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Presentation of psychiatric symptoms in anti-NMDA receptor encephalitis

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ISP Project: Presentation of Psychiatric Symptoms in Anti-NMDA Receptor Encephalitis

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Introduction

The discovery of Anti-NMDA Receptor Encephalitis is quite recent, with the first characterization in 2007 by Dr. Josep Dalmau. He noted 12 women who developed acute psychiatric symptoms, seizures, memory deficits, autonomic dysfunction, and decreased level of consciousness often requiring ventilatory support; many cases were associated with the presence of a teratoma.¹ Presentation of Anti-NMDA Receptor Encephalitis is often associated with a predictable set of symptoms. The neuropsychiatric symptoms noted above are often preceded by viral-like symptoms including lethargy, headache, upper respiratory symptoms, nausea, diarrhea, myalgias, and fever. Psychiatric symptoms then follow about 1 week later, followed by neurologic changes. Given the benign nature of the viral-like symptoms, patients suffering from Anti-NMDA Receptor Encephalitis are often first seen by a psychiatrist. One case series analysis looking at 100 women with Anti-NMDA Receptor Encephalitis showed that 77% of patients presented initially presented with psychiatric symptoms, being first seen by a psychiatrist.¹

Presentation spanning among different ages, genders, and ethnicities can vary. Children under age 18 primarily initially present with neurologic symptoms. Women over age 18 have a uni or bilateral ovarian teratoma 50% of the time, while males with this disease rarely have an underlying tumor.² Though this disease mainly occurs in the young population, it can present in older population (age >45) as well. In the older population, there is a higher occurrence in males (45%) than in the younger population (12%).⁵ Black women have a higher likelihood of having an underlying teratoma compared to other ethnic groups.²

Given the recent discovery and prominent psychiatric nature of presentation of this disease, it is often misdiagnosed as a primary psychiatric disorder.³ A 2011 retrospective study described that Anti-NMDAR Encephalitis is much more common than originally thought. They found an incidence of 400 patients with this disease within 3 years, who represented about 1% of all ICU admissions between the ages of 18-35, suggesting that it is relatively common.² The diagnosis of Anti-NMDAR encephalitis is made by the detection of IgG antibodies to the GluN1 subunit of the NMDAR in serum or CSF.⁴ One study looking at 431 cases noted, “patients with a protracted clinical course or persistent symptoms might be seronegative and have persistently raised CSF titres until symptoms improve”.² This could potentially serve as a useful tool to demonstrate response to treatment; giving an objective marker in addition to symptomatic subjective improvement. Additionally they found that measurement of antibodies in the CSF is more specific than in the serum; no patients in the study were only serum positive.

Early detection, diagnosis, and treatment of this autoimmune encephalitis could reduce morbidity and mortality. A multi-institutional observational study published in 2014 showed predictors of good outcome included early treatment and lack of ICU admission.⁶ In addition, significant persistent cognitive impairments are more common and more severe when there is a delay to diagnosis and treatment.⁷ The ability to make the diagnosis as early as possible in order to treat is highlighted with these results.

After diagnosis, treatment includes immunotherapy and tumor removal if applicable. First line treatment typically includes corticosteroids, intravenous immunoglobulins or plasma exchange while second line therapy is rituximab or cyclophosphamide.³ The aforementioned multi-institutional observational study noted, “472 (94%) underwent first-line immunotherapy or tumor removal, resulting in improvement within four weeks in 251 (53%). Of 221 patients who failed first-line therapy, 125 (57%) received second-line immunotherapy resulting in better outcome than those who did not (OR 2.69, CI 1.24-5.80, p=0.012). During the first 24 months, 394/501 reached good outcome (mRS 0-2; median 6 months), and 30 died. At 24 month follow-up 204/252 (81%) had good outcome. Outcomes continued to improve for up to 18 months after symptom onset”.⁶ While some patients can recover without sequelae, others (85%) have some behavioral or cognitive sequelae.⁸ This includes “deficits in executive function, impulsivity, behavioral disinhibition, and abnormal sleep patterns”.⁸ Deficits in memory secondary to this disease is common; amnesia during the acute course of the disease is seen. Many patients do not recall their neuropsychiatric symptoms in the height of their disease. Furthermore, issues with memory can persist after recovery.⁸

