

Original Research Reports

Psychiatric Autoimmunity: N-Methyl-D-Aspartate Receptor IgG and Beyond

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Background: Descriptions of psychiatric autoimmunity beyond N-methyl-D-aspartate (NMDA) receptor encephalitis are sparse. **Objective:** To report the autoimmune psychiatric spectrum currently recognized in Mayo Clinic practice. **Methods:** Medical record review, testing of stored serum and cerebrospinal fluid for IgGs reactive with synaptic receptors and ion channels, neuronal nuclear and cytoplasmic antigens (including glutamic acid decarboxylase 65-kDa isoform) and case-control comparison were conducted. Patients were categorized into group 1, all adult psychiatric inpatients tested for neural autoantibodies (2002–2011; n = 213), and group 2, all Mayo NMDA receptor IgG-positive patients (2009–2013; n = 13); healthy control subjects were also included (n = 173). **Results:** In group 1, at least 1 serum autoantibody (but not NMDA receptor IgG) was detected in 36 of 213 psychiatric inpatients. In total, 12 patients were determined retrospectively to have high-likelihood autoimmune encephalitic diagnoses. The most commonly detected autoantibody specificities were voltage-gated potassium channel ([Kv1] VGKC)

complex (6) and calcium channel (P/Q type or N type; 5). Symptoms seen were as follows: depressive (8), anxious (7), psychotic (7), disorganized (5), suicidal (3), manic (1) and catatonic (1). In group 2, among 13 NMDA receptor IgG-positive patients, 12 had encephalitis; their psychiatric symptoms were as follows: depressive (9), catatonic (9), disorganized (8), anxious (8), psychotic (7), manic (6), and suicidal (3). Catatonic symptoms were more common in the 12 NMDA receptor IgG-positive patients than in the 12 group 1 patients with high likelihood of encephalitis ($p = 0.002$). Antibody positivities were usually low positive in value among healthy controls (12 of 16 vs 3 of 12 group 1 encephalitis cases, $p = 0.025$). NMDA receptor IgG was not detected in any healthy control subject. **Conclusions:** A spectrum of psychiatric autoimmunity beyond NMDA-R IgG may be under-recognized. Diagnosis is facilitated by combining results of comprehensive psychiatric, laboratory, radiologic, and electrophysiologic evaluations.

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INTRODUCTION

A common presentation of autoimmune encephalopathy is marked disturbance of mood, thought, and behavior, with accompanying cognitive symptoms or seizures.¹ A history of autoimmune disease is a recognized risk factor for the development of mood disorders and psychoses.^{2,3} Evidence of organ-specific autoimmunity is more frequent in patients with

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common psychiatric disorders than in controls. For example, autoantibodies of thyroid, gastric parietal cell, and glutamic acid decarboxylase specificities are reported to be more prevalent in patients with bipolar disorder.^{4,5} Thyroid autoimmunity, celiac disease, autoimmune hemolytic anemia, and Sjögren syndrome are more prevalent among patients with schizophrenia and their family members than in unaffected subjects.⁶ Case reports have implicated autoimmunity as causal in patients with isolated psychiatric symptoms where improvement followed immunotherapy.^{7–10}

In the past decade, neural autoantibody biomarkers have increasingly become available and enabled the classification of CNS disorders of subacute onset as autoimmune, and sometimes paraneoplastic.¹¹ Autoimmune *N*-methyl-d-aspartate (NMDA) receptor encephalitis has been of particular interest to psychiatrists, because 77% of affected patients first present to psychiatry with a broad range of symptoms.^{12,13} Further, the median age at diagnosis (21 years) is similar to that seen in those with bipolar disorder and schizophrenia.^{12,14–16} Neurologic symptoms typically follow psychiatric symptoms and include seizures, movement disorders, autonomic instability, respiratory failure, and coma.¹² Isolated mood and thought symptoms have been reported, but the extent to which common psychiatric disorders can be attributed to NMDA receptor autoimmunity is controversial.¹⁷ Among patients later meeting *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria for schizophrenia, NMDA receptor IgG was reported in 4.3% at first episode of psychosis.¹⁸ A subsequent study did not demonstrate NMDA receptor autoimmunity in a similar patient cohort.¹⁹ Specificity of serum testing for that entity appears suboptimal.²⁰ Historically, psychiatrists have not requested neural autoantibody testing in serum, and even less commonly request lumbar punctures, and thus the retrospective cohorts of patients available for study are limited in number and scope.

