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Management of psychiatric symptoms in anti-NMDAR encephalitis: a case series, literature review and future directions

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ABSTRACT

Anti-NMDA receptor (NMDAR) encephalitis, formally recognized in 2007, has been increasingly identified as a significant cause of autoimmune and paraneoplastic encephalitis. Approximately 80% of the patients are females. The characteristic syndrome evolves in several stages, with approximately 70% of the patients presenting with a prodromal phase of fever, malaise, headache, upper respiratory tract symptoms, nausea, vomiting and diarrhoea. Next, typically within two weeks, patients develop psychiatric symptoms including insomnia, delusions, hyperreligiosity, paranoia, hallucinations, apathy and depression. Catatonic symptoms, seizures, abnormal movements, autonomic instability, memory deficits may also develop during the course of the disease. Presence of antibodies against the GluN1 subunit of the NMDAR in the CSF and serum confirm the diagnosis of NMDAR encephalitis, which also should prompt a thorough search for an underlying tumor. Age, gender, and ethnicity may all play a role, as black females older than 18 years of age have an increased likelihood of an underlying tumor. Treatment is focused on tumor resection and first-line immunotherapy [corticosteroids, plasma exchange, and intravenous immunoglobulin]. In non-responders, second- line immunotherapy [rituximab or cyclophosphamide or combined] is required. More than 75% of the patients recover completely or have mild sequelae, while the remaining patients end up demonstrating persistent severe disability or death. There is a paucity of literature on the management of psychiatric symptoms in this population. Given the neuropsychiatric symptoms in the relatively early phase of the illness, approximately 77 % of the patients are first evaluated by a psychiatrist. Earlier recognition of this illness is of paramount importance as prompt diagnosis and treatment can potentially improve prognosis. We describe two patients diagnosed with NMDAR encephalitis presenting with two different psychiatric manifestations. The first patient presented with psychotic mania and catatonic symptoms, while the second suffered from depression with psychotic and catatonic features refractory to psychotropic medications. We review of the use of psychotropic medications and ECT to address insomnia, agitation, psychosis, mood dysregulation and catatonia in NMDAR encephalitis.

1. Introduction

Anti-NMDA receptor (NMDAR) encephalitis, formally recognized in 2007, has been increasingly identified as a significant cause of autoimmune and paraneoplastic encephalitis [2]. The exact incidence is unknown. Approximately 80% of the patients are females [3]. The characteristic syndrome evolves in several stages, with approximately 70% of the patients presenting with a prodromal phase with fever, headache and malaise; typically, within 2 weeks, patients develop psychiatric symptoms. Catatonic symptoms, seizures, abnormal movements, memory deficits, speech abnormalities, autonomic instability, central hypoventilation, cerebellar ataxia and hemiparesis may also develop during the course of the disease [5]. Abnormal magnetic resonance imaging (MRI), electroencephalography (EEG) and cerebrospinal fluid (CSF) findings were noted in 33%, 90% and 79% of the patients with anti-NMDAR encephalitis, respectively [5]. Presences of antibodies against the GluN1 subunit of the NMDAR in the CSF and/or serum confirm the diagnosis of NMDAR encephalitis, which also should prompt a thorough search for an underlying tumor [2–4]. Age, gender and ethnicity may all play a role, as Asian and African American females older than 18 years of age have an increased likelihood of an underlying tumor, most commonly teratoma [2,3,5,32]. Treatment is focused on tumor resection and first-line immunotherapy (corticosteroids, plasma exchange and intravenous immunoglobulin). In nonresponders, second-line immunotherapy (rituximab or cyclophosphamide or combined) is required [3]. More than 75% of the patients recover completely or have mild sequelae, while the remaining patients demonstrate persistent severe disability or death [3]. There is a paucity of literature on the management of psychiatric symptoms in this population. We describe two patients diagnosed with NMDAR encephalitis presenting with different psychiatric manifestations. The first patient presented with psychotic

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mania and catatonic symptoms sensitive to some antipsychotics, while the second suffered from depression with psychotic and catatonic features refractory to psychotropic medications. We review of the use of psychotropic medications and electroconvulsive therapy (ECT) to address insomnia, agitation, psychosis, mood dysregulation and catatonia in NMDAR encephalitis.

