Anti-NMDA Receptor Antibody Positivity and Presentations Without Seizure, Involuntary Movement, Hypoventilation, or Tumor: A Systematic Review of the Literature

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Patients with anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis may remain undiagnosed and untreated with immunotherapy. To investigate specific features and responses to immunotherapy of atypical anti-NMDAR antibody positivity patients, the authors reviewed and evaluated previous case reports/series including patients without seizure, involuntary movement, hypoventilation, or tumor. Of 22 patients identified, 21 responded to immunotherapy. Two patients had neurological/motor symptoms with few/no psychiatric/cognitive symptoms, and eight had both. Twelve patients presented with psychiatric/cognitive symptoms with few/no neurological/motor symptoms, and ≥1 had memory impairment, catatonia, abnormal MRI or electroencephalogram results. The authors recommend lumbar puncture and examination of anti-NMDAR antibodies for patients with these features.

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Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis was formally recognized in 2007 as a specific type of autoimmune encephalitis.[1] This encephalitis is an immune-mediated disorder associated with immunoglobulin G (IgG) antibodies to the GluN1 subunit of the NMDAR and is most common in young female patients with ovarian teratomas.[2] In the prodromal phase, approximately 70% of patients with anti-NMDAR encephalitis present with nonspecific flu-like symptoms such as nausea, vomiting, fever, headache, and fatigue for about 0–2 weeks. In the progressive phase, typical presentations include initial psychiatric symptoms followed by seizures, memory deficits, decreased level of consciousness, movement abnormalities (e.g., catatonia, dyskinesia, and chorea), autonomic instability, and central hypoventilation.[3] Within the first 4 weeks after symptom onset, most patients (87%) develop typical symptoms irrespective of their age. Immunotherapy and tumor resection (if present) typically lead to positive outcomes, with most patients returning to baseline functions.[4]

Anti-NMDAR encephalitis has now been described in patients of both sexes ranging in age from less than 1 year to over 80 years,[4] and the course of this disorder may be extremely variable. Cases presenting with psychiatric/cognitive symptoms with few or no neurological/motor symptoms have been reported. Of 571 patients with anti-NMDAR encephalitis, 23 (4%) developed isolated psychiatric episodes; of these, five (0.9%) presented at the first episode of encephalitis and 18 at relapse of encephalitis. Of these 23 patients, 83% completely or substantially recovered after immunotherapy and tumor resection (if any).[5] We previously reported an atypical case of anti-NMDAR encephalitis presenting with first-episode psychosis and resistance to antipsychotic treatment, without neurological symptoms or tumor, where disease improved with immunotherapy.[6]

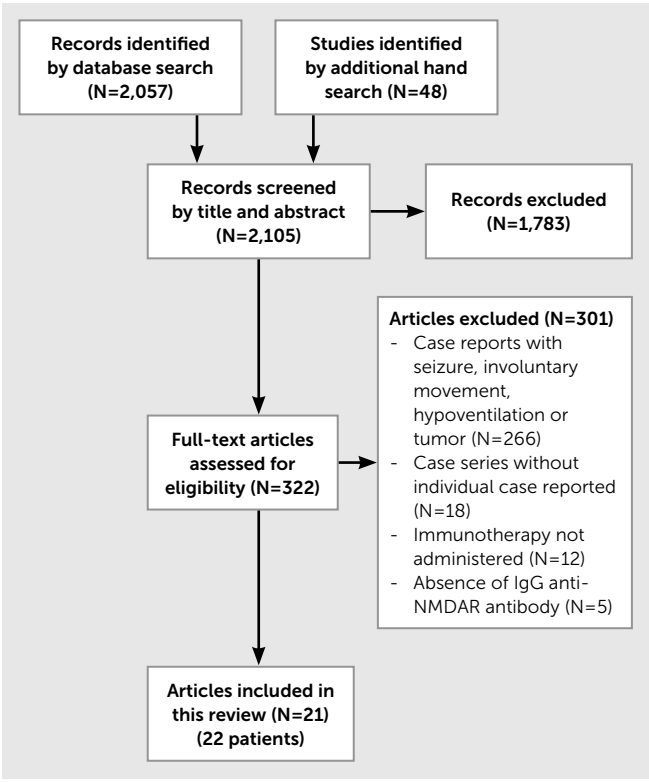
Generally, three out of four patients with anti-NMDAR encephalitis do not consult a general health care service before seeking treatment at a psychiatric department.[2] If patients do not present with typical manifestations, this treatable disorder may remain undiagnosed in psychiatric care settings, which may lead to a delay in the detection of anti-NMDAR antibodies and treatment with immunotherapy. The diversity of clinical characteristics of anti-NMDAR encephalitis and the response to immunotherapy in cases with atypical manifestations remains unclear. We therefore conducted a systematic review of case reports and series of atypical presentations associated with anti-NMDA receptor antibody positivity to investigate the specific symptoms or patterns of patients presenting with psychiatric/cognitive symptoms with few or no neurological/motor symptoms.