In reviewing the current literature of the presentation of Anti-NMDA Receptor Encephalitis in the field of psychiatry, we hope to detail the psychiatric signs and symptoms in order to: standardize the threshold of when to suspect this disease upon presentation of psychosis, when and who to refer the patient to upon suspicion, and how the field of psychiatry can contribute to minimizing the morbidity and mortality of this disease.

Methods

I extensively reviewed 15 case reports (total of 18 patients) of diagnosed cases of Anti-NMDA Receptor Encephalitis. Case reports were chosen for this review if they documented psychiatric symptoms in detail. Psychiatric symptoms were defined as anxiety, mood dysregulation, psychosis, behavioral changes, suicidal ideation/attempt, and insomnia. Though catatonia can be categorized as neuropsychiatric, it was included in this paper as catatonia is a common presenting syndrome in psychiatric institutions.

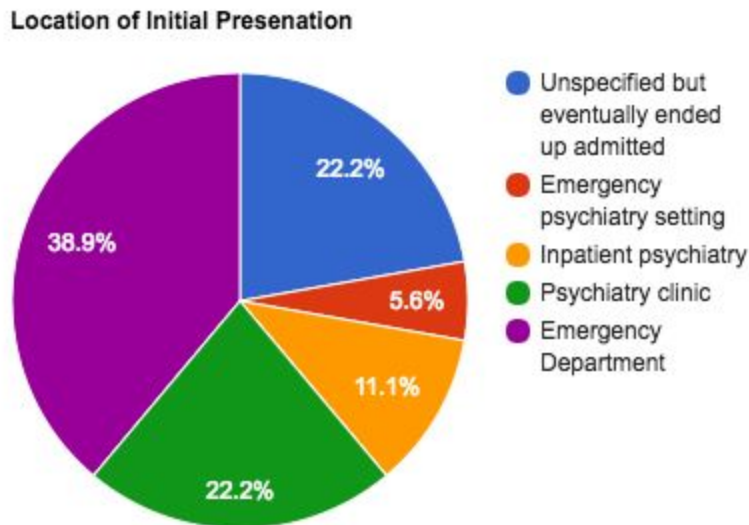
General Presentation

Joseph Dalmau (cite) has outlined characteristic features of anti-NMDAR Encephalitis listed below.⁹ Typically, the disease presents in stages: early, middle, and late. In the early stages of the disease, the patient has flu-like symptoms (headaches, fever, nausea) about 1-2 weeks before acute presentation. In the middle stage, psychiatric symptoms predominate, and in the late stage, autonomic and neurologic signs and symptoms occur.⁹

Characteristic features of the disease:

- A non-specific prodrome: in one series of 100 individuals with encephalitis, 86% had headache, low-grade fever or a viral-like illness (headaches, respiratory or gastrointestinal symptoms) in the weeks prior to acute presentation.¹⁰
- Prominent psychiatric symptoms: agitation, bizarre and disinhibited behavior, delusions, and auditory and visual hallucinations.¹⁰
- Cognitive dysfunction: short-term memory loss and concentration difficulties.¹⁰
- Motor dysfunction: epileptic seizures, dyskinetic movements, including orofacial dyskinesias (grimacing or lip smacking).¹⁰ These abnormal movements, especially orofacial dyskinesia, may present at an early stage and can often provide a clue to the diagnosis.
- Autonomic instability: cardiac dysrhythmia, hypertension, hypersalivation.¹⁰
- Association with known pathology: an association with ovarian pathology has also been identified. Dalmau and colleagues reported that in 59% of cases, the diagnosis was associated with ovarian tumors, primarily ovarian teratomas.¹⁰ As noted above, children under the age of 18 are unlikely to have an associated tumor.¹⁰

