

Anti-N-Methyl-D-Aspartate Receptor Encephalitis in Psychiatry

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Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a recently-discovered autoimmune disorder in which antibodies target NMDAR in the brain. The number of reported cases of anti-NMDAR encephalitis has increased rapidly. Anti-NMDAR encephalitis can be mistakenly diagnosed as psychiatric disorders because many patients present with prominent psychiatric symptoms and visit psychiatric institutions first. Thus, psychiatrists should cultivate a better understanding of anti-NMDAR encephalitis. In this review, we present the mechanisms, epidemiology, symptoms and clinical course, diagnostic tests, treatment and outcomes of patients with anti-NMDAR encephalitis. Furthermore, we discuss the diversity of clinical spectra of anti-NMDAR encephalitis, and demonstrate a differential diagnosis of psychiatric disease from the perspective of psychiatry.

Key words: NMDAR, encephalitis, psychiatric symptom, schizophrenia, mood disorder

In 2005, a syndrome of memory deficits, psychiatric symptoms, decreased consciousness, and hypoventilation in four young women with ovarian teratomas was reported [1]. In 2007, Dalmau and colleagues reported that specific autoantibodies to the N-methyl D-aspartate receptor (NMDAR) were detected in twelve patients, who had similar neurological symptoms, such as psychosis, memory deficits, seizures, dyskinesia, decreased consciousness, and autonomic instability [2]. Of these patients, seven had ovarian teratomas. The authors coined the term 'anti-NMDAR encephalitis', which was initially considered to be a paraneoplastic encephalitis [2]. A further study by the same authors revealed that most cases of anti-NMDAR encephalitis affected children and young adults with or without an associated tumor [3]. Since then, the num-

ber of reported cases of anti-NMDAR encephalitis has rapidly increased. One hundred cases were reported in 2008 [4], 419 cases in 2011 [3], and a long-term prognosis survey of 577 cases was reported in 2013 [5]. A systematic review summarized the clinical symptoms of 633 patients with anti-NMDAR encephalitis in 2018 [6].

Anti-NMDAR encephalitis can be misdiagnosed as other psychiatric disorders, because many patients present with prominent psychiatric symptoms, including anxiety, agitation, depression, manic, bizarre behavior, delusional or paranoid thoughts, and visual or auditory hallucinations [4, 6, 7]. Some patients who had anti-NMDAR antibodies at the initial diagnosis of schizophrenia were reported [8, 9]. We have also found that anti-inflammatory therapy and immunotherapy were effective in a patient with anti-NMDAR antibodies

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who had been initially diagnosed with treatment-resistant schizophrenia [10]. The main presentations of atypical anti-NMDAR encephalitis could be psychiatric or cognitive symptoms, without showing either seizures, involuntary movements, hypoventilation, or associated tumors [11].

In this review, we present the mechanisms, epidemiology, symptoms and clinical courses, diagnostic tests, treatment and outcomes of patients with anti-NMDAR encephalitis from the perspective of psychiatry. We also discuss the diversity in clinical symptoms of anti-NMDAR encephalitis, introducing a differential diagnosis of psychiatric disease.

Pathogenic Mechanisms

Anti-NMDAR encephalitis appears to be triggered by the presence of a tumor, mostly an ovarian teratoma that contains nervous system tissue and expresses NMDAR [12]. The autoantibodies are present in patients' serum and cerebrospinal fluid (CSF), which usually show intrathecal synthesis and high antibody concentration [4]. NMDARs are heteromers of NR1 subunits that bind glycine and NR2 subunits that bind glutamate [13]. All patients' antibodies recognize the N-terminal extracellular domain of NR1, suggesting an antibody-mediated pathogenesis [4, 14]. Anti-NMDAR encephalitis is caused mainly by internalization of NMDAR without complement activation [3-5]. Internalization of NMDAR occurs through antibody binding, capping, and cross-linking of the receptors, and loss of the NMDAR from the cell surface correlates with antibody titer [12]. Decreased synaptic NMDAR content leads to reduced synaptic plasticity, as demonstrated by the report that treatment of rodent neurons with patient CSF blocks molecular signatures of long-term potentiation in the hippocampus [15]. A previous study found that prolonged cerebroventricular infusion of patient antibodies into mice results in progressive memory deficits, anhedonia, and depression-like behaviors [16]. After stopping the infusion of antibodies, there was progressive clinical improvement associated with restoration of NMDAR levels [17].