MATERIALS AND METHODS

Search

This systematic review followed the PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses]

FIGURE 1. Flowchart of the Literature Search[a]



[a] IgG: immunoglobulin G; NMDAR: *N*-methyl-D-aspartate receptor.

guidelines. We reviewed previous case reports and series of atypical presentations associated with anti-NMDA receptor antibody positivity. We searched MEDLINE (PubMed) to perform a systematic review of the literature published prior to December 31, 2015, using the following search terms: ("*N*-methyl-D-aspartate receptor" or "NMDA receptor" or "NMDAR") and ("encephalitis" or "antibody" or "antibodies"). The electronic search was supplemented by a manual search of reference lists of relevant publications. Only articles in English or Japanese were included.

Study Selection

The diagnosis of anti-NMDA receptor antibody positivity was made based on the detection of IgG antibodies against the NR1 subunit of the NMDAR in serum or cerebrospinal fluid (CSF).[2] All articles were evaluated to determine whether case reports without seizure, involuntary movement, hypoventilation, and tumor, which we defined as atypical presentations, were included. We also included patients with psychotropic-induced or catatonia-related movement disorders and who were treated with immunotherapy. We excluded patients who had classic presentations at the first episode of encephalitis but experienced atypical presentations during a relapse of encephalitis. Because the inclusion criteria required confirmation by clinical characteristics and treatment of each patient, we needed to eliminate cohort studies. If that was not possible, we carefully considered each case as an alternative.

Data Extraction

The following data were collected from all articles: author, publication year, sex, age, duration of illness, initial diagnosis, comorbidity, psychiatric/cognitive symptoms, neurological/motor symptoms, abnormal CSF results, MRI and electroencephalogram (EEG) findings, anti-NMDAR antibodies in serum and CSF, immunotherapy, time from initial immunotherapy until clinical improvement, and clinical outcome of patients.

RESULTS

Literature Search

The literature search using the MEDLINE (PubMed) electronic database yielded a total of 2,057 citations. Of these, 322 case reports or series were fully inspected, and 301 were removed from analysis for the following reasons: presence of seizure, involuntary movement, hypoventilation, or tumor (266 articles); case series without individual case reports (18 articles); immunotherapy not administered (12 articles); and absence of IgG anti-NMDAR antibody (five articles). Finally, our review identified 21 articles (22 patients) with atypical anti-NMDA receptor antibody positivity treated with immunotherapy (Figure 1).[5–25] The publication years were 2011 (N=2), 2012 (N=2), 2013 (N=6), 2014 (N=4), and 2015 (N=8) (Table 1).

