

Original Investigation

Frequency and Characteristics of Isolated Psychiatric Episodes in Anti-N-Methyl-D-Aspartate Receptor Encephalitis

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IMPORTANCE Patients with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis often develop prominent psychiatric manifestations. The frequency and type of isolated psychiatric episodes (pure psychiatric symptoms without neurological involvement) either as initial presentation of the disease or as relapse are unknown.

OBJECTIVE To determine the frequency, symptoms, and outcome of isolated psychiatric episodes in a cohort of patients with anti-NMDAR encephalitis.


DESIGN, SETTING, AND PARTICIPANTS Observational cohort of patients diagnosed during a 5-year period (median follow-up, 2 years). A total of 571 patients with IgG antibodies against the NR1 subunit of the NMDAR were included in the study. Antibody studies were performed at the University of Pennsylvania and the University of Barcelona, and clinical information was obtained by us or referring physicians.

MAIN OUTCOMES AND MEASURES Frequency, type of symptoms, and outcome of patients with anti-NMDAR encephalitis and isolated psychiatric manifestations.

RESULTS Of 571 patients, 23 (4%) developed isolated psychiatric episodes, 5 at disease onset and 18 during relapse. For all 23 patients, age (median, 20 years), sex (91% female), and tumor association (43%; ovarian teratoma in all cases) were similar to the population at large. Predominant symptoms included delusional thinking (74%), mood disturbances (70%, usually manic), and aggression (57%). Brain magnetic resonance imaging findings were abnormal in 10 of 22 patients (45%) and cerebrospinal fluid analysis showed pleocytosis in 17 of 22 patients (77%). Eighty-three percent of the patients had full or substantial recovery after immunotherapy and tumor resection when appropriate. After relapse, 17 of 18 patients (94%) returned to a similar or better prerelapse functional level.

CONCLUSIONS AND RELEVANCE Isolated psychiatric episodes are rare but can occur as initial onset or relapse of anti-NMDAR encephalitis. Recognition of these episodes is important because they respond to immunotherapy. In patients with new-onset psychosis, having a history of encephalitis, subtle neurological symptoms, and/or abnormal results on ancillary tests should prompt screening for NMDAR antibodies.

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Anti-*N*-methyl-*D*-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder in which IgG antibodies are directed against the NR1 subunit of the NMDAR. The disorder includes a range of psychotic symptoms early in the course of the disease, followed by neurological involvement and ultimately protracted cognitive and behavioral symptoms.^{1,2} The occurrence of severe behavioral changes reminiscent of a schizophrenia-like illness has fueled speculation that this disorder might define a subset of patients misdiagnosed as having a primary psychiatric disease.^{3,4} To address this possibility, 2 major questions need to be answered. First, do some patients diagnosed as having primary psychiatric disorders, such as schizophrenia or major depressive disorder, harbor IgG NR1 antibodies and respond to immunotherapy? Second, do patients with anti-NMDAR encephalitis commonly have pure psychiatric episodes without neurological involvement? Several recent studies have addressed the former question, with mixed findings suggesting that most patients with well-established primary psychiatric disorders are unlikely to develop IgG NR1 antibodies.⁵⁻⁸ This study addresses the second question by determining the frequency and type of isolated psychiatric symptoms at either disease onset or relapse in a large cohort of patients with anti-NMDAR encephalitis. In addition, we provide the clinical clues that led to the diagnosis of anti-NMDAR encephalitis and the response of psychiatric symptoms to immunotherapy.

Methods

Detailed clinical information of the first episode of encephalitis was obtained for 571 patients.⁹ Follow-up information was obtained at regular intervals after symptom onset (median follow-up for the entire series, 24 months). Information was obtained by us or provided by referring physicians and has been partially reported for 3 patients in the subset described in this study.^{10,11} In all patients, the disorder was confirmed by detection of IgG antibodies against the NR1 subunit of the NMDAR in cerebrospinal fluid (CSF) or serum using reported criteria.^{1,12} All patients had a detailed workup to exclude other disorders, including brain magnetic resonance imaging (MRI) and blood and CSF studies. Isolated psychiatric presentations were defined as episodes (either initial presentation or relapse) that occurred in association with NMDAR antibodies in serum or CSF without neurological involvement. Relapse was defined by the new onset or worsening of symptoms at least 2 months after improvement or stabilization, without any other cause involved, and persistent detection of NMDAR antibodies. The Mann-Whitney *U* test was used to compare the age at onset. In patients who had psychiatric relapses, the Wilcoxon signed rank test was used to compare the delay of treatment in the initial episode of the disease with that of the psychiatric relapse. Studies were approved by the institutional review boards of the University of Pennsylvania and the University of Barcelona.