Psychiatric manifestations of voltage-gated potassium channel ([Kv1] VGKC) complex autoimmunity also have been described.²¹ Descriptions of autoimmune psychiatric disorders are otherwise scarce.

In this study, we had two aims. Firstly, we aimed to describe the clinical and serologic experience of psychiatric autoimmunity at our institution to date.

Many of the patients were historic and had limited antibody testing performed during psychiatric hospitalization, but serum had been stored for future testing. Secondly, we aimed to report the psychiatric spectrum of NMDA receptor autoimmunity at our institution and critically evaluate the pertinence of serum testing for that diagnosis.

METHODS

The study was approved by the Mayo Clinic Institutional Review Board (IRB 13-7297). Medical records for patients seropositive for neural autoantibodies were reviewed independently by J. L. K. and A. M.

Primary outcomes were the frequency of neural autoantibody detection among psychiatric inpatients and controls, and phenotypes of seropositive patients.

Patients

Group 1

These 213 were adult psychiatric inpatients (54% female) whose initial neuropsychiatric evaluation included comprehensive serologic evaluation for neural autoantibodies (January 1, 2002–December 31, 2011). This represented 1.7% of 12,440 unique adult psychiatric patients hospitalized in a 10-year period. Symptoms at serum referral were either psychiatric only (71) or both psychiatric and neurologic (142). Serologic evaluation was prompted by cancer history in 33 patients. Median age at blood draw was 64 years (range: 18–96).

A retrospective assessment of the likelihood of an autoimmune etiology was made for each seropositive patient, based on our experience evaluating other patient groups with autoimmune CNS disorders.^{22,23} High likelihood was assigned when new psychiatric symptoms of subacute onset were accompanied by at least one of the following: new-onset movement disorder, encephalitic-appearing magnetic resonance imaging (MRI), encephalopathic or epileptiform electroencephalogram (EEG), inflammatory cerebrospinal fluid (CSF) (with protein exceeding 70 mg/dL, pleocytosis, or at least 4 CSF-exclusive oligoclonal bands), neural autoantibody at least 50% predictive for cancer (*eMethods*), or past episode of immunotherapy-responsive encephalitis. Movement disorders were evident at presentation and could not be attributed

to medication-induced extrapyramidal side effects. Mildly abnormal EEG findings that could be attributed to medication effect were excluded from consideration.

Group 2

NMDA receptor IgG-seropositive patients seen at Mayo Clinic Rochester in 2009–2013 were included (all 13 of 1082 tested).

Controls. A total of 173 volunteer healthy control subjects were included (57% were female patients; median age 52 years at blood draw [range: 18–84]).

Laboratory Evaluation

Stored serum was available for all patient and control subjects; CSF was available for 10 group 1 patients and all group 2 patients. Autoantibody testing was updated on all specimens to ensure uniformity of testing in all groups. Stability of all historic, archived specimens was assured by frozen storage at -80°C . Serum and CSF specimens were tested by standardized indirect immunofluorescence assays (tissue-based, eFigure 1, and cell-based, Figure 1), radioimmunoprecipitation, enzyme-linked immunosorbent assay, and Western blot (eMethods).^{24–26} Values defined as low positive were as follows: muscle and neuronal ganglionic acetylcholine receptors; VGKC complex and P/Q-type calcium channel (0.03–0.09 nmol/L; normal 0.00–0.02 nmol/L); N-type calcium channel (0.04–0.09 nmol/L; normal 0.00–0.03 nmol/L)^{26,27}; glutamic acid decarboxylase 65-kDa isoform (0.03–19.9 nmol/L; normal 0.00–0.02 nmol/L)²⁸; and striational (skeletal muscle) (1:120–1:3840; normal, <1:120).²⁵

Statistical Methods

Intergroup categorical variables were compared using Fisher exact test.