1.1. Case 1

A 35-year-old Caucasian male with no psychiatric history presented with prodromal symptoms of fever and night sweats followed by a two week course of confusion, bizarre behavior, depression and suicidal ideation. He exhibited illogical speech, tangential thoughts, emotional lability and grandiosity. He demonstrated catatonic symptoms of mutism, impulsivity, posturing, hypoactivity, staring and poor eye contact. Computed tomography of the head, lumbar puncture, MRI of the brain, MR venogram of the brain, electroencephalography (EEG), paraneoplastic panel, urine and blood cultures, HIV, West Nile virus, rapid plasma reagin, erythrocyte sedimentation rate, complete blood count, heavy metals, thyroid-stimulating hormone, electrolyte panel and urine tox screens were all within normal limits. Subsequently, he received a 6-day trial of olanzapine. He then developed muscle stiffness, slurred speech, drooling, catatonic posturing and vomiting. Cessation of olanzapine and a trial of lorazepam 1–2 mg q2h prn led to clinical improvement.

Upon admission to our facility, he continued to display behavioral disinhibition, hypersexuality, poor sleep and appetite. He demonstrated mutism, stared, displayed ambitendency and had periods of impulsivity but was largely hypoactive. He was provided lorazepam 1 mg three times per day to treat his catatonic symptoms, and his speech improved.

An extensive medical workup revealed unremarkable results. Following confirmation of NMDA antibodies positive in both serum and CSF fluid, he received a 5-day course of iv methylprednisolone with mild clinical improvement. The patient then underwent a course of plasma exchange (PLEX) and transitioned to oral prednisone and azathioprine. Secondary to erotomania and behavioral dyscontrol, he was initiated on quetiapine 25 mg bid. He improved in terms of both behavior and mentation. He was discharged on quetiapine 25 mg twice a day and lorazepam 1 mg three times a day as needed. Four months later, he reported resolution of symptoms and a return to his prior functioning.

1.2. Case 2

A 30-year-old woman was admitted to an outside facility for depression with suicide attempt, abdominal pain, nausea, vomiting, intermittent fevers and an unintentional 20-lb weight loss in 2 months. She was recently initiated on desvenlafaxine 50 mg XR po daily for depression and lorazepam 1 mg prn for anxiety. Despite multiple medication trials including sertraline, ziprasidone, quetiapine, olanzapine and valproic, she continued to deteriorate, displayed disinhibition, engaged in self-injurious behaviors, and had hallucinations and delusions. She displayed catatonic symptoms such as mutism, rigidity, posturing, stupor, staring, negativism, withdrawal, autonomic abnormality and combativeness. She was transferred to the Mayo Clinic for further management. All laboratory investigations and imaging were negative. CSF paraneoplastic antibody panel was positive for NMDA Ab.

She received methylprednisolone 1 g for 5 days and initiated on lorazepam 1 mg tid with minimal clinical improvement. She proceeded to have seizure-like activity and was loaded with levetiracetam. EEG monitoring revealed clinical seizures which were managed with levetiracetam 1500 mg bid and valproic acid 500 mg bid.

She was transitioned to oral prednisone 60 mg daily, received seven sessions of PLEX and had minimal improvement. She was started on iv immunoglobulin (IVIG) 0.4 mg/kg for 3 days and was discharged home with plans to continue prednisone 60 mg daily, weekly IVIG infusion × 8 weeks and weekly rituximab infusion × 4 weeks. Agitation was treated with olanzapine 5 mg bid prn.

Following discharge, she missed a dose of IVIG and rituximab, refused therapy and assaulted a staff member during an outpatient visit. She was rehospitalized and started on a 3-day course of IVIG with plan to continue the infusion weekly for 7 more weeks along with rituximab with plan to continue the weekly infusion × 3 weeks, as outpatient EEG revealed some mild diffuse nonspecific slowing of the background but no potentially epileptogenic activity. We recommended scheduled olanzapine 2.5 mg daily, 5 bid as needed. In 4 days, she returned to her baseline.

2. Discussion

Glutamate is the major excitatory neurotransmitter distributed throughout the brain, and glutamate receptors are of two types: inotropic receptors (NMDA, AMPA, kainate), which are ligand-gated cation channels, and metabotropic receptors, which are G-protein-coupled receptors [25]. Of these receptors, NMDA receptors have been studied more extensively given its significant role in normal central nervous system development, neuroplasticity, learning, memory and human behavior. NMDA receptors are made up of two subunits: the NR1 subunit that binds glycine and the NR2 subunit that binds glutamate.