Results

Of 571 patients with anti-NMDAR encephalitis, we identified 23 (4%) with isolated psychiatric symptoms; 5 (0.9%) presented at the first episode of encephalitis and 18 at relapse of encephalitis (Table 1). The median age of these 23 patients (21 women) was 20 years, which was similar to the population at large (median age, 21 years; $P = .45$), and the median clinical follow-up was 25 months (range, 4-72 months). Ten patients (43%) had an identifiable underlying tumor during the disease; it was an ovarian teratoma in all cases. In 5 patients, the teratoma was identified during relapse of encephalitis; 3 of these patients had no history of teratoma and 2 had a recurrent teratoma.

The CSF cell counts were available in 22 patients; 17 (77%) had lymphocytic pleocytosis with or without an elevated protein concentration (Table 1). Findings on brain MRI were abnormal in 10 of 22 patients (Table 1). In 8 patients, abnormalities included unilateral or bilateral nonspecific fluid-attenuated inversion recovery changes involving temporal, frontal, and/or parietal lobes, with transient contrast enhancement in 2 cases. Another patient had mild atrophy in temporal lobes, and 1 patient had a diffusion-restricted abnormality in the corpus callosum (examples shown in the Figure). Electroencephalographic (EEG) results were available for 20 patients, with abnormalities in 15 (either epileptic or nonspecific slowing).

In 5 patients, isolated psychiatric symptoms were the only clinical manifestation of the disease on initial presentation, without eventual development of neurological symptoms. The time from symptom onset until treatment ranged from 2 to 60 weeks (median, 9 weeks). Each of these 5 patients had abnormal findings on MRI. In retrospect, the families of 2 of these patients indicated having noted mild transient facial movements described as excessive blinking, and another patient had hypersalivation. Eighteen patients experienced episodes that were pure psychiatric at relapse. These patients had all been previously diagnosed as having anti-NMDAR encephalitis during a classic presentation with neurological components. The median time from symptom onset until treatment of their relapses was 14 days (range, 3-60 days), compared with 28 days (range, 7-154 days) in the initial episodes ($P = .004$). Given that 64 of the 571 patients in the study experienced a relapse of encephalitis⁹ and that 18 of them occurred with isolated psychiatric symptoms, our findings indicate that 28% of all relapses were pure psychiatric episodes. Five of the 18 patients had more than 1 relapse; of these 5 patients, only 2 had more than 1 relapse with isolated psychiatric symptoms.

In the 23 patients with pure psychiatric episodes, psychotic symptoms with a mood component dominated the clinical picture (Table 1 and Table 2). Seventeen patients (74%) had delusional thinking, 10 (43%) had auditory or visual hallucinations, and 13 (57%) had aggressive behavior; 11 of 18 patients (61%) showed aggression during relapses. Sixteen patients (70%) had a documented mood component during the pure psychiatric episode: 11 were noted to be manic, labile, impulsive, or disinhibited, 4 experienced depressed mood, and