Epidemiology

The exact incidence of anti-NMDAR encephalitis is unknown, but the number of case reports seems to be

more frequent than any other known paraneoplastic encephalitis [3]. A recent review with demographic analyses in 633 patients has shown that the median age of disease onset was 22.6 years (range 8 months to 84 years), and that patients consisted of 492 females (77.8%) and 141 males (22.2%) [6]. A viral prodrome, such as headache (75 cases) and fever (56 cases), at the onset of symptoms was documented in 133 cases (21.0%) [6]. Among all patients, ovarian teratoma was documented in 178 cases (28.1%) and other malignant neoplasms in 28 cases (4.4%) [6]. The teratoma-associated cases were significantly more likely to present with psychiatric symptoms and have psychosis and autonomic symptoms than those without teratoma [6]. However, it is still unknown whether tumors other than teratomas are truly pathogenic of the illness or unrelated coincident disorders [3].

Symptoms and Clinical Course

Patients with anti-NMDAR encephalitis present various symptoms [18]. In a systematic review in 633 patients with anti-NMDAR encephalitis, the symptoms during the course of illness were behavioral (80.3%), neurological (75.5%), seizures (63.2%), autonomic (51.3%), psychotic (45.8%), and cognitive (43.9%) [6]. Among the psychiatric symptoms, the most common were abnormal behaviors (*e.g.* agitated, bizarre, or crying) (80.3%), abnormal speech (*e.g.* mute or echolalia) (50.4%), catatonia (32.7%), hallucinations (31.3%), insomnia (23.4%), mood (24.5%), and delusions (20.5%) [6]. In the previous review in 571 patients with anti-NMDAR encephalitis, 23 (4%) developed isolated psychiatric symptoms [19].

Symptoms progress over a period of days or weeks, with the exception of some patients with anti-NMDAR encephalitis [18, 20]. Patients progress through in several stages of illness and recovery, as first reported by Iizuka *et al.* [21]. They asserted that the clinical course of typical patients sequentially progressed through five phases: prodromal, psychotic, unresponsive, hyperkinetic, and gradual recovery. In the prodromal phase, most patients presented with headache, low-grade fever, or a non-specific viral-like illness within 2 weeks before hospital admission [4, 21]. It is unknown whether the prodromal symptoms form part of an early immune activation, or result from a non-specific infection that facilitates crossing of the blood-brain barrier

by the immune response [4]. In the psychotic phase, patients had emotional disturbances (*e.g.*, apathy, lack of emotion, depression, loneliness, or fear), cognitive decline, and prominent schizophrenia-like symptoms, including disorganized thinking, compulsive ideation, delusions, hallucinations, and loss of self-awareness [21,22]. In this phase, most patients had seizures, reduced verbal output, and developed decreased consciousness [4,20]. In the unresponsive phase, patients were mute, akinetic, and unresponsive to verbal commands while keeping their eyes open, resembling catatonia [23]. They also presented bizarre and inappropriate smiling, athetoid dystonic postures, echo phenomenon, and catalepsy-like symptoms [4,21]. In the hyperkinetic phase, patients gradually developed orolingual dyskinesia such as lip licking or chewing, and athetoid dystonic postures of the fingers [21]. At this stage, most patients had symptoms of autonomic instability, including labile blood pressure, bradycardia or tachycardia, hyperthermia, and diaphoresis, and some patients developed central hypoventilation, requiring ventilator support [4,21,22]. The recovery phase from this disorder is typically slow and gradual after immunotherapy or anti-inflammatory therapy [3].