NMDAR abnormalities have been implicated in the pathophysiology of schizophrenia and affective disorders in several studies [8,9] based on genetic studies associating NMDAR gene polymorphisms and schizophrenia, on animal and postmortem studies and also on the emergence of psychotic and neurocognitive symptoms similar to those in schizophrenia following the use of NMDAR antagonists like phencyclidine and ketamine. Antagonists at both the glycine and the glutamate binding site of the NMDAR have been shown to produce psychotomimetic effects [9], and it has been hypothesized that dopaminergic dysfunction in schizophrenia could be secondary to NMDA receptor hypofunction [11]. In anti-NMDA receptor encephalitis, antibodies to the NMDA receptor cause an internalization of NMDA receptors, resulting in a progressive but reversible loss of surface receptors, which leads to decreased NMDA receptor function [3]. The downstream consequences of NMDAR hypofunction may include a decrease in GABA inhibition on prefrontal cortex (PFC), inducing disorganized cortical hyperactivity [17], excessive release of acetylcholine and increase in glutamatergic transmission in PFC at the non-NMDA receptors (AMPA) [16]. Therefore, it is not surprising that anti-NMDAR encephalitis can present with varied psychiatric manifestations. Antibody titers in CSF correlate with the severity of clinical illness, and the clearance of antibodies often results in return to baseline functioning.

Given the neuropsychiatric symptoms in the relatively early phase of the illness, approximately 77% of the patients are first evaluated by a psychiatrist [2]. Earlier recognition of this illness is of paramount importance because prompt diagnosis and treatment can potentially improve prognosis [5]. Therefore, clinicians should be highly suspicious of this disease when there is an atypical presentation of a psychiatric disorder along with prodromal and neurological symptoms in young patients to avoid misdiagnosis and delay in treatment. While immunotherapy is the mainstay in the treatment of this disease [2–5], a number of psychotropics have been used to manage the psychiatric symptoms. Also, adequate management of the emotional and behavioral symptoms has an impact on the patients' capacity to be able to receive immunotherapy [7]. A literature search on PUBMED using different search terms to identify studies focusing on the management of psychiatric symptoms in this disease yielded very few

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results [1]. For the purpose of discussion, psychiatric symptoms are categorized as mood symptoms, psychotic symptoms and catatonic symptoms in this paper.

3. Psychotic symptoms and agitation

The psychotic symptoms often include delusions, hallucinations and aggression. Both typical and atypical antipsychotics have been used either alone or in combination to manage these symptoms [7]. Typical antipsychotics, especially highly potent dopamine antagonists like haloperidol, can cause extrapyramidal symptoms (EPS) including akathisia, dystonia and tremors, which can worsen agitation [14]. Extrapyramidal symptoms can also confound the picture and mimic the dyskinesias resulting from the disease itself. Therefore, patients who have severe agitation could benefit from using more sedating atypical antipsychotics or judicious use of typical antipsychotics along with a medication to treat EPS, such as benztropine, diphenhydramine or trihexyphenidyl. Also, neuroleptic malignant syndrome (NMS) and anti-NMDAR encephalitis have overlapping symptoms including altered mental status, fever, abnormal movements and autonomic disturbances which can result in a delay of diagnosis of anti-NMDAR encephalitis [12]. Clozapine and structurally similar antipsychotics (olanzapine, loxapine and amoxapine) have been shown to prevent NMDA receptor antagonist toxicity [30], but the phlebotomy requirements of clozapine might make it difficult to administer.

Other antipsychotics that have been used include chlorpromazine, aripiprazole, risperidone and ziprasidone [1,14]. Severe agitation requiring midazolam has been reported [13]. NMDAR encephalitis presenting with psychosis during pregnancy and postpartum psychosis has been reported, though is rare [6,15].

4. Mood symptoms

Mood lability and mania have been reported more frequently than depression. Mood stabilizers like lithium [1,12] and valproic acid [1] have been used to treat manic symptoms; the latter confers the additional benefit of increased sedation, sleep and seizure prophylaxis/ treatment and can be administered intravenously if needed. Augmentation with benzodiazepines can also be considered. Sleep disturbances, especially insomnia, are usually managed with benzodiazepines, trazodone, melatonin and clonidine.

5. Catatonic symptoms

Catatonic symptoms including mutism, withdrawal, staring, posturing and negativism associated with both affective and psychotic symptomatology have been reported. While benzodiazepines remain the first line of choice to treat the catatonic symptoms [18] it would also help with sleep and aid in prophylactic treatment of seizures. Antipsychotic use in catatonia is controversial because it could precipitate NMS.

