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Anti-NMDA Receptor Encephalitis in Psychiatry

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Abstract

Anti-NMDA receptor encephalitis is an autoimmune disorder in which antibodies attack NMDA (*N*-methyl-D-aspartate)-type glutamate receptors at central neuronal synapses. Symptoms include a highly characteristic set of neurologic deficits, but also prominent psychiatric manifestations that often bring mental health professionals into the course of care. Distinct phases of illness have become increasingly appreciated, and include a range of psychotic symptoms early in the course of the disease followed by more severe fluctuations in consciousness with neurologic involvement, and ultimately protracted cognitive and behavioral deficits. Young women are most commonly impacted and an ovarian teratoma is sometimes associated with the syndrome. Patients respond well to immunotherapy, but psychiatric symptoms can be challenging to manage. We provide an up to date review of this disorder and highlight the role of psychiatry in diagnosis, symptomatology, and treatment.

Keywords

NMDA receptor; autoimmune; synapse; paraneoplastic; schizophrenia

INTRODUCTION

Since the original characterization of anti-NMDA receptor encephalitis in 2007 [1], a rapidly growing literature has described many aspects of this fascinating disorder [2,3,4]. The resulting syndrome commonly begins and ends with profound psychiatric disturbances, and the cognitive and behavioral manifestations have begun to attract increased attention [5,6]. Initially, anti-NMDA receptor encephalitis was thought to exclusively be a paraneoplastic disorder, occurring in young females in association with an ovarian teratoma [7]. It is now appreciated to occur with or without a tumor, and can arise in children and young adults, both male and female. The most recent works have described greater than 400 patients with this syndrome [3], and a retrospective study found that ~1% of all ICU admissions in patients between the ages 18–35 had this autoimmune synaptic encephalitis [8]. Anti-NMDA receptor encephalitis, therefore, appears to be relatively common, particularly in comparison to similar autoimmune or paraneoplastic disorders [9]. Here, we discuss the

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course of illness, diagnosis, pathogenic mechanisms, and management, focusing on those issues most relevant to psychiatric care.

PHASES OF DISEASE

As described in a number of reports [3,7,10], anti-NMDA receptor encephalitis appears to have discrete and often predictable phases of illness (Fig. 1). An understanding of these stages can help anticipate appropriate patient needs and medical management, as well as facilitate earlier diagnosis of the syndrome.

Prodrome and Initial Psychiatric Symptoms

In retrospective accounts of illness, ~70% of patients experience a viral-like prodrome including lethargy, headache, upper respiratory symptoms, nausea, diarrhea, myalgias, and fever. These symptoms occur an average of 5 days (no more than 2 weeks) prior to onset of behavioral changes [3,10]. Psychiatric manifestations of anti-NMDA receptor encephalitis are broad and varied; given the frequent absence of neurologic symptoms during this period, patients are often first seen by a psychiatrist [2,6]. Psychotic symptoms predominate, including delusional thought content, perceptual disturbances, and disorganized thoughts and behaviors [2,3,4]. Specifically, patients usually exhibit anxiety/fear and agitation, along with paranoid ideation, mood lability, and bizarre behaviors with personality change. Many patients can become combative and aggressive, though asociality and blunted affect are common as well. Interestingly, while psychotic symptoms are common in adults, the pediatric population often manifests with manic symptoms such as irritability and behavioral outbursts, sleep dysfunction, hyperactivity, and hypersexuality [4].

In addition to behavioral changes, cognitive deterioration and abnormal speech often develop. Short-term memory deficits and confusion are common (albeit challenging to detect given the severity of psychiatric symptoms), as are difficulties in normal activities of daily living. In some cases, the cognitive changes might be more protracted in the early phase of disease, and perhaps subsyndromal, for instance causing isolated difficulties in school performance [3,11]. Patients of all ages frequently experience progressive decline in speech and language, including alogia, echolalia, perseveration, mumbling, and mutism [3,4]. These alterations in speech often persist throughout other stages of disease. In sum, the initial psychiatric phase of the syndrome appears to last 1–3 weeks [2,10], though some cases raise the possibility of a longer course of behavioral and personality changes at attenuated levels preceding symptomatic presentation [1,3].

