED) with behavioral symptoms and who was later medically hospitalized with psychiatric and neurologic consultation. Described are the multiphase phenomena, as well as the coordination of the psychiatry, neurology, and internal medicine services in diagnosing the unusual symptoms of this still poorly understood disease entity. Patient details have been de-identified to ensure privacy.

Case Report

The patient was a 40-year-old African-American female without previous psychiatric history and a medical history of hypertension. She was brought to the ED by her family, who were concerned about the sudden onset of unusual behavior. She had been sent home from work earlier that day due to inability to complete her normal tasks. Her son noted that she was 'not making sense, being forgetful and not acting like herself'. The patient reportedly smoked marijuana after she came home. However, her son indicated her behavior was odd even before her drug use and then worsened throughout the day, prompting medical attention. Her family reported a recent stressor of the death of her mother several months earlier. The patient was notably agitated in the ED, appeared confused, and tried to leave. She was given intramuscular ziprasidone and lorazepam to calm her. Initial laboratory studies included a comprehensive metabolic panel and a complete blood count, both of which were unremarkable. Her alcohol level was zero, and her urine drug screen was positive for cannabinoids only. Computed tomography of her brain was negative for any acute process (Table 1). She was placed under involuntary psychiatric commitment and held for the ED psychiatric team to evaluate. Her provisional diagnosis was a substance-induced psychotic disorder.

While in the emergency room for several days, the patient was described as hyper-religious, intermittently agitated, and not sleeping. Haloperidol and lorazepam were employed on an as-needed basis to help control her behavior. She was able to be calm at times, and she reported a poor recollection of what brought her to the ED. She endorsed daily use of cannabis. By the third day in the emergency room, she became more disorganized in her speech and began reporting paranoid ideation about a coworker she felt had 'put a root' on her. A rapid plasma reagin (RPR) and human immunodeficiency virus (HIV) were checked, which were both non-reactive. Given her repeated bouts of agitation and administration of antipsychotic agents, a creatinine phosphokinase level was ordered, which was elevated at 1526 U/L. The decision was made to admit her to the hospitalist (internal medicine) service for mild rhabdomyolysis, and the psychiatric consultation-liaison (CL) team was consulted.

When evaluated by the psychiatric CL service, the patient was noted to exhibit disorganized speech and behavior, with perseveration on particular words and phrases. Initial psychiatric consultation also noted autonomic instability with fluctuating heart rate and hypertension. Risperidone was prescribed for psychotic symptoms, and inpatient psychiatric hospitalization was recommended. Lorazepam was briefly continued to aid with agitation and to cover for possible alcohol withdrawal, given the presence of intermittent tachycardia and hypertension. Over the course of the ensuing week, the patient continued to exhibit disorganized behavior and perseverative speech, though she became increasingly somnolent, with marked fluctuations of blood pressure and heart rate. Risperidone and lorazepam were discontinued given lack of efficacy and concern for over-sedation. Due to the absence of a previous psychiatric history, persistence of psychotic symptoms, autonomic instability, and increasing somnolence, a medical cause of symptoms was considered likely. Testing for autoimmune encephalitis, particularly anti-NMDAR encephalitis, was recommended. A nasogastric tube was placed because of poor oral intake, and a lumbar puncture was performed. The neurology service was consulted and agreed with the presumptive anti-NMDAR encephalitis diagnosis. An MRI of the brain was ordered following neurology consultation, the results of which were unremarkable (Table 1). Initial results of the lumbar puncture showed lymphocytic pleocytosis with oligoclonal bands (Table 2).

The patient became increasingly verbally unresponsive over the following week with continued autonomic instability. She was noted to visually track at times, but often stared blankly. Owing to her declining condition, intravenous immunoglobulin (IVIG) was initiated on an empiric basis for anti-NMDAR encephalitis. Shortly thereafter, cerebrospinal fluid CSF and serum anti-NMDAR antibodies returned with a positive result, confirming the diagnosis. Although the patient was nonverbal, she would occasionally make eye contact and look about the room. She was noted to have several brief episodes of tonic-clonic seizure activity.

Table 1.   Neuroimaging.