Clinical Characteristics

Table 1 shows the clinical characteristics of 22 patients, including eight male and 14 female patients. The age range was 4–70 years (mean, 30.6 years; median, 30 years). The mean±standard deviation (range) duration of illness (N=19) was 31.3±69.2 (0.15–286) weeks. Seven patients were initially diagnosed with primary psychiatric disorders. Five patients had other comorbid autoimmune disorders/antibodies: systemic sclerosis (N=1), multiple sclerosis and Sjögren's syndrome (N=1), rheumatoid arthritis (N=1), aquaporin-4 antibody positive (N=1), and Hashimoto's thyroiditis (N=1). Twelve patients presented with psychiatric/cognitive symptoms with few or no neurological/motor symptoms. Two patients had few or no psychiatric/cognitive symptoms but did have neurological/motor symptoms. The remaining eight patients showed both types of symptoms. The distribution of psychiatric indications was psychotic symptoms (N=10), affective symptoms (N=8), and catatonic symptoms (N=6). Of the 12 patients who presented with psychiatric/cognitive symptoms with few or no neurological/motor symptoms, six (50%) had one of the following: memory impairment, catatonia, or abnormal MRI or EEG results, and six (50%) had two or more of these symptoms.

Test Results

Of 22 patients, abnormal CSF, MRI, and EEG results were confirmed in 16 (pleocytosis, N=12; elevated protein, N=8; oligoclonal band, N=8; unknown, N=2), 12, and 8 patients,

TABLE 1. Cases With Atypical Anti-NMDA Receptor Encephalitis Treated With Immunotherapy[a]

Case No./ Author/ Publication Year	Sex/Age (Years)	Duration of Illness	Initial Diagnosis/ Comorbidity	Psychiatric and Cognitive Symptoms	Neurological and Motor Symptoms	Abnormal Results for CSF/MRI/EEG	Anti-NMDAR/ Abnormal Serum CSF	Immunotherapy (Order of Treatment)	Time From Initial Immunotherapy Until Clinical Improvement	Immunotherapy Response
1. Zandi et al./2011[7]	Male/19	3 months	SCZ/–	Auditory hallucinations, thought disorder, grandiose delusions, deficits of recall and verbal fluency	Nil	NA/NA/NA	+/NA	PE, steroids	3 weeks	Very much improved
2. Suzuki et al./2011[8]	Female/70	6 months	NA/SSc	Dementia (10/30 on MMSE)	Ataxia, tremor, rigidity, muscle weakness	+/+/ NA	+/+	Steroids, CTX	NA	Very much improved
3. Lekoubou et al./2012[9]	Female/34	1 month	ADEM/–	Psychomotor agitation, echolalia and echopraxia, incoherent speech, delusions of persecution	Walking difficulties, disorientation, cerebellar ataxia, hemiparesis	+/+/NA	NA/+	IVIg, steroids, RTX	<6 months	Much improved
4. Lebon et al./2012[10]	Female/16	2 months	Primary psychotic disorder/–	Mutism, refusal to eat, infantile behavior, auditory hallucinations, incoherent speech, memory impairment, executive deficit, attention deficit	Nil	–/–/+	+/NA	Steroids, IVIg	9 months	Very much improved
5. Yuan et al./2013[11]	Female/22	3 weeks	NA/–	Affective lability, grandiose thoughts, paranoid delusion, auditory and visual hallucinations, deficits of verbal fluency, visuospatial deficit, hemispatial neglect, memory impairment	Nil	+/–/+	NA/NA (Positive in serum or CSF or both)	Steroids, IVIg, PE, RTX	6 months	Much improved