More than 75% of all patients eventually have substantial recovery that occurs in inverse order of symptom development, and the decline of anti-NMDAR antibody titers could be associated with the abatement of neurological symptoms [3,18]. However, a recent study did not find the association between the antibody titers and psychiatric symptoms [24].

Diagnostic Tests and Criteria

A majority of patients with anti-NMDAR encephalitis show abnormal findings on magnetic resonance imaging (MRI), electroencephalogram (EEG), or CSF [6]. In 706 patients with anti-NMDAR encephalitis, MRI was abnormal in 35.6%, EEG abnormal in 83.0%, and CSF abnormal in 76.4% [6]. In MRI findings, T2 or fluid attenuated inversion recovery (FLAIR) signal hyperintensity could be seen in the hippocampi, cerebellar or cerebral cortices, frontobasal and insular regions, basal ganglia, or brainstem [3,6]. A recent systematic review of MRI findings in anti-NMDAR encephalitis also demonstrated that the most common abnormal findings are T2/FLAIR medial temporal and frontal hyperintensity and leptomeningeal contrast

enhancement [25]. In EEG, non-specific, slow, and disorganized activity was seen in most patients [3,6]. However, some patients occasionally showed a unique EEG pattern named “extreme delta brush”, characterized by rhythmic delta activity at 1-3 Hz with superimposed bursts of rhythmic 20-30 Hz beta frequency activity riding on each delta wave [26]. Slow, continuous, rhythmic activity in the delta-theta range predominates in the catatonic-like stage [27]. In CSF findings, moderate lymphocytic pleocytosis, normal or mildly increased protein concentration, and CSF-specific oligoclonal bands were seen in many patients [3,6].

Graus *et al.* have currently presented the diagnostic criteria for anti-NMDA receptor encephalitis [28]. For the diagnosis of “probable” anti-NMDAR encephalitis, all of the below criteria is required: 1) at least three of the six clinical symptoms (abnormal behavior or cognitive dysfunction, speech dysfunction, seizures, movement disorder/dyskinesia/rigidity/abnormal postures, decreased level of consciousness, and autonomic dysfunction/central hypoventilation) accompanied by a systemic teratoma, 2) at least one of the laboratory study results (abnormal findings on EEG, such as focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush, and in abnormal CSF findings, such as pleocytosis or oligoclonal bands, and 3) reasonable exclusion of other disorders. For the diagnosis of “definite” anti-NMDAR encephalitis, diagnosis can be made in the presence of one or more of the 6 symptoms and IgG anti-GluN1 antibodies after reasonable exclusion of other disorders. Antibody testing should include CSF analysis because anti-NMDAR antibody-testing is more sensitive in CSF than serum [29].

Treatment and Outcomes

In 2011, Dalmau *et al.* proposed the algorithm for the treatment of anti-NMDAR encephalitis, that has been widely used [3]. They recommended that antibody studies be done on both serum and CSF for patients suspected of anti-NMDAR encephalitis because periodic screening of serum and CSF is useful to assess the effects of treatment, especially in the central nervous system [3,5]. Antibody-positive patients should be examined for the presence of an underlying tumor, mainly an ovarian teratoma or a testicular germ-cell tumor [3,5,30]. After removal of underlying tumors,