Neurologic Complications

Early psychiatric changes are followed by more global alterations in consciousness and decreased responsiveness, sometimes progressing to a catatonic-like state with mutism and eyes open [10], while other times demonstrating increased agitation [3]. This stage is accompanied by abnormal movements, such as orofacial dyskinesias, dystonic posturing, and choreic-like movements of limbs, as well as autonomic instability (hyperthermia, tachy- or bradycardia, hypo- or hypertension) [2,10]. In children, abnormal movements are often part of the presenting picture rather than occurring later in the disease process [4,5]. Another common complication at this stage is hypoventilation, particularly in adults, and often central in origin; one large study described 2 months of ventilatory support required on average [2].

Seizures are also a prominent feature of anti-NMDA receptor encephalitis, and though unpredictable, may have increased intensity and frequency earlier in illness [3]. In fact, one study found that over 25% of female patients between the ages of 18–45 with new onset epilepsy (and in most cases with additional neuropsychiatric symptoms) harbored anti-

NMDA receptor antibodies, and no other etiology for seizures could be identified [12]. Seizures are partial motor or complex, and occur in nearly 80% of cases [2,4]. Of note, patients are treated in the intensive care setting during this phase, and many experience fluctuating levels of consciousness in the midst of these severe neurologic symptoms, at times revealing an agitated, labile, or even dissociative state [2,3].

Recovery and Relapse

Individual cases of anti-NMDA receptor encephalitis described withdrawal or near withdrawal of care in patients before more widespread awareness of the syndrome and potential for recovery [3]. Although aggressive treatment is the norm [2], the natural course of disease suggests some patients have a prolonged course of illness but can show spontaneous neurological improvement [10]. Many challenges face these patients even with appropriate supportive care and therapy (details on treatment below). The process of recovery is in many ways a reversal of the phases of illness described above, and hospitalization of ~3–4 months is normally required [3]. Autonomic and respiratory functions normalize, followed by resolution of movement abnormalities. As in many complex medical illnesses, cognitive and psychiatric functions are often the slowest to improve, with frequent re-emergence of agitation and psychotic disturbances in these patients as they regain consciousness and expressive faculties. Highly sedating medications are often required, frequently impeding cognitive recovery in the acute hospital stay. Compared to other synaptic encephalitides [13], the relapse rate in anti-NMDA receptor encephalitis is relatively low (~20–25%), sometimes triggered by discontinuation of medication, and often with substantial and prolonged symptomatic improvement between episodes [2,14].

Late-Phase Cognitive and Behavioral Sequelae

Beyond the acute stages of illness, patients with anti-NMDA receptor encephalitis take considerable time to return to their baseline function. Approximately 85% of patients who ultimately make a full recovery have significant cognitive and behavioral abnormalities upon hospital discharge, requiring supervision and rehabilitation [2,3,6]. Symptoms include deficits in executive function, impulsivity, behavioral disinhibition, and abnormal sleep patterns [2]. Prolonged psychiatric abnormalities have not been well described in cohorts, but individual case reports illustrate persistent symptoms. One case describes a young man who was 18 years old at onset of the illness, and 1.5 years later still had limited cognitive abilities. By 2 years post onset he had more improvement with regard to cognitive functions, though still remained internally pre-occupied at times and exhibited odd behaviors [15]. Other patients have protracted symptoms resembling Kluver-Bucy or Kleine-Levin syndromes, with hypersexuality, hyperphagia, hypersomnia, irritability, or blunted affect [3]. Amnesia for the entire acute phase of illness is common, and memory deficits may persist. Future work will continue to assess such post-encephalitis patients over time to examine lingering psychiatric and neurocognitive abnormalities.

EPIDEMIOLOGY AND DIAGNOSIS

While originally described in association with ovarian teratomas in young women, the largest study of anti-NMDA receptor encephalitis patients now includes over 400 patients and shows with clarity the population characteristics of those affected [3]. Approximately 80% of patients are women, and in those greater than 18 years of age, ~50% have an underlying tumor (overwhelmingly found to be ovarian teratoma). Only 5% of men >18 years old have an identifiable tumor. The younger a patient is, the less likely he or she is to have any associated tumor. Moreover, black females are more likely to have a teratoma than other ethnic groups.

