# Chronic Schizophrenia Later Diagnosed with Anti-NMDA Receptor Encephalitis: Case Report and Review of the Literature

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## Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder caused by Ig G auto-Ab directed against the NR1 subunit of the NMDA glutamate receptor (1). The binding of IgG antibodies induces a reversible internalization of the receptors (2). Decreased activity of NMDA receptors is known to be associated with both the positive and negative symptoms of schizophrenia (3). The early stages of the illness are characterized by psychiatric symptoms. As the illness progresses, neurologic symptoms emerge, and in the most severe stage of the illness, autonomic instability and respiratory collapse can occur. During the stage of the illness when psychiatric symptoms predominate in the presentation, anti-NMDAR encephalitis may be misattributed to a primary psychiatric disorder. Most of the literature thus far has described such misdiagnoses in patients with first-episode psychosis (4-6). There appear to be no documented cases of chronic schizophrenia that were definitely later reclassified as anti-NMDAR encephalitis. Here we report what we believe to be the first reported case of misdiagnosis of anti-NMDAR encephalitis as chronic schizophrenia.

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## Case Report

Ms. A is a 25-year-old female with a history of schizophrenia diagnosed four years prior and multiple subsequent psychiatric hospitalizations, who was evaluated in our medical emergency department, transferred from an outside psychiatric inpatient unit, for investigation of altered mental status (AMS), unilateral facial stiffness, and cough. Psychiatry was consulted. She was noted to be disorganized and agitated and had unilateral facial twitching. Her medications included lithium, divalproex sodium, clozapine, and the long-acting injectable formulation of paliperidone palmitate (last dose two weeks prior). An infectious workup was unremarkable. Intravenous lorazepam, given as empiric treatment for suspected catatonia, rendered no benefit. She was discharged back to the inpatient psychiatric facility. One week later she re-presented to this hospital with difficulty breathing and frothing at the mouth. She was noted to be conscious and awake, intermittently physically agitated, but nonverbal and not following commands or withdrawing from painful stimuli. Rhythmic orofacial grimacing was prominent with intermittent unilateral lead-pipe rigidity. She had autonomic instability with variable heart rate and blood pressures. Creatine kinase (CK) was initially elevated to 972 and peaked at 1,797. She was admitted to the medical intensive care unit (ICU) with neurology and psychiatry consulting.

The differential diagnosis included delirium, severe antipsychotic-mediated extrapyramidal symptoms and neuroleptic malignant syndrome (NMS). Supportive care and amantadine were started for suspected NMS. Lumbar puncture (LP) showed mild elevation in the cerebrospinal fluid (CSF) white blood cell count (13/uL), with 98% lymphocyte predominance and normal protein and glucose. In

subsequent days, the patient continued to have autonomic instability, with even wider-ranging pulse and blood pressures, fever peaking at 38.3 degrees Celsius, and oxygen desaturation to 71% prompting intubation and sedation.

One week later, results from the autoimmune panel showed elevated NMDA Ab IgG in the serum (1:640) and CSF (1:160). The diagnosis was revised to anti-NMDAR encephalitis. First-line treatment with pulse steroids, plasmapheresis, and intravenous immunoglobulin (IVIG) was initiated. Her serum NMDA IgG Ab titers improved to 1:20 with first-line treatment, and there was improvement in her autonomic instability. Magnetic resonance imaging (MRI) and transvaginal ultrasound of the pelvis did not demonstrate an occult tumor.

Approximately one month after admission and two weeks after her last IVIG treatment, she appeared more paranoid and psychotic. She was initiated on haloperidol and divalproex sodium to treat her psychiatric symptoms, with haloperidol, lorazepam and diphenhydramine as needed for paranoia and physically aggressive behavior. She was subsequently transferred to the inpatient psychiatric unit for further behavioral stabilization. There, medications were adjusted to the following regimen: divalproex sodium 2,500 mg/day (level of 89.5 ug/mL), clozapine 450 mg/day (level of 766 ng/mL), lithium 1,500 mg/day (level of 0.5 mmol/L), and chlorpromazine as needed for acute agitation. Episodes of behavioral disruption became less frequent and severe, although she remained paranoid. Repeat serum NMDA IgG Ab titer two months after immunotherapy treatment increased to 1:80 from a previous titer of 1:20. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was administered to assess attention, visuospatial, language, and memory abilities. The patient's performance suggested significant deficits in attention, language, learning, memory, and visuoconstruction, noted to be in excess of what would be expected in a primary or mood-related psychosis. The Montreal Cognitive Assessment (MoCA) averaged 12 out of 30 on three administrations over a one-month period, with major deficits in all domains. Her motor exam was notable for dysdiadochokinesias and myoclonus. Divalproex sodium was stopped after she developed mild hyperammonemia, though her motor exam remained unchanged.