RESULTS

Patients

Clinical, serologic, radiologic, electrophysiologic, treatment, and outcome data are documented

in Tables 1–3, eTables 1 and 2, Figure 1 and eFigure 1.

Group 1: Adult Psychiatric Inpatients (2002–2011)

Just 1.7% of this hospitalized cohort had autoantibody testing requested. Of 213 patients, 36 (17%) had one or more neural autoantibodies detected (in no case NMDA receptor IgG). Among them, 19 seropositive patients were women (53%); median age was 68 years (range: 33–96).

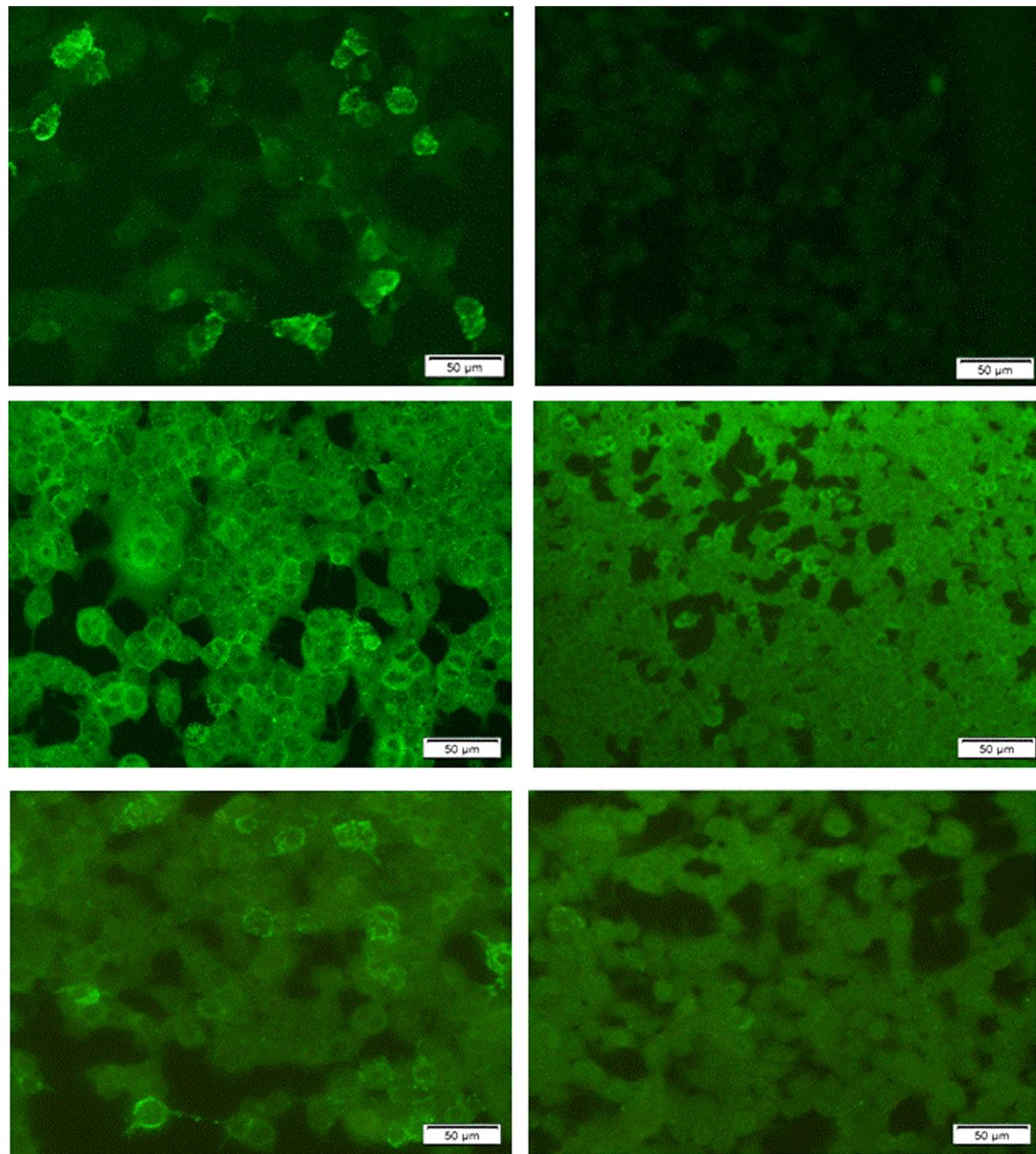
Psychiatric symptoms in the seropositive patients were as follows: depressive (23), psychotic (22), anxious, (20), bizarre or disorganized behavior (10), suicidal (10), manic or hypomanic (7), and catatonic (3). Primary diagnoses for 7 patients with isolated psychiatric symptoms were psychotic mania (3), major depression (2; 1 with psychosis), and psychotic disorder not otherwise specified (2). Neurologic disorders included memory complaints or confusion (24), abnormalities of movement (15—abnormal gait 8, rigidity 7, tremor 5, dyskinesia 3, and myoclonus 3), peripheral neuropathy (5), dysphagia (3), speech and language disorders (6—dysarthria in 3 and decreased verbal output/mutism in 3), and seizures (1). Movement disorders were evident at presentation and could not be attributed to extrapyramidal side effects of medication.