Computed tomography scan of the head	**FINDINGS**: The fourth, third, and both lateral ventricles were demonstrated and appear normal. There was no shift of the midline structures in the infra- or supratentorial regions. No abnormal areas of increased or decreased attenuation were noted. No abnormal intra- or extra-axial fluid collections were noted. Images at bone windows show no evidence of fracture or sutural diastasis. **CONCLUSIONS:** No acute intracranial abnormality.
Brain MRI	**FINDINGS:** There was no evidence of any acute or recent infarct or any prior hemorrhage. There were no extra-axial collections. No T2 or FLAIR signal changes are seen throughout the brain. There is no mass effect or edema. No osseous or overlying soft tissue findings are noted. Post-gadolinium sequences show no enhancing mass or vascular lesion. The brain is morphologically normal with appropriate ventricles and CSF spaces. Midline and posterior fossa structures are intact and normally formed. **IMPRESSION:** Unremarkable MRI of the brain.

CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

Table 2.   CSF findings.

	Value	Normal range
Total protein	32.9 mg/dL	15–45 mg/dL
Glucose	74 mg/dL	40–70 mg/dL
Color/appearance	Colorless/clear	Colorless/clear
Nucleated cells	53/µL	0–8/µL
Red blood cells	0/µL	0/µL
Monocyte/histiocyte (%)	7%	0–30%
Lymphocyte (%)	93%	28–96%
Cryptococcal antigen	Negative	Negative
VDRL	Negative	Negative
IgG	2.8 mg/dL	0–6 mg/dL
Oligoclonal band number	2	0–1
Albumin index	4.5	0–9
IgG synthesis rate	<0.0 mg/d	0 mg/d
IgG index	0.6	0.28–0.66
IgG/albumin ratio	0.16	0.09–0.25
Oligoclonal bands	Positive	Negative
NMDA IgG antibody titer	1:40	<1:1
Meningitis/encephalitis PCR panel	Negative for all organisms	Negative

CSF, cerebrospinal fluid; IgG, immunoglobulin G; NMDA, N-methyl D-aspartate; PCR, polymerase chain reaction; VDRL, venereal disease research laboratory.

The decision was made to transfer her to the nearby tertiary care hospital for continued treatment on the internal medicine service with neurologic consultation. An 8-day course of IVIG was completed, and the patient had pan-MRI to assess for possible associated malignancy, the result of which was negative. IV corticosteroids were administered for an additional 5-day course, followed by a plasma exchange. She remained mute and minimally responsive, with significant autonomic instability. She was placed on levetiracetam for seizure control. After completion of plasma exchange, rituximab was initiated. The patient displayed minimal response to these treatment measures initially, and she was transferred to a subacute floor for potential nursing home placement. However, the patient started to become more responsive approximately 60 days into her hospitalization when she exhibited intermittent agitation and some spontaneous speech. Her speech was described as limited but notably fluent and without dysarthria. Psychiatry was reconsulted, and the patient was initiated on low-dose quetiapine. Moreover, scheduled clonazepam was recommended to manage her behavior. Over the course of the subsequent 2 months, she became increasingly verbal and less agitated, and she was able to work with physical therapy. Four months into her hospitalization, she was described as still having some confusion and cognitive deficits, but 'dramatically improved', and she no longer required psychotropic medication. Her family agreed to discharge to home with 24-hour supervision, and she returned home approximately 130 days after her initial presentation. At her outpatient medicine follow-up, 5 weeks after her discharge, she was described as 'continuing to improve' in terms of her cognitive and functional status. At her latest neurology follow-up, 5 months after her discharge, she was felt to be close to baseline and was approved to return to work. Table 3 illustrates the patient's timeline of events in chronologic detail.

Table 3.   Timeline of events.