if any, first-line immunotherapy consists of methyl-prednisolone, intravenous immunoglobulins and plasma exchange given alone or in combination [3,30]. If no response to first-line therapy is seen after 10 days, second-line immunotherapy, consisting of rituximab, cyclophosphamide, or both is recommended [3,30]. Substantial improvement was defined as full recovery or minimum deficits estimated by physicians and family members as recovery of more than 90% of function [4]. All other patients are judged to have little improvement or no change [5]. The process of recovery happens in the reverse order of symptom presentation, and recovery can be incomplete or delayed by many months [3,30]. Dalmau *et al.* showed that 81 (77%) of 105 patients had substantial improvement, and five patients (5%) died [3]. In the long-term cohort study of patients with anti-NMDAR encephalitis, 394 (79%) of 501 patients achieved a good outcome and 30 (6%) died during the first 24 months [5]. The study indicated that predictors of good outcome were early treatment and no admission to an intensive care unit. Furthermore, current study has developed a grading score, called the "NEOS score", that predicts neurologic function 1 year after diagnosis of anti-NMDAR encephalitis and consists of five variables: intensive care unit admission, treatment delay > 4 weeks, lack of clinical improvement within 4 weeks, abnormal MRI, and CSF white blood cell count > 20 cells/ μ l [31]. This score could help estimate the clinical course following diagnosis.

Whereas many studies have reported the effectiveness of immunotherapy, little study has investigated the effects of antipsychotics for anti-NMDAR encephalitis-induced psychiatric symptoms. A current review included 159 cases of anti-NMDAR encephalitis treated with antipsychotics, including haloperidol (36.5%), risperidone (25.8%), olanzapine (23.3%), quetiapine (13.2%), and aripiprazole (6.9%) [6]. Antipsychotics were stopped due to suspected neuroleptic malignant syndrome in 42 cases, and the effectiveness of anti-epileptics was inconsistent [6]. Since treatment of psychiatric symptoms of anti-NMDAR encephalitis is complicated by resistance to traditional psychotropic agents, electroconvulsive therapy (ECT) may be of use in refractory cases. A current systematic review of ECT cases showed that there was improvement of psychiatric symptoms in 65.2% of cases, and there was no complication in 86.7% of cases, with four cases prematurely ceasing ECT with further encephalitic deterioration

[32]. ECT can be an effective and safe adjuvant treatment for refractory psychiatric symptoms in anti-NMDAR encephalitis.

Differential Diagnosis from Schizophrenia

Many patients with anti-NMDAR encephalitis visit psychiatric institutions first due to the prominence of psychiatric symptoms as the initial symptoms [33]. Several studies have shown that approximately 80% of patients with anti-NMDAR encephalitis were initially seen by psychiatrists [4,7]. The mechanisms underlying psychotic symptoms of anti-NMDAR encephalitis may support the glutamate hypothesis of schizophrenia [34]. The glutamate hypothesis of schizophrenia is founded largely on the similarity of psychotic symptoms associated with NMDAR antagonists such as phencyclidine and ketamine [35,36]. Anti-NMDAR encephalitis demonstrates that NMDAR hypofunction results not only in psychosis, but also in cognitive impairment, mood changes, and other symptoms of schizophrenia [33]. Furthermore, the link between infection and schizophrenia has suggested the involvement of immunologic processes [37]. Prior to discovery of anti-NMDAR encephalitis, Bechter hypothesized that schizophrenia is a "mild encephalitis" because many patients with schizophrenia exhibited symptoms beyond psychosis (cognitive impairment, catatonia, and autonomic dysfunction) though pathognomonic auto-antibodies remain elusive [38]. Anti-NMDAR encephalitis is often preceded by prodromal symptoms suggesting a viral process, and that the viral process can develop into an immune-mediated dysfunction of synaptic transmission [39].

Several studies demonstrated the prevalence of anti-NMDAR antibodies in patients with schizophrenia. Steiner *et al.* investigated the prevalence of anti-NMDAR antibodies in serum of patients with acute schizophrenia (N=121) and healthy controls (N=230), identifying anti-NMDAR antibodies in 15 subjects, primarily those with an initial schizophrenia diagnosis (12 of 121, 9.9%) and controls (1 of 230, 0.4%) [8]. They also investigated the prevalence with additional samples, and anti-NMDAR antibodies were identified in schizophrenia (18 of 184, 9.9%) and controls (25 of 357, 7.0%) [40]. The prevalence of anti-NMDAR antibodies (any immunoglobulin isotype) in patients with schizophrenia was reported to be 8.6% (93 of 1,081), almost

identical to that of healthy controls (137 of 1,272, 10.8%) [41]. The isotype analysis in this study indicated that NR1 IgG antibodies are extremely uncommon and that IgA or IgM antibodies are frequent. In contrast to IgG antibodies, which are highly specific to anti-NMDAR encephalitis, the clinical significance of IgA and IgM antibodies is uncertain [42]. Hara *et al.* also indicated that IgG antibodies were highly specific for anti-NMDAR encephalitis and caused a decrease of the levels of NMDAR, but that IgA or IgM antibodies occurred nonspecifically and did not alter the receptor levels [43].