Location of Initial Presentation



Acute Onset of Psychiatric Symptoms

Patient	Time course to Psychiatric symptoms
1	Acute onset of altered mental status and seizures after stabilization (no time course noted), started exhibiting hallucinations and bizarre thoughts. ¹²
2	10 days before admission: acute onset of intermittent dizziness and transient loss of consciousness. These symptoms occurred more frequently and then she displayed odd behavior. ¹³
3	6 months before admission: anxiety, felt tense, and fatigue. She had a stressful job, worked alone in the night shifts, and felt exhausted and afraid of going to work. 2 weeks prior to admission, the patient had a fever up to 39.1°C for several days, complained of headaches and tingling in the right temporal region. 1 week before admission she complained of tension, anxiousness, insomnia for five days, auditory and visual hallucinations, disorganized behavior, mood lability. ¹⁴
4	Sudden onset of generalized tonic-clonic seizures that were preceded by recent memory loss, visual hallucinations, and abnormal behavior (no time course noted). ¹⁵

5	Abrupt change in behavior, deteriorating over a duration of three weeks. ¹⁶
6	Acute onset of posturing and involuntary movements of left toes, reduced arm swing and generalized slow movements, progressing to fearful and preoccupied attitude, crying spells and hallucinations accompanied by functional deterioration. ¹⁷
7	<p>4 day history of stuttering episode with concentration difficulties, then had a 2 day history of subtle chorei form movements (perioral, hands), memory impairment, decreased mobility, lack of right hand grip, paraesthesia of the left hemibody, dysarthria, and tinnitus.</p> <p>In the following days, orofacial dyskinesia worsened and developed a swallowing disorder, speech deterioration, vomiting, wide pupils and facial flush, right upper limb weakness associated with paranoid delusions, as well as auditory and olfactory hallucinations.¹⁸</p>
8	<p>Developed insomnia 15 days before admission.</p> <p>1 day before the admission experienced a feeling of traveling through space and time, and could not recognize her parents or distinguish colors. Also displayed abnormal and incomprehensible behavior and speech such as intermittent restlessness, excitement, and loud yelling, and endorsed suicidal and homicidal ideations.¹⁹</p>
9	Acute onset of seizures in the context of high levels of generalized anxiety, social withdrawal, obsessive thoughts, reported having thoughts inserted into her mind, memory impairment, and described some strange mental and somatic phenomena: she felt her thoughts were ‘stronger and clearer’, she was irritable and erratic, she said one eye felt cold, and she experienced one foot as extraordinarily heavy. ²⁰
10	5-day history of sleeplessness, agitation, and auditory hallucinations. ²¹
11	Insomnia, agitation, irritability and fear of death which began 3 months after a normal delivery. Time course not noted. ²²
12	Retrograde amnesia of events prior to her presentation or how she came to hospital. Presented with hallucinations, generalized fear, paranoia, agitation, and disorganized behavior and behavior. ²³
13	Fever and night sweats followed by a two week course of confusion, bizarre behavior, depression and suicidal ideation. ²⁴
14	Depression with suicide attempt, abdominal pain, nausea, vomiting, and intermittent fevers (No time course noted). Unintentional 20-lb weight loss in 2 months. ²⁴
15	16 days before presentation: fever and headache

	11 days before presentation: emotional changes, anxiety, obsessive thoughts, inability to complete complex motor tasks ¹¹
16	3 weeks before presentation: general fatigue 18 days before presentation: involved in car accident, since then developed depression and became obsessive about intolerable loneliness 15 days before presentation: complained of smelling a foul smell, forgetfulness, difficulty concentrating, family noted strange behaviors ¹¹
17	13 days before admission: common cold 6 days before admission: headache and anxiety 5 days before admission: confusion, inability to complete complex motor tasks, fear, odd behaviors 2 days before admission: became incoherent, odd behaviors continued 1 day before admission: agitation, screaming “I want to die” ¹¹
18	8 days before admission: fever and emesis 3 days before admission: forgetfulness, difficulty using a cellular phone, gradual loss of self-awareness, unintelligible and incoherent speech, odd behavior ¹¹

Hallucinations

67% (n=12) of cases reported presence of hallucinations at some point during the course of the disease. Visual and auditory hallucinations were most common, while there was only one case of reported olfactory hallucinations. All cases documented the presence of hallucinations within the first two weeks of acute symptom presentation. Most hallucinations terminated after months of immunotherapy treatment, but 2 cases reported persistence of hallucinations even after months of immunotherapy and clinical improvement.