Table 1. Characteristics of Patients With Discrete Psychiatric Episodes^a

Sex/ Age, y	Abnormal Result			Anti-NMDAR Ab		Tumor	Predominant Psychiatric Symptoms	Immunotherapy (Order of Treatment)	Prerelapse vs Post- relapse Clinical Status	Recovery at Last Follow-up, mo
	MRI	EEG	CSF	CSF	Serum					
Initial Episode										
F/13	X		NA	+	NA	X	Delusions, mania, suicidality	(1) Steroids; (2) IVIg	...	Full, 24
F/18	X		X	+	+	X	Delusions, AVH, hyperphagia	(1) Steroids, IVIg	...	Full, 34
M/19	X	X	X	+	NA		Aggression, delusions, mania	(1) Steroids; (2) AZA	...	Full, 25
F/20	X	NA	X	+	+		Delusions, depression	(1) Steroids, IVIg; (2) RTX; (3) MMF	...	Full, 37
F/46	X	X	X	+	NA		Aggression, AVH, delusions	Unknown	...	No improvement, 4
Relapse										
F/12		X		+	-		Aggression, delusions, disinhibition, echolalia	(1) Steroids, IVIg (initial); (2) plasmapheresis, CTX, RTX, MMF (relapses)	Equal	Full, 46
F/13		X		+	+		Aggression, AVH, delusions, suicidality	(1) Steroids (initial); (2) steroids; (3) IVIg; (4) RTX, CTX; (5) MMF (relapses)	Worse	Substantial (>75%), 72
F/13		NA	X	+	+		Aggression, delusions, lability	(1) Steroids; (2) IVIg (initial); (3) MMF; (4) RTX; (5) plasmapheresis (relapses)	Equal	Full, 47
F/14	NA			+	+	X ^b	Delusions, lability	(1) Steroids, IVIg	Equal	Full, 35
F/15		X	X	NA	+	X ^c	Aggression, AVH, delusions	(1) Steroids, IVIg	Better	Full, 47
F/16			X	+	+		Aggression, catatonic mania	(1) Steroids, IVIg	Equal	Substantial (>75%), 39
F/17		X	X	+	+		Depression	(1) Steroids; (2) IVIg; (3) plasmapheresis (initial); (4) IVIg, steroids; (5) MMF (relapses)	Equal	Full, 22
F/18		X	X	+	+	X ^d	Mania	(1) Steroids; (2) IVIg (initial); (3) untreated (relapse); (4) IVIg (relapse)	Equal	Full, 13
F/24		X	X	+	-	X	Aggression, delusions, mania	(1) IVIg; (2) steroids, RTX	Equal	Full, 20
F/24		X	X	+	+	X	Delusions, AVH	(1) Plasmapheresis; (2) steroids; (3) IVIg; (4) AZA	Equal	Substantial (>75%), 16
F/26	X	X	X	+	+	X ^c	Aggression, mania	(1) Plasmapheresis; (2) IVIg; (3) RTX	Equal	Substantial (>75%), 28
F/28	X	X	X	+	-		Aggression, AVH, delusions, mania	(1) Steroids, IVIg; (2) CTX, RTX	Equal	Full, 36
F/30		X	X	+	NA	X ^c	Aggression, AVH, delusions	(1) Steroids; (2) RTX, CTX	Equal	Died (PE) 25
F/30	X	X	X	+	-		Aggression, AVH, delusions, depression	(1) Steroids; (2) IVIg; (3) plasmapheresis; (4) CTX	Equal	Severe deficits, 80
F/34		X	X	+	-	X ^e	Aggression	(1) Steroids (initial); (2) IVIg (relapse)	Better	Substantial (>75%), 22
F/34		NA		+	NA		AVH, delusions	(1) Steroids; (2) IVIg (initial); (3) steroids, IVIg (relapse)	Equal	Full, 23
M/34	X			+	-		AVH, delusions, mood changes	(1) Steroids (initial); (2) steroids (relapse)	Equal	Substantial (>75%), 44
F/62	X	X	X	+	NA		Disinhibition	(1) Steroids, IVIg; (2) CTX (initial); (3) steroids, CTX; (4) RTX (relapse)	Equal	Severe deficits, 20

Abbreviations: Ab, antibodies; AVH, auditory/visual hallucinations; AZA, azathioprine; CSF, cerebrospinal fluid; CTX, cyclophosphamide; EEG, electroencephalography; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; NA, not available; NMDAR, *N*-methyl-D-aspartate receptor; PE, pulmonary embolism; RTX, rituximab; ellipses, not applicable; +, positive; -, negative.

^a Empty cells indicate normal findings.

^b Recurrence of ovarian teratoma at relapse.

^c Tumor only found at relapse; earlier screening negative.

^d New ovarian teratoma (other site) at relapse.

^e Ovarian teratoma seen at initial episode but only removed at relapse.

Table 2. Symptoms in Patients With Isolated Psychiatric Episodes

Symptom	Timing of Isolated Psychiatric Episode, No. (%)		
	All	Initial	Relapse
Aggression	13 (57)	2 (40)	11 (61)
Auditory/visual hallucinations	10 (43)	2 (40)	8 (44)
Delusions	17 (74)	5 (100)	12 (67)
Mood	16 (70)	3 (60)	13 (72)
Manic	7 (30)	2 (40)	5 (28)
Depressed	4 (17)	1 (20)	3 (17)
Labile, disinhibited, impulsive	4 (17)	0	4 (22)
Other	1 (4)	0	1 (6)
Insomnia	7 (30)	1 (20)	6 (33)
Memory	6 (26)	3 (60)	3 (17)

1 had a change in mood without further specification. In 3 of 5 patients with initial psychiatric presentations, the neurological examination only suggested memory problems, which were difficult to confirm owing to the severity of psychiatric symptoms; 3 of 18 patients with psychiatric relapses had residual cognitive changes from previous episodes of encephalitis (2 of them had a Korsakoff-like syndrome that remained unchanged during the psychiatric relapse).