Day	Clinical information
1	Admitted to ED for bizarre behavior (confusion, paranoia, forgetful). Family noted several days of headache and malaise. Med workup normal, positive for cannabinoids on UDS. Placed on commitment in psych holding area.
2	Religiously preoccupied, paranoid, requesting cannabis. Requiring PRN meds for agitation. Thought process remained disorganized.
4	CPK elevated, patient admitted to general medicine floor. Continued medical workup.
6	CPK improved. Psychiatry C&L team notified. Patient is paranoid and reporting persecutory delusions. Still requiring PRNs for agitation. Answers a majority of questions with the word, 'day'. Thought process disorganized. Risperidone started, and lorazepam for possible withdrawal. Repeating sentence fragments such as 'Did you find?'. Patient spitting out food.
8	Family expresses concern about LP. CSF testing postponed by family.
12	No response to medications. Patient continues to worsen. Noted to have autonomic instability: (HTN, tachycardia). Risperidone discontinued. Family agrees to LP. NG tube placed due to poor PO intake. EEG: Background of moderate amplitude alpha activity with some slowing. No abnormal paroxysmal activity. No focal slowing is seen.
13	Patient non-verbal. Lumbar puncture performed.
14	Tongue fasciculation noted on exam. Remains non-verbal. LP revealed pleocytosis (53 nucleated cells, 2 oligoclonal bands). Neurology consulted, adding MRI and serum anti-NMDAR Ig. Patient repeating same word for long periods of time while pulling at wrist restraints, alternating right and left.
16	IVIG started for presumed autoimmune encephalitis. Patient still requiring antihypertensive medications. Not responding to stimuli in the room. Non-verbal. Anti-NMDAR labs still pending.
17	Continued IVIG. Expanded medical workup. Brief seizure activity reported by nursing.
18	Laboratory results positive for anti-NMDAR antibodies in serum and CSF. Myoclonic activity noted on exam and levetiracetam started.
20	IVIG continued. Levetiracetam continued. Patient noted to be tachypneic, tachycardic, and diaphoretic. Generalized twitching of jaw, left leg, thorax.
21	Patient not responding after 5 days of IVIG. Five-day course of solumedrol initiated. Two more episodes of being tachypneic, tachycardic, and diaphoretic with generalized muscle twitching. MRI of brain unremarkable. MRI of pelvis reveals no ovarian mass.
23	On day 4 of solumedrol, patient again getting out of bed and yelling 'take' repeatedly to nursing. Continuing to see autonomic instability with elevated temperatures.
26	Plasmapheresis started. Continued to have some autonomic instability. Still not following commands.
31	Completed plasmapheresis. Patient still not interacting with environment or following commands. ' Continues to have periods of autonomic instability. Some brief periods of lucidity noted.
32	Rituximab initiated for refractory anti-NMDAR encephalitis. Patient continues to have autonomic instability, managed by internal medicine. Plan for one infusion weekly for 4 weeks, and then one infusion monthly for 6 months.
39	Patient tracking but otherwise not responding appropriately to commands. Received second dose of rituximab.
41	Transaminitis noted. Patient became septic. Rituximab discontinued and sepsis treatment initiated.
50	Patient still encephalopathic but more verbal. Statements are disorganized. Appears to be trying to interact with family.
65	Psychiatry reconsulted to assist with agitation. Patient started on low dose quetiapine. Patient continues to be more talkative but remains disorganized. Receiving lorazepam PRN for agitation, replaced with scheduled clonazepam. Patient's agitation improved. She appears to be slowly making progress but remains disorganized.
120+	Described as 'dramatically improved' and no longer on psychotropic medications. Patient discharged to home health care and is brought to outpatient neurology appointments with the assistance of family. Five weeks after discharge is noted to have continued improvement.

C&L, consultation and liaison; CPK, creatine phosphokinase; CSF, cerebrospinal fluid; ED, emergency department; LP, lymphocytic pleocytosis; NMDAR, N-methyl D-aspartate receptor; PRN, as needed; UDS, urine drug screen.

Overview of anti-NMDAR encephalitis

History

NDMA encephalitis first appeared in medical literature in 2005 when four women were found to have similar presentations that mimicked either an acute psychotic episode, recent drug use, or malingering. They each had a similar combination of psychiatric symptoms, autonomic instability, and seizures. Additionally, they had CSF inflammatory abnormalities and a neurological syndrome that improved after tumor resection, immunotherapy, or both.[14] Further investigation utilizing techniques in immunohistochemistry confirmed suspicion of a teratoma-associated encephalitis. In 2007, Dalmau and colleagues described that 12 women with similar symptoms were found to have antibodies that predominantly immunolabeled the cell surface of hippocampal neurons and reaction with NMDA subunit 2B (NR2B)/NMDA subunit 2A (NR2A) subunits of the NDMA receptor. Eleven of these patients were found to have an ovarian teratoma with NR2 subunits, and eight of them improved or recovered after tumor resection and immunotherapy.[1] It was evident that this was a previously unknown autoimmune process and case reports of other patients with anti-NMDAR encephalitis began to emerge. Although there are no clear estimates of prevalence rates, more than 1000 cases have been reported, which greatly increased after clinical recognition of the disease.[15] The exact incidence of anti-NMDAR encephalitis is unknown. It can affect all age groups but is usually low in prevalence in individuals greater than 50 years old, and affects females more than males (80% of patients are women[3]). It is now considered that anti-NMDAR encephalitis is the most common cause of autoimmune encephalitis after acute demyelinating encephalitis.[16]

Typical clinical presentation

In 70% of patients, there is a prodromal period, averaging 5 days but up to 2 weeks, of a viral-like illness with symptoms of headache, fever, malaise, myalgia, upper respiratory symptoms, nausea, and diarrhea.[17] They often then present to hospitals after they develop psychotic symptoms, such as delusions, hallucinations, and paranoia. Memory loss, as well as difficulty with sustained attention, may occur. Symptoms of hyper-religiosity and disorganization in both thought process and behavior may occur. They may become agitated or afraid to the point of combativeness. The initial presentation is suggestive of psychosis, and may be mistaken for being substance induced, or malingering.