Overall, 10 patients (28%) had at least one coexisting autoimmune disease (Table 1 and eTable 1). Moreover, 11 patients (31%) had a history of cancer. In 3 patients, cancer was detected at 1, 7, and 8 years after serologic evaluation.

Antibody seropositivity was identified during hospitalization in 19 patients, or in the retesting of stored serum for this study (17 patients). Among 10 CSF specimens available, none yielded a positive antibody result. Detected serum autoantibodies had the following specificities: glutamic acid decarboxylase 65-kDa isoform, 10 patients (median value = 0.11 nmol/L, range: 0.03–225); VGKC complex, 7 patients (median value = 0.08 nmol/L, range: 0.06–0.64); striational, 7 patients (median value = 1:1920, range: 1:240–1:61,440); ganglionic AChR, 6 patients (median value = 0.10 nmol/L, range: 0.05–0.15); muscle AChR, 5 patients (median value = 0.87 nmol/L, range: 0.07–6.42); N-type calcium channel, 4 patients (median value = 0.17 nmol/L, range: 0.05–0.99); P/Q-type calcium channel, 3 patients (median value = 0.05 nmol/L, range: 0.04–0.10); and collapsin response mediator protein-5, 1 patient.

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FIGURE 1. NMDA Receptor IgG (GluN1 Transfected) HEK-293 Cell-Based Assay, Tested at 1:10 Dilution. Transfected Cells are Shown on the Left and Nontransfected Control Cells on the Right. The Top Row Demonstrates a Positive Control Serum Finding. The Middle Row Demonstrates a Low Positive Serum From an Encephalitis Patient. The Bottom Row Demonstrates the Same Patient Serum After Removing Nonspecific Reactivity by Preabsorption of Serum With Bovine Liver Powder; Cells Expressing NMDA Receptor Protein are More Readily Identifiable.



Twelve patients had high likelihood of an autoimmune neuropsychiatric diagnosis. Of these 36 patients, 12 (33%) were determined retrospectively by us to have high likelihood of an autoimmune neuropsychiatric disorder (**Tables 1 and 2**). In addition to psychiatric symptoms of subacute onset (all 12 patients), the diagnostic clues included cognitive symptoms (9), concurrent movement disorders of subacute onset (6—dyskinesia in 3, gait disorder in 3, tremor in 2, and rigidity in 1), EEG of moderate or severe slowing or focal or multifocal abnormalities including epileptiform discharges (6), inflammatory CSF (5), brain MRI consistent with inflammation (4), neural autoantibody highly predictive for a paraneoplastic cause (collapsin response mediator protein-5 IgG, 1), and past history of immunotherapy-responsive encephalitis (1).