Insomnia

11% of cases (n=2) reported severe insomnia as a significant symptom at various points in their illness. Patient 7 had severe insomnia and nightmares about 8 months after acute symptom presentation. This was after several months in an unresponsive state in the ICU and continuous immunotherapy. Once her neurological state had improved, her psychiatric symptoms presented.¹⁸ Patient 8 had insomnia starting 2 weeks before her acute symptoms began. Insomnia was treated with irregular administrations of trazodone, clozapine, and clonazepam. The effect of medications was not documented.¹⁹

Fear/Sense of doom

61% of cases (n=11) demonstrated generalized or specific fear and/or a sense of doom. 4 of the 11 patients expressed fear secondary to delusions. The remainder of the patients had a generalized sense of fear not secondary to any reported delusion or hallucination.

The sense of fear and doom secondary to delusions or hallucinations had varied presentations. Patient 5 was an 11 year old girl with a unique presentation. The patient's acute symptoms were precipitated by her witnessing her father's post-accident amputation of his right hand. She did not witness the accident but she did see the bloody bandaged stump. About a week after the onset of her symptoms (crying spells, saying that her left hand was not working, dragging her left foot, biting of her fingers and mucosa of her cheeks, restlessness) she was described as being fearful because she felt that a ghost was coming after her and trying to harm her.¹⁶ Patient 8 was a 25 year old female who refused voluntary hospitalization because she feared that she would die in the hospital.¹⁹ Patient 11 was a 25 year old female who developed a fear of death 3 months postpartum. She reported seeing demons in her dream and believed that they were in her body and would kill her.²²

Some patients felt fear independent of a reported delusion or hallucination. Patient 10 was a 32 year old female reported extreme anxiety with a feeling of imminent doom.²¹ Patient 12 was a 27 year old female who appeared easily frightened by noises and other people at the time of symptom presentation. Because of her fear, she repeatedly attempted to leave the hospital.²³

Catatonic symptoms

61% of cases (n=11) presented with catatonic symptoms at some point during their illness. Though retarded catatonic symptoms were more prevalent, excited catatonic symptoms were present as well.

Behavioral issues (5/18)

28% (n=5) of cases reported significant behavioral issues, many times leaving the patient a danger to self or others. Patient 7 was a 22 year old female who displayed psychomotor agitation with overt aggressive behavior including throwing objects around the room, slapping her hands on the bed, trying to pull out the feeding tube, which the treatment team found very difficult to control. The patient sometimes required sedation and physical restraint for short periods.¹⁸ Patient 10 was a 32 year old female who due to frequent fluctuations in mental state, seclusion and restraint were required to ensure the patient's safety, despite treatment with olanzapine at 20 mg/day.²¹

Strange behavior

61% (n=11) demonstrated strange behavior during their illness. One paper noted that two cases had bizarre and inappropriate smiling in the setting of being akinetic, and unresponsive to verbal commands while keeping their eyes open. Patient 10 was a 16 year old girl who stared menacingly at her family that they deemed uncharacteristic.²¹

Suicidal ideation

33% (n=6) of patients expressed suicidal ideation at some point during their illness. 2 out of these 6 patients had unsuccessful suicide attempts. Patient 7 was a 22 year old female who demonstrated depressive symptoms and suicidal ideation which lead to an attempt for self-harm with a knife and strangulation with a cable. The patient requested that the care team “let her die”¹⁸ and requested to be killed.¹⁸ Patient 11 was a 25 year old female who complained of seeing demons in her dreams and believed that they were inside her body and would kill her. Because of these dreams and delusions, the patient attempted to strangle herself and jump out of a window. She was restrained to her bed almost 24 hours a day to prevent self-harm.²²

Varied response to antipsychotics

Among the 18 patients studied, 11 were prescribed antipsychotics for psychiatric symptoms. Response to antipsychotics was clinically variable. Clinical symptoms worsened for 6 patients, there was no effect on 4, and one had an improvement in psychiatric symptoms but motor symptoms worsened.