Treatment at this stage includes antipsychotics and sedatives due to psychotic symptom presentation. In our experience, individuals may respond poorly to antipsychotics when compared to typical patients on the schizophrenia spectrum. Patients may also differ from typical first break psychosis in that they may have insight that their thoughts are disorganized.

As the disease progresses, its presentation begins to differ from that of typical psychosis with the onset of autonomic dysfunction (often hypertension, hyperthermia, tachycardia, and hypoventilation), seizures, and movement disorders. Within this same timeframe, the patient may develop catatonia. Speech and verbal abilities decline. There may be stereotypical automatisms such as lip smacking and teeth clenching.[18] Patients may still become agitated and require pharmacological sedation between periods of catatonia.

Differential diagnosis

The mild encephalitis (ME) hypothesis suggests a pathogenetic mechanism of low-level neuroinflammation sharing symptom overlap between anti-NMDAR and other psychiatric disorders including schizophrenia. Various factors are implicated in triggering the neuroinflammatory process, including autoimmunity, which in turn is the etiologic pathway in anti-NMDAR. Clinical symptoms of anti NMDAR encephalitis may mimic schizophrenia and psychotic spectrum disorders.[19] Because it is so common for these patients to be initially seen and evaluated for new onset psychosis,[20] this will be discussed separately to assist with diagnostic clarity.

Ruling out schizophrenia

According to the Diagnostic and Statistical Manual for Mental Disorders 5, to diagnose schizophrenia, patients must exhibit two Criterion A symptoms (delusions, hallucinations, disorganized speech) for a significant portion of at least 1 month. Disorganized behavior or negative symptoms may also be present. The patient may have had prodromal symptoms for weeks or months before their initial presentation, which may consist of avolition, mild hallucinations or delusions, unusual or odd beliefs, and or social withdrawal.[21] Many patients exhibit depressive symptoms prior to meeting diagnostic criteria for schizophrenia. New onset psychosis typically occurs in late teens to 30s. Females generally present at a later age than males. There is often a family history of mental illness, but this is not always the case. Many patients with schizophrenia do not have insight into their illness. For example, they are less likely to view their hallucination as such and instead are likely to incorporate them into delusional thoughts. In our experience, our patient had insight into her cognitive decline. At times, she seemed to be pleading for help while acknowledging her thoughts were disordered by nodding. Substance-induced psychosis may also be considered, but this typically resolves in the absence of substance use. Patients often present to EDs and are psychotic due to the influence of substances such as methamphetamine, cocaine, or cannabis. However, their symptoms typically resolve rapidly.

Abnormalities in CSF and autoantibodies can occur in individuals with schizophrenia as well as those with anti-NMDAR encephalitis. Elevated inflammatory cytokines, immunoglobulins, and elevated cell counts within the CSF have been noted in 40–70% of individuals with schizophrenia and affective psychosis.[19] However, this antibody-associated

mechanism is considered to be transient in schizophrenia and suggestive of a mild encephalitis syndrome. Studies have shown that anti-NMDA receptor IgG subclass antibody positivity is found in a minority of individuals with schizophrenia.[22]

The differential diagnosis also includes other viral encephalitides (cytomegalovirus [CMV], Epstein–Barr, herpes simplex virus [HSV], varicella zoster virus [VZV], human immunodeficiency virus [HIV], human herpesvirus 6 [HHV6]/human herpesvirus 7 [HHV7], arbovirus, rabies virus), other autoimmune causes (limbic encephalitis, other paraneoplastic encephalitides, systemic lupus erythematosus, antiphospholipid syndromes, Sjögren's syndrome, Graves' disease, Hashimoto's encephalitis, vasculitis), and toxic/metabolic disorders (drug ingestion, porphyria, mitochondrial disorders).[18] When antipsychotics have been used for initial presenting symptoms, neuroleptic malignant syndrome enters the differential. It may be difficult to differentiate this from the autonomic symptoms seen in anti-NMDAR encephalitis. In our experience, we found patients with anti-NMDAR encephalitis to be less responsive to typical antipsychotic treatments. These patients may require multiple antipsychotics leading to increased risk of side effects, such as neuroleptic malignant syndrome.[23]