At hospitalization, the primary diagnoses for those 12 patients were mood disorder (7; 2 with psychotic features), cognitive disorder (4), and conversion disorder (1). Psychiatric phenomenology included depressive symptoms (8), anxiety (7), psychosis (7), bizarre or disorganized behavior (5), suicidal ideation (3), catatonic symptoms (1), and hypomanic or manic symptoms (1). All had comorbid neurologic symptoms: confusion or memory complaints (10), movement disorder (6), and seizures (1).

Immunotherapy was undertaken in 3 of 12 patients (intravenous methylprednisolone 1 g, daily for 5 days)—2 improved and the third had worsening agitation. A trial of intravenous corticosteroids was recommended for 2 additional patients, but longitudinal data were lacking. We retrospectively considered an autoimmune psychiatric disorder likely in the remaining 7 patients; autoimmune encephalopathy was diagnosed clinically in one of those patients 88 months after psychiatric hospitalization.

Twenty-four patients had serologic findings of uncertain significance. For 24 seropositive patients, the neuropsychiatric significance of serologic findings was uncertain (**eTable 1**). None were diagnosed with autoimmune psychiatric disorder or received a trial of immunotherapy. They had normal cognition or new-onset cognitive symptoms consistent with a primary psychiatric disorder (e.g., poor concentration in major depression, disorganized thoughts in mania, or psychosis), 13; chronic cognitive symptoms, 9; or prior similar psychiatric presentations, 11. Only 3 patients had symptoms beyond those consistent

with the underlying psychiatric illness: rigidity/spasticity, 1; paresthesias and tremor, 1; and transient severe confusion postoperatively, 1. Testing in the 24 patients included MRI of head (0 of 24 suggested encephalitis), CSF (6 of 9 had isolated mild elevation of protein, ranging from 52 to 67 mg/dL), and EEG (5 of 15 had moderate diffuse slowing).

Group 2: NMDA Receptor IgG–Seropositive Patients

CSF testing has higher sensitivity and specificity than serum. Among the 1082 Mayo Clinic Rochester patients for whom NMDA receptor IgG testing was specifically requested (2009–2013), 13 had positive results (1%), **Table 3** and **eTable 2**. Median age at symptom onset was 27 years (range: 14–49); 12 (92%) were women. In only 8 of these 13 patients was NMDA receptor IgG detected in serum (62%), and in 1 patient it was detected only in serum (cell-based assay). That patient had chronic depression, fibromyalgia, and subjective cognitive complaints, without clinical or paraclinical evidence of encephalitis. She was excluded from further investigation.

Mood, thought, speech, and catatonic symptoms were most common. NMDA receptor IgG was detected in CSF of the remaining 12 patients, and inflammatory markers were elevated in all instances. Their recorded psychiatric symptoms were depressive (9), catatonic (9), disorganized behavior (8), anxious (8), psychotic (7), hypomanic or manic (6), suicidal (3; 2 with suicidal gesture or attempt), and behavioral disorder not otherwise specified (1). Of the 12 patients, 9 were evaluated in hospital for psychiatric indications before final diagnosis. All but 1 had psychiatric, neurologic, or medical hospitalizations, at Mayo Clinic or elsewhere. Moreover, 2 were psychiatrically hospitalized at Mayo Clinic, but after 2011, and thus did not meet criteria for group 1. Neurologic symptoms followed in 8 of the 9 patients who had an initial psychiatric symptom. Psychiatric and neurologic symptoms began simultaneously in 2 patients. In the 12th patient, onset of mild psychiatric symptoms (anxiety) began after seizure and aphasia onset. In the single male patient in the cohort, overt neurologic symptoms did not develop at any stage, but he had cognitive inefficiency, thought and behavioral disorganization, and mutism in the illness course.