Diagnosis in patients with anti-NMDA receptor encephalitis requires studies of cerebrospinal fluid (CSF). CSF findings include moderate lymphocytic pleocytosis and elevated protein, as well as oligoclonal bands in ~60% of cases [3]. Most importantly, nearly all patients have intrathecal synthesis of antibodies recognizing the NMDA receptor. Firm diagnosis is made by demonstrating that CSF and/or serum contain antibodies against NMDA receptors in multiple distinct lab preparations [1,2]. Other studies have not proven to be as diagnostic: brain MRI is normal in 50% of all cases, and abnormal MRIs commonly show T2 or FLAIR hyperintensities in cortical or subcortical brain regions, sometimes with mild or transient contrast enhancement [1,2,3]. EEG is usually abnormal, showing slow and disorganized activity in the delta/theta range, sometimes with superimposed electrographic seizures [2]. Based on population findings, a primary concern in a female suspected to have this syndrome would be evaluation for an ovarian teratoma by MRI, CT scan, or ultrasound [3].

Given the myriad of symptoms described in these patients, the differential diagnosis may be large and often focus initially on viral encephalitis (hyperthermia, mental status change, seizures, CSF pleocytosis) [2,7]. Seventy-five percent of patients first present to a psychiatrist; thus, acute psychosis and mania +/− psychotic features would be considered, as would drug abuse or malingering. Particularly following treatment of psychotic symptoms with an antipsychotic, onset of altered mental status, rigidity, hyperthermia, and autonomic instability might be suggestive of neuroleptic malignant syndrome (NMS). In addition, many patients with anti-NMDA receptor encephalitis have been described with elevated creatine kinase [4]. Other synaptic encephalitides could present similarly to anti-NMDA receptor encephalitis [13,16], and a variety of autoimmune disorders with neuropsychiatric manifestations should be considered as well [11]. In children, the psychiatric manifestations bring into consideration a differential diagnosis of early onset schizophrenia, late onset autism, and childhood disintegrative disorder [17].

PATHOGENESIS

The underlying cellular mechanisms causing this syndrome are relatively well understood. Antibodies bind the NMDA receptor, leading to its internalization from the cell surface and a state of relative NMDA receptor hypofunction [2,18]. Other synaptic proteins and synaptic structure are unaffected [18]. CSF titers of anti-NMDA receptor antibodies correlate with clinical illness, and both the synaptic effects and severity of symptoms are reversible with clearance of antibodies [2]. Thus as with other synaptic encephalitides, the auto-antibodies themselves appear to be pathogenic [19], as opposed to syndromes associated with antibodies against intracellular targets in which cytotoxic T-cell mechanisms appear to be causative [20,21]. In addition, NMDA receptor antagonists [22,23] and rodent models of reduced NMDA receptor expression [24] mimic multiple aspects of this disorder. While the brain region-specific and circuit-wide impact of anti-NMDA receptor antibodies remains to be explored, the mechanisms of anti-NMDA receptor encephalitis strengthen the hypothesis that NMDA receptor hypofunction might have a role in schizophrenia and psychosis [25].

TREATMENT AND OUTCOMES

As would be expected with a newly discovered syndrome, best-practice care is still being established in patients with anti-NMDA receptor encephalitis. Yet, expert opinion provides increasingly clear guidelines for treating the auto-antibody and immune response. Early recognition is foremost because outcomes are best in patients treated early in the course of disease [3]. After diagnosis, treatment focuses on immunotherapy and appropriate treatment of a tumor if it exists. Corticosteriods and intravenous immunoglobulin (IVIg) or plasma exchange are recommended in managing the immune response; these therapies appear to

work best in the scenario where an underlying tumor has been removed [2,3,4,14]. The use of plasma exchange is challenging in agitated patients or cases with autonomic instability, and IVIg is often preferred. Approximately 75% of patients have full recovery or mild deficits, while 25% remain severely disabled or die; mortality is estimated to be 4% [2,3]. In patients without an underlying tumor, first line immunotherapy is often not sufficient, and treatment with rituximab or cyclophosphamide may be required. Current recommendations suggest using either or both second line immunotherapies if no improvement is observed with corticosteroids and IVIg [3]. In patients without a tumor (in whom relapse is more common), continued immunosuppresion with mycophenolate mofetil or azathioprine is recommended for at least 1 year and periodic screening for an ovarian teratoma over 2 years [3].