Overall, 19 of 23 patients (83%) had full or substantial recovery after treatment of the disease with immunotherapy and, when applicable, removal of the teratoma. Four of the 5 patients with initial psychiatric presentations had full recovery by 24 months; from the fifth patient, we have limited data indicating that she had not recovered 4 months after symptom onset (Table 1). Fifteen of 18 patients (83%) with pure psychiatric relapses had full recovery or substantial improvement, 2 had severe residual deficits, and 1 died of a thromboembolism after complete psychiatric recovery. Table 1 shows the comparison of the level of recovery attained after the initial episode of the disease with that attained after the psychiatric relapse: 15 patients returned to the same prerelapse functional level, 1 improved partially without reaching the prerelapse level, and 2 improved to a better functional status. In these latter 2 cases, the relapse of encephalitis led to additional immunotherapy, and in one of them a previously unknown teratoma was detected and removed.

Two representative patients seen by us are described. One of the patients had isolated psychiatric symptoms at disease onset and the other had them at relapse of encephalitis.

Patient 1

A 19-year-old man with no psychiatric or medical history was initially admitted for behavioral changes in the setting of a non-specific left frontotemporal abnormality found on brain MRI after a motor vehicle collision. The patient drove off the road but was unable to recall the circumstances. His parents described that he had been “acting strangely” during the preceding few months, often not remembering events and repeating words. He was discharged following the MRI at an outside hospital but was brought to the University of Pennsylvania emergency department after becoming acutely agi-

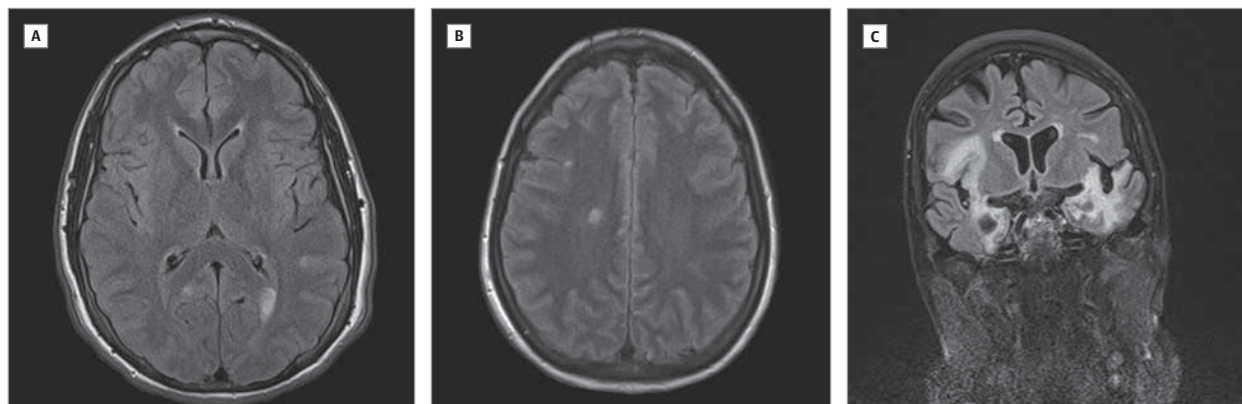
tated prior to a scheduled EEG, with yelling, crying, and combative behaviors. There were no preceding fevers, headaches, or substance use. Aside from the subacute cognitive symptoms described, there were no neurological abnormalities noted, although in retrospect the parents described excessive eye blinking that they thought was due to anxiety.

Psychiatry consult observed the patient to be manic during hospitalization. He was routinely observed to be speed walking in the halls of the hospital, with decreased sleep, pressured speech, and inappropriate laughing. He exhibited grandiosity and delusional thinking. He began treatment with valproic acid for management of symptoms as well as intravenous methylprednisolone for concern of a demyelinating disease. Because of the abnormal MRI findings, a more extensive workup was pursued. Findings on EEG were normal, but CSF analysis revealed lymphocytic pleocytosis and NMDAR antibodies were detected. No other CSF abnormalities were found. Tumor screening was negative. After behavioral stabilization, the patient was discharged on valproic acid, prednisone, and azathioprine. During the next 9 months, the patient returned to near behavioral baseline, and both prednisone and valproic acid were tapered off. He remained on immunosuppression with azathioprine. No further complications or relapses have arisen.