TABLE 1. Group 1 (Likely Autoimmune Psychiatric Disorders), Clinical and Serological Characteristics

Patient no/sex/age	Ab specificity, value	Axis I diagnosis at hospitalization	Psychiatric symptoms	Similar past psychiatric presentation	Predominant neurologic, speech, or language symptoms	Subacute cognitive decline	Encephalitis history	Cancer history	Coexisting autoimmune disorder
1/F/33	CCN-type 0.99 nmol/L CCP/Q-type 0.04 nmol/L	Conversion disorder. Delusional parasitosis	Anxiety, delusions of parasitosis, and insomnia	N	Dyskinesias, dysesthesias, tremor, gait abnormality, and seizures	N	N	N	Hypothyroidism
2/F/54	CCP/Q-type, 0.1 nmol/L	Mood disorder NOS, with psychotic features, possibly owing to a general medical condition	Labile, irritable mood, dysphoric, anxious, disinhibited, paranoid, decreased need for sleep, and agitation	N	Confusion	Y	N	N	Type 1 diabetes mellitus, cutaneous lupus, and hypothyroidism
3/F/63	VGKCC,* 0.17 nmol/L, Lgi1-IgG	Major depressive disorder	Depressive symptoms, suicidal ideation, insomnia, and agitation	N	Memory complaints	Y	Y	N	N
4/F/66	GAD65,* 225 nmol/L	Major depressive disorder, with psychotic features	Depressed mood, anxiety, paranoia, and disorganized behavior	Y, during severe encephalitic episode	Confusion, getting lost, and unable to cook	Y	Y	N	N
5/F/66	CCN-type, 0.29 nmol/L CCP/Q-type, 0.05 nmol/L	Major depressive disorder, with psychotic features	Depressed mood, anxiety, and hallucinations	N	Dyskinesias, restless legs, and dysphagia	N	N	N	N
6/F/68	Str, 1:61,440	Major depressive disorder. Dementia NOS	Depressed and labile mood, anxiety, disorganized thoughts and behavior, catatonic symptoms, and repeated suicide attempts	N	Confusion, severe memory impairment, rigidity, and tremor Long speech latency and markedly reduced verbal output/mutism	Y	N	Renal cell carcinoma	N
7/F/69	Str, 1:7680, CRMP5**	Dementia, frontotemporal type	Personality changes, inappropriate social behavior, disorganized thought process, paranoia, and agitation	N	Cognitive decline	Y	N	Breast adenocarcinoma	N

8/F/77	VGKCC,* 0.08 nmol/L Str, 1:3840	Delirium. Cognitive disorder NOS	Depressed mood, anxiety, hallucinations, agitation, disorganized behavior, insomnia, and confusion	N	Confusion and gait imbalance	Y	N	N	N
9/M/57	α 3 gAChR, 0.15 nmol/L VGKCC, 0.07 nmol/L	Major depressive disorder	Depressed mood, anxiety	Y, but with new cognitive symptoms	Cognitive decline	Y	N	N	N
10/M/60	VGKCC, 0.64 nmol/L Lgi1-IgG	Delirium due to VGKC encephalitis	Disorganized thought and behavior, psychosis, and agitation	N	Confusion and dyskinesias.	Y	N	N	N
11/M/68	Str, 1:240	Major depressive disorder	Severe depression and suicidal ideation	Y, but with new cognitive symptoms, neurologic symptoms, and greater severity of depression	Cognitive decline, confusion, peripheral neuropathy, and gait unsteadiness	Y	N	Lung squamous cell carcinoma	N
12/M/77	VGKCC* 0.09 nmol/L	Dementia, Alzheimer type, with behavioral disturbance	agitation, aggression, and disinhibition	N	Subacute worsening of chronic cognitive disorder	N	N	Rheumatoid arthritis and Sjogren syndrome	

Ab = antibody; α 3 gAChR = nicotinic acetylcholine receptor, neuronal ganglionic type [containing α 3 subunit]; CCN-type = N-type calcium channel; CCP/Q-type = P/Q-type calcium channel; CRMP5 = collapsin response mediator protein; F = female patient; GAD65 = glutamic acid decarboxylase 65-kDa isoform; M = male patient; N = No; NOS = not otherwise specified; Str = striational (skeletal) muscle; VGKCC = voltage-gated potassium channel complex; Y = yes.