While a consensus has begun to emerge on management of neurologic symptoms, control of psychiatric manifestations is at times more elusive. Though not systematically studied, a wide variety of interventions have been tried during the course of disease, ranging from high dose neuroleptics to ECT. Review of the literature and personal experiences/communications suggest that in many cases of anti-NMDA receptor encephalitis, high dose dopamine blockade exacerbates dyskinetic and dystonic movements when used in an agitated patient [4,5], though it is unclear whether this stems from excessive blockade in what is often a neuroleptic naïve patient. Certainly use of drugs like haloperidol might further confound distinguishing anti-NMDA receptor encephalitis from NMS. Highly sedating medications, such as anticholinergics, benzodiazepines, and valproic acid have proven helpful in many cases, as have more sedating antipsychotics like quetiapine or chlorpromazine [4,5] (MSK, JD, unpublished observations). These reports also cite trazodone or clonidine as adjunctive agents for managing sleep. ECT has been used successfully in a few patients [4,26,27], but the improvement is usually partial or transient and treatment of the underlying etiology is almost uniformly required. We suggest initiating treatment with quetiapine in patients with anti-NMDA receptor encephalitis who have psychotic symptoms and agitation. Acutely agitated or psychotic patients who refuse oral medications often respond well to thorazine; again, we emphasize the need to avoid high potency antipsychotics. Patients with comorbid or isolated mood symptoms (usually lability and/or mania) appear to improve with mood stabilizers like valproic acid, which has the added benefit of seizure prophylaxis and intravenous formulation.

CONCLUSIONS

Anti-NMDA receptor encephalitis represents the first and best described syndrome in a new class of autoimmune synaptic encephalitides that have been elucidated over the past 5 years. This complex disorder requires sustained management and coordination of care between multiple medical specialties. The involvement of psychiatrists at many phases of disease suggests a familiarity with the syndrome to be essential, particularly early on when appropriate diagnosis might help anticipate neurologic decompensation. A few retrospectively evaluated cases have been described with an apparently milder form of the disorder that is purely psychiatry in nature [28,29], suggesting that anti-NMDA receptor encephalitis might sometimes be misdiagnosed as a primary psychiatric illness. In our experience, patients referred with pure psychiatric symptoms usually have subtle neurological findings, representing milder or “formes frustes” of the disorder. However, we have seen patients with relapses characterized by isolated psychiatric manifestations; these patients often have CSF pleocytosis with increased NMDA receptor antibody titers. Whether prompt recognition and treatment prevented progression to a full-blown syndrome is currently unclear. Future clinical work will need to examine more fully the psychiatric manifestations of the disorder and how to provide optimal care, not only during acute hospitalization but also in the prolonged recovery process.

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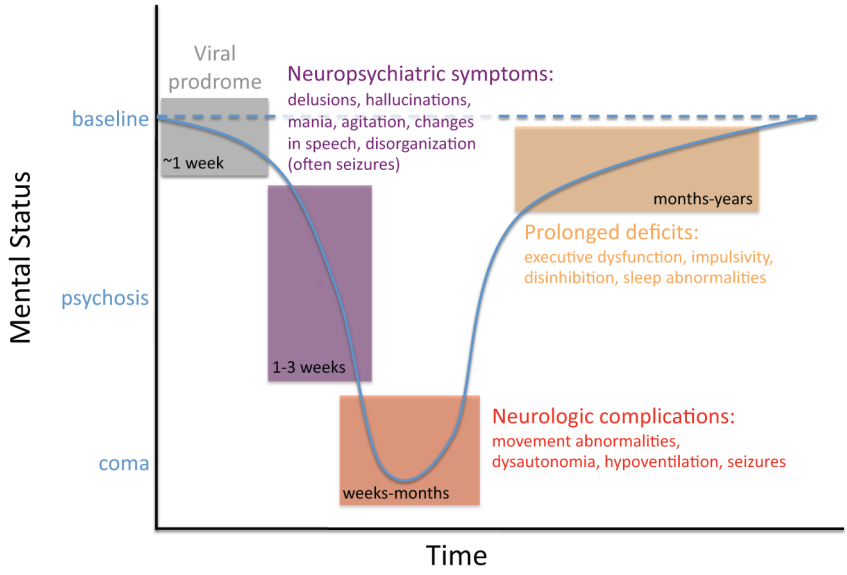

Fig. 1.
Phases of illness in anti-NMDA receptor encephalitis.