Patient 2

A 28-year-old woman with no psychiatric or medical history initially presented with bizarre behaviors and visual hallucinations. She appeared delusional and grandiose at this time. She was treated for bacterial and suspected herpes simplex virus encephalitis without improvement after admission. Findings on brain MRI, CSF studies, and EEG were normal. She was transferred to an inpatient psychiatric facility, where a psychiatrist noted rhythmic right upper extremity movements, leading to admission to the University of Pennsylvania neurology service for suspected encephalitis. Three weeks after symptom presentation, the patient had witnessed seizures and was intubated. Studies of CSF revealed NMDAR antibodies and she began treatment with intravenous immunoglobulin and steroids, with gradual improvement but a prolonged hospital course. Tumor screening was negative. She was transferred to inpatient psychiatry prior to discharge and ultimately made a

Figure. Brain Magnetic Resonance Images of 3 Patients With Isolated Psychiatric Symptoms



A, Magnetic resonance image of patient 3 obtained at the initial episode of encephalitis with pure psychiatric symptoms; note the fluid-attenuated inversion recovery signal abnormalities in the left parietal lobe and adjacent to the splenium of the corpus callosum. B, Magnetic resonance image of patient 17 showing cortical and subcortical fluid-attenuated inversion recovery changes in

the right frontal lobe identified during a relapse of encephalitis manifesting with isolated psychiatric symptoms. C, Magnetic resonance image of patient 23 showing bilateral, extensive cortical and subcortical fluid-attenuated inversion recovery changes identified during a relapse of encephalitis manifesting with isolated psychiatric symptoms.

full recovery; she was maintained on oxcarbazepine for approximately 1 year and then no medication.

Thirty-three months after the first episode, she began demonstrating increasingly bizarre behavior in the context of tetrahydrocannabinol use and poor sleep. She was preoccupied with religion and became anxious, labile, and disinhibited. Hypersexuality, paranoia, and mania were prominent. She was admitted to the University of Pennsylvania neurology service and was extremely agitated and violent, requiring prolonged restraints. Analysis of CSF revealed an increase of NMDAR antibody titers compared with those obtained during the phase of recovery of the initial episode 29 months earlier (1:64 at relapse vs 1:8 initially). No neurological symptoms were noted throughout the hospitalization and no tumor was found. She was treated with intravenous immunoglobulin and steroids, followed by rituximab and cyclophosphamide. Psychiatric symptoms were managed with valproic acid, quetiapine, and chlorpromazine. The patient was transferred to inpatient psychiatry and discharged 10 days later. She remained stable from a neurological and psychiatric perspective at multiple outpatient visits for at least 4 months.

Discussion

We describe 23 patients with anti-NMDAR encephalitis who developed isolated psychiatric symptoms either as initial episode of the disease (5 patients) or as relapse of encephalitis (18 patients). Predominant symptoms included delusional thinking, auditory or visual hallucinations, and manic and aggressive behavior. The fact that 5 patients had initial psychiatric presentations without neurological symptoms or history of encephalitis suggests that some cases of anti-NMDAR encephalitis can be mistaken for a primary psychiatric disorder. These 5 patients were identified because they had abnormal brain MRI findings, explaining why a more comprehensive investigation including CSF analysis was pursued and implying some

degree of underdiagnosis in those without abnormal findings on ancillary tests. This possibility is discussed in further detail later. Eighty-three percent of patients with isolated psychiatric episodes of anti-NMDAR encephalitis had good outcomes owing to immunotherapy and tumor removal when applicable, supporting the autoimmune origin of the psychiatric symptoms. Remarkably, 15 of 18 patients who had previous episodes of encephalitis improved to a similar prerelapse functional status and 2 patients recovered to a better functional status, likely as a result of the detection and removal of a previously unnoted ovarian teratoma in one patient and additional immunotherapy in the other.