Worsening in clinical course after initiation of antipsychotics ranged from onset of catatonic symptoms to worsening neurologic and autonomic symptoms. Patient 3 was a 34 year old woman who expressed paranoia, the feeling of depersonalization/derealization, anxiety, and hallucinations was initially treated with risperidone, fluvoxamine, diazepam, and flurazepam. Her clinical response was variable; there were periods of improved mental condition but she periodically became disorganized, confused, anxious and paranoid. After about a week of treatment, she became aggressive toward staff and occasionally became somnolent or stuporous. Prior treatment was stopped and she was started on a low dose of clozapine; sulpiride and haloperidol were eventually added, but her clinical presentation was still variable. Clozapine was switched to olanzapine, but the patient became negativistic and mute. All antipsychotic doses were tapered and discontinued, but the patient was mainly somnolent and mute.¹⁴ Patient 8 had a previous diagnosis of schizophrenia. Naturally, a relapse of schizophrenia was first considered, and ziprasidone 120 mg/day along with as needed haloperidol or olanzapine were administered to control symptoms of aggression after admission. After two weeks of ineffective antipsychotic treatment, modified electroconvulsive therapy was initiated. After one session, the patient’s condition deteriorated with “fluctuations in consciousness, autonomic symptoms, carphology, orofacial dyskinesic movements, urinary incontinence, visual hallucinations, amnesia, and intermittent hypermyotonia”.¹⁹ Patient 13 received a 6 day trial of olanzapine but he developed

muscle stiffness, drooling, catatonic posturing, and vomiting. Olanzapine was stopped and a trial of lorazepam 1-2 mg every two hours improved those symptoms.²⁴

One patient developed neuroleptic malignant syndrome after antipsychotic treatment. Patient 11 was treated with risperidone and a benzodiazepine for delusions, hallucinations, and psychomotor excitement. One week later, she developed “confusion, cogwheel rigidity, fever, increase in serum creatine phosphokinase levels, and leukocytosis”.¹¹ She was diagnosed with neuroleptic malignant syndrome and antipsychotics were discontinued. Two weeks after successful treatment of neuroleptic malignant syndrome, the patient was treated with aripiprazole and electroconvulsive therapy for further psychiatric treatment; she then had a generalized seizure. Since her delusions and hallucinations persisted and she was a danger to herself, she was restrained 24 hours a day.²²

For 4 patients, treatment with psychotropic drugs was ineffective. Patient 14 was initiated on desvenlafaxine 50 mg XR daily for depression and lorazepam 1 mg as needed for anxiety. Despite treatment with sertraline, ziprasidone, quetiapine, olanzapine and valproic acid, she continued to deteriorate clinically. She continued to engage in self-harm behaviors and had hallucinations and delusions. Additionally, she started to display catatonic symptoms.²⁴

The effectiveness of antipsychotics for one patient presented a mixed picture. Patient 6 was treated with antipsychotics and electroconvulsive therapy for “fearful and preoccupied attitude, crying spells and hallucinatory behavior in the context of posturing and involuntary movements of left toes, reduced arm swing and generalized slow movements”.¹⁷ These treatments improved her psychotic symptoms but worsened her motor symptoms.