Collateral information obtained during psychiatric hospitalization was particularly useful in helping to refine her diagnosis. Her family reported that Ms. A was an adopted child who was diagnosed with ADHD at age 5, with her first psychiatric admission at age 11 for behavioral problems. However, up until age 21 she was without psychotic symptoms, working and living independently. At that point, she presented twice to a medical emergency department with symptoms suggestive of a viral syndrome, such as myalgia, diarrhea, and fatigue. At that time she was noted to be vaguely paranoid and acting oddly with latent and sluggish speech. The following month, she was admitted to a psychiatric hospital for unspecified psychosis. While hospitalized, four months after her initial presentation with viral symptoms, she developed tachycardia and fever, with severe agitation, requiring a transfer to the medical ICU. Her CK was mildly elevated at that time to 4,000. Her electroencephalogram (EEG) showed no epileptic activity, and brain MRI was normal. An LP was performed, interpreted as normal, though with four lymphocytes in the CSF. A paraneoplastic panel was recommended, but it is unclear whether it was ever performed. Transvaginal ultrasound was negative for evidence of ovarian tumor. She underwent a course of electroconvulsive therapy, which was terminated after eleven sessions due to vital sign abnormalities, such as tachycardia and fever. Ultimately, clozapine was initiated after failed trials of olanzapine and divalproex sodium. She was still noted to be disorganized with difficulties in speech. She was subsequently transferred to a state psychiatric hospital for ongoing treatment, where she had a prolonged 336-day admission, notable for significant episodes of agitation, poor response to antipsychotic medications including clozapine, and residual myoclonic jerks. She was discharged on multiple psychoactive medications, including clozapine, lithium, paliperidone palmitate, and divalproex sodium.

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In light of the additional collateral information suggesting the course of her symptoms followed the typical progression of anti-NMDAR encephalitis and given a plateau in her response to first-line treatment, the decision was made to pursue second-line immunotherapy. She received concurrent standard second-line treatment with a total of two cyclophosphamide (750 mg per square meter) and four rituximab (375 mg per square meter) treatments. Cyclophosphamide was discontinued as her episodes of agitation improved dramatically following her first treatment with cyclophosphamide, and consistent improvement in her condition was noted for the next month with no further episodes of agitation. She was more socially engaged, with brighter eye contact and more reactive affect. Her memory subjectively improved, and a repeat MoCA improved to 21

out of 30 within four weeks of treatment with cyclophosphamide and rituximab. Her clozapine dose was decreased to 200 mg daily, and lithium dose was decreased to 1,200 mg daily as her psychiatric symptoms greatly improved with second-line immunotherapy. She was discharged home with outpatient traumatic brain injury rehab, outpatient psychiatric care with plan to slowly taper clozapine and lithium, and outpatient neurology follow-up to evaluate the need for further treatment for anti-NMDAR encephalitis.

## Discussion

Anti-NMDAR encephalitis was first described in 2007 by Dalmau et al. who identified twelve patients with encephalitis and neuropsychiatric symptoms found to have serum or CSF antibodies to the NMDA receptor (7). In a subsequent case series, they reported 100 patients with encephalitis and NR1-NR2 antibodies, 91 of which were women. Interestingly, all patients presented with psychiatric symptoms or memory problems. Many were found to have seizures, decreased consciousness/unresponsiveness, dyskinesias, autonomic instability, and hypoventilation. Fifty-nine percent had tumors, most commonly ovarian teratomas (1). There are no current estimates of prevalence rates, but over 500 cases have been reported (3). There appears to be a progression of clinical signs and symptoms commonly beginning with a non-specific prodromal period, including headache, low grade fever or viral-like illness in the weeks prior to clinical presentation, commonly followed by psychiatric and cognitive manifestations. Psychiatric symptoms include anxiety, insomnia, agitation, delusions, and hallucinations. Cognitive features may include memory deficits, concentration difficulties, and language dysfunction. In the late phase of the illness, motor and neurological symptoms (e.g., seizures, aphasia, impaired consciousness, and dyskinetic movements, including orofacial dyskinesias), autonomic instability and hypoventilation occur, often necessitating intensive care management. These advanced presentations usually occur on the order of weeks to months after the first onset of symptoms (2, 3, 8-10).

Immunoglobulin (Ig) G antibodies to the NMDA receptor subunit may be detected in the serum, but if anti-NMDAR encephalitis is suspected, an LP to detect antibodies in the CSF should be performed, as positive CSF studies can occur even in the absence of serum antibodies. Antibody titers are correlated with clinical symptoms and may be used as a marker for treatment response. CSF in 80% of cases shows mild lymphocytic pleocytosis, normal or mildly increased protein, and CSF-specific oligoclonal bands. Brain MRI is normal in 70% of cases. EEG can show non-specific slowing. Steroids, IVIG, plasma exchange, and tumor removal (when present) are the first-line treatment. Rituximab and cyclophosphamide have been used as second line (3). Second-line treatment is indicated in patients with a partial response to first-line treatment and no evidence of a teratoma (11).