In several case reports, the use of ECT has demonstrated improvement in psychotic and catatonic symptoms in NMDAR encephalitis patients who had inadequate response to other treatment options [1,10,19,42–44].Although the mechanism of ECT is not entirely clear, it has been reported to increase the mRNA for the NMDA subunits NR2A and NR2B [21] and increased sensitivity of hippocampal 5-HT3 receptors, resulting in increased release of glutamate and gamma-aminobutyric acid [22]. ECT may be warranted in life-threatening malignant catatonia or catatonia refractory to other treatments based on the symptomatic improvement in those case reports. However, ECT should be considered as a last resort and only after a thorough medical workup ruling out relative or potential contraindications in anti-NMDAR encephalitis such as refractory status epilepticus, life-threatening arrhythmias or cardiac arrest, sepsis, respiratory distress or autonomic instability. Further research addressing the safe use and the efficacy of ECT in this condition is clearly needed in order to make more definitive treatment recommendations.

Despite its complex symptomatology, anti-NMDAR encephalitis has a good prognosis, and prompt immunotherapy results in substantial improvement in majority of the patients. Both our patients returned to premorbid functioning with appropriate treatment. Our patient described in Case1 experienced untoward extrapyramidal side effects from some antipsychotics, so benzodiazepines and low doses of quetiapine were used to treat his behavioral dyscontrol and catatonia. In contrast, our second patient failed multiple medication trials and required high doses of benzodiazepine and olanzapine to manage aggressive behaviors.

The NMDA hypofunction model of psychosis suggests that drugs such as olanzapine, clozapine and lamotrigine could arrest the acute neurotoxic process associated with NMDAR hypofunction [33]. Animal models have demonstrated that some antipsychotic agents (e.g., clozapine and haloperidol) reverse the hypermetabolism induced by NMDA antagonism [34]. NMDAR antagonists exacerbate psychiatric symptoms in healthy individuals, while schizophrenic symptoms are improved with agents that enhance NMDAR function [35–38]. Judicious use of psychotropic medications may thus lessen symptom burden associated with anti-NMDA receptor encephalitis while patients concurrently receive multidisciplinary treatment. Therefore, psychotropic medications are generally recommended to be continued as symptomatic management until the patient's clinical presentation returns back to baseline, which usually corresponds with immunosuppressive treatment.

6. Future directions

While psychotropic medications have been used for management of psychiatric symptoms associated with NMDAR encephalitis, response may be limited, and their role in increasing glutamate and GABA neurotransmission as an adjunct to immunotherapy has not been explored. The NMDA hypofunction in schizophrenia is slightly different from that in anti-NMDAR encephalitis in that there is a reversible loss of surface NMDAR in the latter. Small clinical trials using direct glycine receptors agonists like glycine, D-serine, D-alanine, D-cycloserine and glycine transport inhibitors as adjunctive treatments to antipsychotics have demonstrated improvement in positive and negative symptoms of schizophrenia, theoretically by increasing glutamatergic neurotransmission [9]. A recent meta-analysis by Tsai and Lin showed that glycine, D-serine and sarcosine were better than D-cycloserine in improving most domains in schizophrenia when added to risperidone or olanzapine, but not clozapine [39]. Can glycine agonists or glycine transporter inhibitors be used in anti-NMDAR encephalitis? Will the loss of NMDAR preclude the use of these agents in anti-NMDAR encephalitis? The answers to these questions are unknown, and there are no published reports on the use of these agents in this condition to the best of our knowledge.

Medications targeting metabotropic glutamate receptors [9] or non-NMDA glutamate receptors (AMPA receptors) [23] may have a potential role in compensating for the reduced glutamate transmission as a consequence of NMDAR loss, or α-2 selective benzodiazepine-like agents may enhance GABAergic neurotransmission in PFC to reduce cortical hyperactivity [24] and can provide new treatment options. Paradoxically, memantine, a partial non-competitive antagonist, has been shown to be effective in catatonic schizophrenia [40] and treatment-resistant schizophrenia [41] as an add-on with clozapine.

GABAergic medications and α-2 adrenergic agonists prevent the excessive acetylcholine release resulting from NMDA receptor hypofunction and have been shown to prevent NMDA receptor hypofunction neurotoxicity in rat brain [26,27]. Other medications that have been shown to be neuroprotective against the untoward downstream effects of NMDA receptor hypofunction include 5-HT2A

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agonists [28], antiepileptics [29] and antimuscarinics [31]. These options could be future areas of interest and may aid in reducing or preventing the neurocognitive sequelae from NMDA receptor hypofunction in anti-NMDA receptor encephalitis [20].

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