continued

TABLE 1, *continued*

Case No./ Author/ Publication Year	Sex/Age (Years)	Duration of Illness	Initial Diagnosis/ Comorbidity	Psychiatric and Cognitive Symptoms	Neurological and Motor Symptoms	Abnormal Results for CSF/MRI/EEG	Anti-NMDAR/ Abnormal Serum CSF	Immunotherapy (Order of Treatment)	Time From Initial Immunotherapy Until Clinical Improvement	Immunotherapy Response
6. Yau et al./2013[12]	Female/5	1 week	NA/–	Fluctuating level of consciousness, mutism, impaired speech, irritability	Nil	+/–/+	–/+	IVIg	1 week	Very much improved
7. Tüzün et al./2013[13]	Female/42	2 weeks	NA/–	Mild Executive Deficit	Double vision, difficulty walking, limited vertical gaze	+/+/–	+/+	Steroids	2 months	Very much improved
8. Leypoldt et al./2013[14]	Male/24	1 day	Relapse of HSVE/–	Mania, irritability, racing thoughts, pressured speech, memory impairment, attention deficit	Nil	+/+/–	+/+	Steroids	1 week	Much improved
9. Kayser et al./2013[5]	Male/19	2–3 months	Demyelinating disease/–	Aggression, excessive eye blinking, grandiosity, delusional thinking	Nil	+/+/–	+/NA	Steroids, AZA	9 months	Very much improved
10. Kayser et al./2013[5]	Female/20	NA	NA/–	Delusion, depression	Nil	+/+/NA	+/+	Steroids, IVIg, RTX, MMF	NA	Very much improved
11. Kuppuswamy et al./2014[15]	Male/35	2 weeks	Primary psychotic disorder/–	Depression, suicidality, grandiosity, impulsivity, mutism, posturing, staring, ambitendency	Nil	–/–/–	+/+	Steroids, PE, AZA	4 months	Very much improved
12. Finke et al./2014[16]	Male/67	2 weeks	HaNDL/–	Confusion, agitation, aggressiveness, retrograde amnesia, memory impairment, attention deficit	Transient hemiparesis, transient aphasia	+/–/+	–/+	Steroids, PE, AZA	6 weeks	Much improved
13. Byrne et al./2014[17]	Male/4	2 days	NA/–	Confusion, agitation	Dysphasia, coma	–/+/+	+/NA	Steroids	4 days	Very much improved

continued

TABLE 1, *continued*

Case No./ Author/ Publication Year	Sex/Age (Years)	Duration of Illness	Initial Diagnosis/ Comorbidity	Psychiatric and Cognitive Symptoms	Neurological and Motor Symptoms	Abnormal Results for CSF/MRI/EEG	Anti-NMDAR/ Abnormal Serum CSF	Immunotherapy (Order of Treatment)	Time From Initial Immunotherapy Until Clinical Improvement	Immunotherapy Response
14. Takeda et al./2014[18]	Male/35	6 days	Herpes encephalitis/–	Delirium, violent behavior, delusions, disorientation	Diplopia, paraparesis, hypoesthesia, ptosis	+/+/NA	NA/+	Steroids, PE, CTX	12 months	Much improved
15. Fleischmann et al./2015[19]	Female/37	5.5 years	NA/MS and SS	Delusions, bizarre behavior, aggressiveness, memory impairment, Dementia (14/30 on MMSE), disorientation, executive deficit	Gait ataxia, dysarthria	+/+/ NA	+/+	Steroids, AZA, CTX, NTL, PE, MTX	Nonresponse	Death (urosepsis)
16. Cuende et al./2015[20]	Female/61	3 months	NA/RA	Memory loss	Dizziness, unsteady gait, muscle weakness, speech problems	+/–/NA	+/+	IVig	NA	Very much improved
17. Kruse et al./2015[21]	Female/14	NA	NA/–	Anxiety, depressed mood, disinhibited and disorganized behavior, reduced verbal output, slow speech, learning difficulty	Transient arm numbness, difficulty with complex motor tasks	+/–/+	–/+	NA	NA	Very much improved
18. Sühs et al./2015[22]	Female/23	2 years	Psychiatric disorder/–	Fearful behavior, stereotypical repetitive movements, loss of orientation, memory impairment, executive deficit	Nil	+/–/+	+/NA	Steroids	1 month	Very much improved
19. Orengo et al./2015[23]	Female/29	3 months	NA/serum aquaporin-4 antibody positive	Anorexia, abulia, mutism, immobility, nonsensical speech, memory impairment	Imbalance and vertigo, facial numbness, ataxia	+/+/NA	–/+	Steroids, PE, RTX	NA	Much improved