Diagnostic evaluation

There are many types of encephalitis, each with differing presenting symptoms and biomarkers, and it is important to be able to minimize delays in both assessment and treatment.[24] If anti-NMDAR encephalitis is suspected, CSF studies should be obtained. CSF reveals lymphocytic pleocytosis or oligoclonal bands. CSF protein can be elevated or normal. Glucose is also normal. Laboratory tests are also available to test the CSF for anti-NMDAR antibodies for confirmation. Serum anti-NMDAR antibodies assays are not as sensitive as CSF studies. In one study, out of 250 patients that had anti-NMDAR antibodies in CSF, only 214 had antibodies in serum (sensitivity 100 versus 85.6%).[25] Brain MRI studies are normal or show transient fluid-attenuated inversion recovery (FLAIR) or contrast-enhancing abnormalities.[3] EEGs generally reveal nonspecific abnormalities such as diffuse slowing. They may reveal extreme versions of the 'delta brush pattern', which are transient patterns characterized by a slow delta wave with superimposed fast activity.[26] The extreme delta brush that appears to be unique to anti-NMDAR encephalitis may suggest a more prolonged illness, but it was only seen in 7 of 23 patients in a study by Schmitt and colleagues.[27]

Treatment and prognosis

Once NDMAR encephalitis is confirmed, patients should be screened for teratoma or germ cell tumors. Although the etiology of this disease was first described in the presence of ovarian tumors, it has been shown to only be the case in 38% of the patients overall and in 46% of women.[28] In some patients, tumor resection results in noticeable neurological

improvement in days or weeks.[29] Immunotherapy is the treatment with or without the presence of a tumor and involves trials of corticosteroids, intravenous immunoglobulins, or plasma exchange. One study suggested choosing concurrent IVIg (0.3 g/kg per day for 5 days) and methylprednisolone (1 g/day for 5 days) over plasma exchange.[3] If patients show minimal improvement, the next line of therapy is immunosuppression, using rituximab or cyclophosphamide, with continued immunosuppression (mycophenolate mofetil or azathioprine) for at least 1 year.[30] In our case, the patient showed the best results from rituximab therapy.

Early identification and treatment has been associated with better outcomes.[31] When identified and treated early, patients may have also shown less frequent hippocampal damage.[32] However, up to 25% of patients may have severe deficits or die, approximately 50% of patients achieve full recovery, and 46% of patients continue to have mild and severe deficits.[33] Dalmau and colleagues also reported that recovery of anti-NMDAR encephalitis develops as a multistage process that occurs in the reverse order of symptom appearance.[3] Even patients that make a full recovery may require years before reaching their previous level of functioning. Some studies suggest a 12–24% chance of relapse, which may occur many years after initial presentation and appears more likely if immunotherapy was not used.[34,35]

A new tool to predict outcomes in patients with anti-NMDAR encephalitis at 1 year from symptom onset has been gaining attention recently. Balu and colleagues used data from 382 patients to develop a 5-point prediction score, which they called the anti-NMDAR Encephalitis One-Year Functional Status (NEOS) score.[36] This score was developed using multivariate logistic regression modeling and is determined by five variables, each worth 1 point each. The variables include intensive care unit (ICU) admission, treatment delay of greater than 4 weeks, lack of clinical improvement within 4 weeks, abnormal MRI, and CSF white blood cell count greater than 20 μL. The score was strongly associated with the probability of poor functional status at 1 year (3% for 0 or 1 point to 69% for 4 or 5 points).[36] This may be of use to the provider when discussing prognosis with family members, whereas, in the past, these discussions may have been more nebulous. Of note, the authors found that of patients in their cohort with poor functional status at 1 year, 35% of them recovered to good functional status at 2 years. Using this score system in our own patient, we find that with no ICU admission, less than 4 weeks before starting immunotherapy, a lack of clinical improvement within 4 weeks, normal MRI, and CSF white blood cell count greater than 20 μL, her NEOS score would be a 2. This is associated with a good functional status at 1 year probability of nearly 90%. Our patient is currently getting approval to return to work, approximately 10 months after initiating treatment.

Conclusion

Anti-NMDAR encephalitis is a serious, potentially fatal condition that is often initially confused with schizophrenia spectrum

mental illness. As a relatively newly understood condition, it is increasingly diagnosed in inpatient settings as more providers become aware of its presentation. This review contributes to the growing body of literature by presenting a case presentation and the timeline of symptoms seen over the course of the illness. Key findings in the literature about anti-NMDAR encephalitis are highlighted to facilitate diagnostic consideration and treatment.

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