Discussion

Solely psychiatric presentations without development of neurological symptoms in anti-NMDAR encephalitis are rare but do occur. An observational study out of University of Pennsylvania and Barcelona showed that 23/571 patients (4%) developed isolated psychiatric episodes, 5 at disease onset and 18 during relapses. They could have been easily misdiagnosed as a primary psychiatric disorder but they were identified because they had abnormal brain MRI findings, which led to a more comprehensive investigation including CSF analysis. Of note, isolated psychiatric presentation is associated lower antibody titer.¹⁴ More commonly in anti-NMDAR encephalitis, a patient’s psychiatric symptoms are embedded in multiple neurologic and autonomic signs and symptoms.

Neurologic and/or autonomic abnormalities surrounding psychiatric symptoms should trigger a workup for this disease. Patient 3’s case study discussed the process of coming to the diagnosis. After the patient presented with psychotic symptoms, she became somnolent and stuporous.

Because of these neurologic symptoms that are typically absent in a primary psychotic disorder, encephalitis was put on the differential and the diagnosis was quickly made.¹⁴ Patient 5 had an interesting history because her psychosis presented after a traumatic event, and her psychosis incorporated the trauma in the form of nihilistic ideas. Because of the timing of events, the diagnosis of acute and transient psychotic disorders was made. However, the treatment team noted “the appearance of extrapyramidal manifestations in psychiatry ward initially thought to be catatonic symptoms in hinted us to go for relevant investigation that made the diagnosis clear.”¹⁶ Similarly, patient 10 presented with an abrupt onset of hallucinations and confusion and then eventually had fluctuations in mental status and seizures. These neurologic signs led the staff to put anti-NMDAR encephalitis at the top of the differential.²¹

Acute onset of psychiatric symptoms with any of the other signs listed above (neurological signs and cognitive decline, autonomic instability) should trigger serum testing for anti-NMDAR antibodies. In my review, not all cases laid out a specific time course, but from the cases that did list a time course, the longest duration of onset of psychiatric symptoms was 3 weeks. The case report for patient 7 discussed, “in our patient, the rapid progression of mental fatigue and concentration difficulties to psychotic symptoms and auditory and olfactory hallucinations together with neurological impairment (delirium, abnormal movements, speech deterioration) were highly suggestive of an organic cause, rather than a primary psychiatric disorder”.¹⁸

The psychiatric symptoms documented in the cases studied were: hallucinations, insomnia, catatonic symptoms, fear/sense of doom, behavioral issues, strange behavior, suicidal ideation, suicide attempt, and varied response to antipsychotics. Of those listed, the most notable that are not typical of a primary psychiatric disorder were varied response to antipsychotics and an intense fear/sense of doom.

The ineffectiveness of antipsychotics to improve psychiatric symptoms and sometimes worsening clinical symptoms were quite striking. Of the 18 patients studied, **only** one patient had psychiatric improvement after the administration of an antipsychotic, but this was at the expense of worsening motor symptoms. The only effective treatment for psychotic symptoms documented in the cases studied was immunotherapy; treatment of the underlying disease. Patient 8 was an informative case because she had a diagnosis of schizophrenia 7 years before her diagnosis of anti-NMDAR encephalitis. She had symptoms of with social withdrawal, delusions of persecution and reference, and auditory hallucinations. The onset was gradual and progressive. The medical team was unable to clarify if it was truly schizophrenia before her most recent presentation, or if her previous psychotic symptoms were due to anti-NMDAR encephalitis relapses. However, treatment with antipsychotics was helpful in the past for controlling her psychotic symptoms. In her most recent admission which led to the diagnosis of anti-NMDAR encephalitis, antipsychotics were not helpful in relieving psychiatric symptoms

thus modified electroconvulsive therapy (MECT) was administered. Her condition deteriorated and she was suspected to have neuroleptic malignant syndrome after one MECT session.¹⁹ It is unclear if the suspected NMS was due to treatment of antipsychotic medication, MECT, a natural progression of anti-NMDAR encephalitis, or a combination of those factors. 54% of cases in my study that were treated with antipsychotics had a worsening clinical picture and 36% had no positive response to antipsychotics. This high rate of varied response indicates that there should be an increased suspicion for anti-NMDAR encephalitis if the patient is in the correct demographic (young female or male) and is unresponsive to antipsychotics or if there is an exacerbation of neurologic symptoms. This also indicates that clinicians should use caution when considering psychiatric treatment with antipsychotics and/or ECT in anti-NMDAR encephalitis.