continued

TABLE 1. *continued*

Case No./ Author/ Publication Year	Sex/Age (Years)	Duration of Illness	Initial Diagnosis/ Comorbidity	Psychiatric and Cognitive Symptoms	Neurological and Motor Symptoms	Abnormal Results for CSF/MRI/EEG	Anti-NMDAR/ Abnormal Serum CSF	Immunotherapy (Order of Treatment)	Time From Initial Immunotherapy Until Clinical Improvement	Immunotherapy Response
20. Gahr et al./2015[24]	Male/34	1 week	Psychotic mania/–	Impulsivity, aggressiveness, hostility, dysphoric mania paranoid ideation hyper-religiosity	Nil	+/+/NA	+/+	Steroids, IVIg	NA	Very much improved
21. Senda et al./Epub ahead of print 2015[6]	Female/33	2 years	SCZ/HT	Auditory and visual hallucination, delusions of persecution, delusion of control agitation, memory impairment, executive deficit	Nil	–/–/–	NA/+	Steroids, IVIg	3 months	Much improved
22 Lalanne et al./2015[25]	Female/31	NA	Psychotic depression	Melancholia, depression, cenesthopathy, memory impairment, attention deficit	Nil	NA/+/+	NA/+	Steroids, IVIg	5 weeks	Very much improved

[a] Ab: antibody, ADEM: Acute disseminated encephalomyelitis, ADHD: attention deficit hyperactivity disorder, AZA: azathioprine, CSF: cerebrospinal fluid, CTX: cyclophosphamide, EEG: electroencephalogram, HaNDL: headache with neurological deficits and cerebrospinal fluid lymphocytosis, HSVE: herpes simplex virus-1 encephalitis, HT: Hashimoto's thyroiditis, IVIg: intravenous immunoglobulin, MMF: mycophenolate mofetil, MMSE: Mini-Mental State Examination, MS: multiple sclerosis, MRI: magnetic resonance imaging, MTX: mitoxantrone, NA: not available, NMDAR: *N*-methyl-D-aspartate receptor, NTL: natalizumab, PE: plasmapheresis, RA: rheumatoid arthritis, RTX: rituximab, SCZ: schizophrenia, SSc: systemic sclerosis SS: Sjögren's syndrome.

respectively. In two patients, the results of all three tests were normal. Of 16 patients with anti-NMDAR antibodies in the CSF, serum antibodies were negative in four patients, positive in eight patients, and unknown in four patients.

Immunotherapy and Outcome

The frequencies of immunotherapy, in order of declining frequency were: steroids, 19/21; intravenous immunoglobulin, 9/21; plasmapheresis, 7/21; azathioprine, 4/21; rituximab, 4/21; cyclophosphamide, 3/21; and others, 3/21. The immunotherapy of case 17 was unspecified. Fourteen patients (64%) fully recovered, seven patients (32%) were much improved by immunotherapy, and one patient died (urosepsis). The time from initial immunotherapy until clinical improvement ranged from 4 days to 12 months (N=14; mean, 15.4 weeks; median, 7.5 weeks). Among 19 patients, 16 patients (85%) had not shown typical symptoms of anti-NMDAR encephalitis four weeks after symptom onset, and three patients recovered within the first 4 weeks of onset after treatment with immunotherapy. The remaining three patients could not be assessed because of insufficient information.

DISCUSSION

Diversity of Clinical Characteristics

The manifestations of anti-NMDAR antibody positivity are heterogeneous. Atypical presentations associated with anti-NMDA receptor antibody positivity occurred over a wide age range in both men and women and presented with diverse psychiatric/cognitive and/or neurological/motor symptoms. It was frequently associated with other autoimmune diseases. There were various forms of abnormal brain MRI, CSF, and EEG results in atypical cases as observed in typical cases. Patients who presented with psychiatric/cognitive symptoms with few or no neurological/motor symptoms had at least one of the following symptoms: memory impairment, catatonia, or abnormal MRI or EEG results. Although early diagnosis and implementation of appropriate immunotherapy might have prevented the disease from progressing to typical presentations

in some cases, most patients (85%) in the selected case reports/series had not presented with typical symptoms of anti-NMDAR encephalitis four weeks after symptom onset. However, all atypical cases of anti-NMDAR encephalitis are probably not published systematically.