Patients in this cohort were followed up closely, so new behavioral abnormalities may have led to prompt diagnosis and treatment of relapses. It is possible that some isolated psychiatric episodes observed at relapse might have progressed to neurological involvement if not treated early in the course. However, comprehensive analysis of the 571 patients revealed that those with other monosymptomatic or milder forms of the disease (eg, isolated movement disorders or brainstem dysfunction) did not necessarily progress to multisymptom disease despite prolonged periods without treatment.^{9,13} Similar observations were previously made in a smaller series of 6 patients with relapses of anti-NMDAR encephalitis, which showed in 4 patients that symptoms were more limited than during the initial episode (eg, 2 patients had speech problems, 1 had ataxia, and 1 had psychiatric symptoms).¹¹ Moreover, in our study, 3 of the 5 patients with pure psychiatric symptoms on initial presentation did not receive appropriate treatment until 9, 17, and 60 weeks after symptom onset, which is well beyond the expected window of neurological deterioration (neurological decline often occurs within 2-3 weeks of psychiatric symptoms).

While the current work focuses on the frequency and type of isolated psychiatric symptoms in patients with anti-NMDAR encephalitis, several recent studies have explored whether patients with well-defined psychiatric disorders (eg,

schizophrenia, major depressive disorder, borderline personality disorder) had NMDAR antibodies. These studies help to address the bias toward patients with abnormal ancillary findings identified here. One study reported the presence of NMDAR antibodies in serum of 3 of 46 patients (6%) with first-onset schizophrenia; the target subunit (eg, NR2 vs NR1) was not determined and only 1 of the patients appeared to improve after immunotherapy.⁸ In contrast, another series examined serum from 80 patients with first-onset psychosis who met *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition, text revision) criteria for schizophrenia-spectrum illness 1 year later, along with 40 control patients.⁵ No patients in either group had NR1 IgG antibodies, consistent with the findings of another smaller series of patients with schizophrenia.⁶ More recently, Steiner et al⁷ examined the prevalence of NMDAR antibodies in serum from 121 patients with initial diagnosis of schizophrenia, 70 with major depressive disorder, 38 with borderline personality disorder, and 230 healthy individuals. The NR1 IgG antibodies were identified in only 2 patients, who in retrospect had a classic picture of anti-NMDAR encephalitis. IgA, IgM, or IgG antibodies reacting with NR2 were identified in 10 of 119 patients (8%) with schizophrenia and 2 of 70 patients (3%) with major depressive disorder. However, the causative antibodies in anti-NMDAR encephalitis are not IgA or IgM subtypes, but NR1 IgG antibodies. The clinical significance of NMDAR IgA and IgM antibodies in these disorders deserves further study given that similar antibodies have been reported in dementia¹⁴ and viral encephalitis.¹⁵ Considering the large number of patients studied with well-defined psychiatric disorders such as schizophrenia, depression, or borderline personality disorder,⁷ it is highly unlikely that NR1 IgG antibodies are present or involved in these diseases. However, to our knowledge, there are no systematic analyses of patients with new-

onset psychosis without neurological symptoms seen in psychiatric centers. Many of these patients are not studied with MRI or EEG, and only a small minority may have CSF evaluations. In this setting, the possibility of anti-NMDAR encephalitis is still rarely considered and most patients are not tested for NR1 IgG antibodies.

Findings from this study have several practical implications. For patients with a history of anti-NMDAR encephalitis, any behavioral change might represent relapse. In these patients, serum and CSF antibody testing should be obtained if possible, and they should be treated aggressively with immunotherapy and symptomatic management of psychiatric symptoms.^{1,3} No specific guidelines exist for treatment of psychiatric symptoms in this setting, but clinical experience and anecdotal evidence suggest use of highly sedating medications such as quetiapine, chlorpromazine, valproic acid, and benzodiazepines³; high-potency antipsychotics like haloperidol have been observed to exacerbate motor symptoms in patients with anti-NMDAR encephalitis. In this series, most patients received steroids, but generally for a short period.³ Most importantly, an interdisciplinary approach to management is needed. Given that relapses may represent the presence of a previously unidentified or recurrent tumor, patients should have tumor screening, mainly focusing on a teratoma of the ovary. In patients presenting to a psychiatrist with new-onset psychosis or mania, history of illness and other clinical data should serve as a guide as to whether CSF and serum analysis is necessary (keeping in mind that in 15% of patients, antibodies are detected only in CSF).⁹ History of encephalitis or encephalopathy of unclear etiology, mild neurological abnormalities such as transient facial twitching, and abnormal but nonspecific findings on EEG or MRI are all examples of findings that might prompt antibody studies.

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