In a retrospective study of neuroleptic intolerance in patients with anti-NMDAR encephalitis, 21 out of 45 patients (47%) who were admitted to an inpatient psychiatric unit were “transferred to a medical unit for a suspicion of antipsychotic intolerance characterized by high temperature, muscle rigidity, mutism or coma, and biological results suggesting rhabdomyolysis”.²⁵ 36 total patients received antipsychotics, and 58% of those developed neuroleptic malignant syndrome. Among all of the 21 patients, antipsychotic drugs were administered hours to days before the presentation of high temperature, which the study noted suggested neuroleptic malignant syndrome. No difference was seen between the tolerance of first and second generation antipsychotics. This study also found that patients who received antipsychotic drugs developed fever more frequently than patients who did not (19 of 36 patients [53%] vs 11 of 75 patients [15%]).²⁵ This sensitivity to neuroleptics in patients with the disease further notes the importance of using caution in prescribing antipsychotics for patients with anti-NMDAR encephalitis.

One small German study suggested routine antibody testing in patients with first presentation of psychosis might be worthwhile.²⁶ Serum was tested from a cohort of 46 patients at first presentation of psychosis. 6.5% (n=4) of patients had serum anti-NMDAR antibodies or antibodies to components of potassium channel complexes (VGKCs, associated with potassium channel antibody-associated limbic encephalitis). Those patients with positive results were retrospectively interviewed and investigated. All antibody positive cases fulfilled DSM IV criteria for schizophrenia. 3 out of the 4 patients were positive for anti-NMDAR antibodies. 2 out of the 3 patients were antibody negative by 3 years without immunotherapy. The third out of the 3 anti-NMDAR positive patients received immunotherapy after being partially responsive and then relapsing during 4 months of treatment with antipsychotics. He improved clinically and functionally after a 7 month follow up on no antipsychotic medication. None of the 3 anti-NMDAR antibody positive patients showed neurological deficits in the course of their disease. None of the chronic schizophrenia controls case series had NMDAR antibodies, but this likely because NMDAR and VGKC antibodies spontaneously drop over time.²⁶ This data suggests a critical window early in the disease for detection and treatment. It also suggests that a

small portion of patients who have a diagnosis of schizophrenia or any other psychotic disorder could have an organic cause of their symptoms rather than a primary cause. The implication on a larger scale is misdiagnosis and treatment of these patients. A larger study looking at the cost/benefits of testing serum for anti-NMDAR antibodies in first presentation psychosis would provide us with a better understanding of if this is efficacious in providing better treatment.

Solely psychiatric presentations without development of neurological symptoms in anti-NMDAR encephalitis are rare but do occur. An observational study out of University of Pennsylvania and Barcelona showed that 23/571 patients (4%) developed isolated psychiatric episodes, 5 at disease onset and 18 during relapses.¹⁴ They could have been easily misdiagnosed as a primary psychiatric disorder but they were identified because they had abnormal brain MRI findings, which lead to a more comprehensive investigation including CSF analysis. Of note, isolated psychiatric presentation is associated lower antibody titer.¹⁴ More commonly, a patient's psychiatric symptoms are embedded in multiple neurologic and autonomic signs and symptoms.

It is imperative to put anti-NMDAR encephalitis on the differential when a young woman or man presents with acute onset psychosis in addition to neurologic or autonomic signs and symptoms. The time to treat should be minimized in this disease, as missing it could be fatal. Additionally, there is a need for a large study examining the effectiveness of a systematic screen for anti-NMDAR antibodies in first episode psychosis in order to capture the true prevalence of this disease. This will help differentiate organic causes of psychosis and primary psychotic disorders, consequently informing varying diagnoses, treatment, and prognosis.

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