Response to Immunotherapy

Given the 95% response rate in our review, immunotherapy seems to be as effective in atypical cases as in typical cases. Ten patients (48%) responded to first-line immunotherapy (steroids, intravenous immunoglobulin, and plasmapheresis). Of note, this study may have a publication bias. Clinicians are more likely to report patients who have good clinical outcomes. One of the main reasons for this is that if a patient does not respond to immunotherapy, the clinician is less likely to interpret that antibody as pathogenic in that patient and would not consider these cases to be anti-NMDAR encephalitis.

Detection of Anti-NMDAR Antibodies

Based on our literature review, the presence of anti-NMDAR antibodies in both serum and CSF should be examined to expedite the detection and subsequent treatment of this treatable disorder. We recommend a lumbar puncture for patients with memory impairment, catatonia, or abnormal MRI or EEG results even if these patients do not show neurological/motor symptoms. In some cases, anti-NMDAR antibodies in the CSF were positive, whereas serum antibodies were negative. A previous study showed that the sensitivity of NMDA receptor antibody testing is higher in the CSF than in serum.[26,27] Caution is advised when interpreting a positive serum result for anti-NMDAR antibody detection in the absence of CSF inflammatory findings or autoantibody detection in the CSF.[28] However, the greatest challenge in real-world clinical settings in psychiatric hospitals is the difficulty in conducting lumbar puncture because of the technical expertise required or the patients' uncooperative behavior because of their psychiatric symptoms.

Definition of Atypical Presentations

The definition of atypical presentations associated with anti-NMDA receptor antibody positivity used in this study may have advantages and disadvantages. We defined cases without seizure, involuntary movement, hypoventilation, and tumor as atypical presentations because primary psychiatric disorders typically are not associated with these symptoms or tumor, and we had a strong awareness of excluding the classic symptoms of anti-NMDAR encephalitis and evaluating the efficacy of immunotherapy without tumor resection. However, the presence of tumor is sex and age dependent.[4,29] A very small percentage of young males with anti-NMDAR encephalitis present with a tumor. Furthermore, tumors may not be a criterion tested for in primary psychiatric presentations and can be asymptomatic. Currently, more patients are being diagnosed and treated earlier compared with a few years ago and therefore may not develop hypoventilation. We included cases with a decreased level of consciousness (stupor), speech disorders, or autonomic imbalance because primary psychiatric disorders with catatonia produce those symptoms.[30] However, our inclusion criteria might be overly restrictive. Some case reports were not included despite reporting atypical presentations of anti-NMDAR encephalitis: a case with seizure and parkinsonism including micrographia,[31] a case with IgM NMDAR antibody associated encephalitis mimicking bipolar disorder,[32] two cases with intellectual disability and autism presenting with seizure and malignant catatonia,[33] a case with fever of unknown origin, catatonia, mood disorder and ovarian teratoma,[34] and two cases with autobiographical age awareness disturbance syndrome with seizure or involuntary movement.[35] Because we excluded case series and cohort studies without individual case reports, nine cases of acute psychosis without clear clinical neurological involvement or seizure that were treated with immunotherapy[36] were not included. Of these nine patients, six patients achieved symptomatic remission, and two patients responded clinically. However, the clinical characteristics, abnormal test results, immunotherapy, and outcome of each patient were not determined.

CONCLUSIONS

Because psychiatrists are often consulted for anti-NMDAR encephalitis patients, psychiatrists should be aware of the atypical presentations of anti-NMDAR encephalitis and consider it during the differential diagnosis of patients with memory impairment, catatonia, or abnormal MRI or EEG results, and consult with neurologists without hesitation. If not appropriately diagnosed, patients can be exposed to a prolonged period of psychotropic drug treatment, which have a number of side effects, and the chance of recovery may decrease. As with typical anti-NMDAR encephalitis cases, atypical cases present with psychiatric symptoms and behavior disorders with a high frequency at an early stage or throughout the disease course.

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