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Cases of anti-NMDAR encephalitis that present in the stage of the illness predominated by psychiatric symptoms—in the absence of other neurological signs or symptoms—may be misattributed to a primary psychiatric disorder, such as schizophrenia. Indeed, up to 5–10% of cases of first-onset psychosis may, in fact, be a manifestation of anti-NMDAR encephalitis (3). It is less clear whether a psychotic illness present for months to years may ever represent anti-NMDAR encephalitis. Zandi et al. observed anti-NMDAR serum antibodies in approximately 6% (3 of 46) of patients with first-onset schizophrenia, but no patients with chronic schizophrenia (4). Steiner et al. reported 10% of 121 patients, with both recently diagnosed and chronic schizophrenia, had anti-NMDAR antibodies. This included anti-NMDAR antibodies of the IgA, IgG, and IgM classes. After excluding those patients lacking IgG anti-NMDAR antibodies, only two patients initially classified as having schizophrenia were appropriately reclassified as having anti-NMDAR encephalitis. Of note, both of these patients were presenting for first-episode psychosis (5). Tsutsui et al. found positive anti-NMDAR antibodies in 4 of 51 patients with diagnoses of schizophrenia or schizoaffective disorder in the absence of any clinical signs of encephalitis; however, it is unclear whether these positive antibodies were of the IgG class, or if the positive NMDAR antibodies played a causative role in the psychiatric symptoms (12). In a recent case, a patient with a seven-year diagnosis of schizophrenia was later identified to also have anti-NMDAR encephalitis. The relationship of the anti-NMDAR encephalitis diagnosis and the patient's longstanding schizophrenia diagnosis was unclear since the patient did not experience any symptoms specific to anti-NMDAR encephalitis in the preceding seven years she carried the diagnosis of schizophrenia. Therefore, it was not established in this case that there was a misdiagnosis of chronic schizophrenia (13).

Ms. A's symptoms fit the typical time course of anti-NMDAR encephalitis, from the onset of a viral prodromal period prior to her first psychiatric presentation, with progression to critical medical illness within a few months. Her

**Table1 Comparison between Schizophrenia and Anti-NMDAR Encephalitis***

| Schizophrenia | Anti-NMDAR Encephalitis |
|---|---|
| Sub-acute onset with concurrent decline in function | Rapid onset over ~2 weeks, often following viral illness |
| *Positive symptoms:* hallucinations, delusions, disorganized speech and behavior; *Negative symptoms*: flat affect, poverty of speech; *Cognitive impairment* in attention, memory and executive function | *Psychiatric:* agitation, hallucinations, delusions; *Cognitive*: memory, concentration, and language dysfunction; *Neurological:* seizures, aphasia, and dyskinetic movements; *Autonomic instability* |
| Level of consciousness not affected | Change in level of consciousness |
| Stable symptoms until treated | Symptoms can fluctuate in severity |
| Subtle impairments of sensory integration, motor coordination, and sequencing, antipsychotic-mediated extrapyramidal symptoms and tardive dyskinesia, catatonia | Dyskinetic movements, including orofacial dyskinesias, choreoathetoid movements, dystonia, rigidity |
| No autonomic symptoms | Autonomic symptoms including tachycardia, fluctuating blood pressure |

* Similarities and differences between schizophrenia and anti-NMDAR encephalitis in onset of presentation, symptoms, and effect on consciousness, motor function, and autonomic stability.

autonomic instability at this time remitted spontaneously; however, she had poor response to antipsychotic medications, and continued to have psychiatric and neurological symptoms, such as myoclonic jerks, for the next four years. Ultimately, the return of autonomic instability with hypoventilation requiring intensive level of care prompted the further workup and diagnosis of anti-NMDAR encephalitis. This case is worthy of recognition, as anti-NMDAR encephalitis can explain both this patient's chronic psychotic symptoms and acute presentation.

## Conclusions

Anti-NMDAR encephalitis should be considered in patients with psychosis who present with AMS, abnormal movements, and a poor response to conventional antipsychotic treatments, even in those patients who have a long-standing diagnosis of schizophrenia (see Table 1). A prior diagnosis of schizophrenia should not be taken as a given in patients who are subsequently diagnosed with anti-NMDAR encephalitis, and instead requires a careful review of the history of the patient's progression of symptoms. In such cases, collaboration among mental healthcare providers, neurologists and other medical consultants can help facilitate diagnosis and life-saving treatment.

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