A recent study has shown the prevalence of anti-NMDAR antibodies in patients with early psychosis. In the study of first-episode psychosis, 3 of 46 patients had anti-NMDAR antibodies in their serum (6.5%) [44], and another study reported that 7 of 228 patients were seropositive (3%). [45]. In addition, it was reported that no patient with first-episode psychosis had anti-NMDAR antibodies (0 of 70), but 1 patient of 6 with a clinical high risk for psychosis was seropositive, although antibodies were not found in his CSF [46]. Nevertheless, there has been no study investigating anti-NMDAR antibodies in CSF, rather than serum, of patients with psychiatric illness. Although the evaluation procedure is invasive, further studies investigating the antibodies in CSF would be important since anti-NMDAR antibody-testing is more significant in CSF than serum [29].

Differential Diagnosis of Mood Disorder

Like schizophrenia, the pathophysiology of mood disorder is associated with dysfunction of the glutamatergic system, such as malfunction of clearance and metabolism of glutamate [47, 48]. A number of studies have demonstrated that environmental stress induces an increase in glutamate release in various brain areas, and an excess of synaptic glutamate causes neurotoxicity [49, 50]. Patients with mood disorder have dysregulation of the glutamine/glutamate cycle and significantly higher glutamine levels in serum and CSF as compared to normal controls [51, 52]. At the molecular level, expression of NMDA glutamate receptors as well as glutamate transporter have been found to be altered in postmortem brain tissue from patients with mood disorder [53]. Moreover, ketamine, one of the NMDAR antagonists, has been reported to have an anti-depres-

sant effect [54, 55], even in treatment-resistant mood disorders [56]. Memantine, a low-affinity NMDAR antagonist, is also reported to have a significant effect in patients with treatment-resistant mood disorders [57].

In spite of this evidence that demonstrated altered glutamatergic neurotransmission in mood disorders, there have been few studies of the relationships between anti-NMDAR encephalitis and mood disorders. In addition, the isotypes of anti-NMDAR autoantibodies showed a broader distribution like schizophrenia. The prevalence of anti-NMDAR antibodies in the serum of patients with depression has been reported: 5.1% (5 of 99) in any immunoglobulin isotype, but 0% (0 of 99) in the IgG isotype [40]. In another study of patients with affective disorders, 16.2% (24 of 148) were seropositive in any immunoglobulin isotype, but only 3.4% (5 of 148) in IgG [41]. Since there have been no studies investigating relationships between anti-NMDAR encephalitis and mood disorder using CSF examination, further studies will be required for patients with mood disorder, just like schizophrenia.

Conclusion

In this review, we evaluated anti-NMDAR encephalitis from the perspective of psychiatry. When psychiatrists occasionally examine patients with anti-NMDAR encephalitis in psychiatric institutions, we recommend that psychiatrists should be aware of the following three points: 1) subacute clinical course through 5 phases (prodromal, psychotic, unresponsive, hyperkinetic, and gradual recovery), 2) presence of neurological features such as orolingual dyskinesia, and 3) abnormal findings in CSF, EEG and MRI. Anti-NMDAR encephalitis may contribute to our understanding of the interaction between psychosis, autoimmunity, and glutamatergic function. Since the majority of patients with anti-NMDAR encephalitis visit psychiatric institutions at the beginning of illness, psychiatrists must cultivate a better understanding of anti-NMDAR encephalitis.

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