* Antibody identified during the study.

** Western blot positive.

TABLE 2. Group 1 (Likely Autoimmune Psychiatric Disorders), Ancillary Test Findings, Treatment, and Outcomes

Patient no.	EEG	MRI of head	CSF abnormalities	Autoimmune etiology suspected?	Immunotherapy pursued?	Response to immunotherapy	Follow-up period (months)
1	Moderate generalized slowing; L posterior temporal and central sharp waves and spikes	T2 hyperintensity L hippocampus	ND	N	N	N/A	10
2	Normal	Normal	Protein, 109 WBC, 19	N	N	N/A	127
3	R temporal slowing and epileptiform discharges.	T2 signal hyperintensity R hippocampus	None	N	N	N/A	0
4	Normal	Normal	ND	N	N	N/A	20
5	ND	Normal	None	Y	Recommended	N/A	3
6	Moderate diffuse and focal L temporal slowing	Normal	ND	N	N	N/A	0
7	Normal	Normal	None	N	N	N/A	0
8	Moderate slowing, and bitemporal epileptiform discharges	Normal	ND	N	N	N/A	66
9	Normal	R hippocampal atrophy	Protein, 79	Y	Y	Improved mood and subjective cognitive complaints	0
10	Moderate diffuse slowing and multifocal epileptiform discharges	T2 hyperintensity R caudate, bilateral globus, pallidus, thalamci, and putamina, and L hippocampus, and L frontal lobe	Protein, 112	Y	Y	Marked improvement in behavior and cognition	70
11	Normal	Normal	Protein, 160 WBC, 8	Y	Recommended	N/A	4
12	Moderate to severe generalized slowing	Normal	Protein, 71	Y	Y	Worsening agitation with IV methylprednisolone	0

CSF = cerebrospinal fluid; EEG = electroencephalogram; IV = intravenous; L = left; MRI = magnetic resonance imaging; N = No; ND = not done; N/A = Not applicable; R = right; WBC = white blood cell count; Y = Yes.

Normal values for CSF: protein, 0–35 mg/dL; WBC, 0–5/ μ L.

Of 12 patients, 10 had prominent mood symptoms: depressive (9) and manic (6). In addition, 3 patients had suicidal ideation, of whom 2 attempted suicide. Psychotic symptoms were common (7) but usually were preceded by mood symptoms. Psychotic symptoms were prominent early in only 3 patients.

All 12 patients had abnormalities of speech or language. In total, 3 patients were initially hyperverbal; another talked rapidly (though infrequently), often omitting the final syllables of words. Additionally, 3 patients exhibited repetitive/perseverative speech, 2 exhibited echolalia, and another 2 exhibited neologisms. Moreover, 5 were noted to have word-retrieval difficulties. A marked decrease in verbal output developed ultimately in all 12 patients. Periods of mutism varied in duration. All had cognitive inefficiency or impairment, and 11 had neurologic symptoms: abnormal movement (8), seizures (7), and disorders of strength and sensation (2).

The psychiatric and neurologic symptoms were similar among the 12 patients with NMDA receptor encephalitis and the 12 patients in group 1 with high likelihood of an autoimmune diagnosis. Catatonic symptoms ($p = 0.002$) and abnormalities of speech or language ($p < 0.001$) were more common in the NMDA receptor encephalitis group.

Controls

Among 173 healthy volunteers (psychiatric histories unknown, eTable 3), 16 were seropositive for glutamic acid decarboxylase 65-kDa isoform (6 [3.5%]) or for 1 or more neural-specific autoantibodies (12 [6.9%]: VGKC complex, 5; ganglionic acetylcholine receptor [AChR, 3]; P/Q-type calcium channel, 2, N-type calcium channel, 1; and striational, 1. None had NMDA receptor IgG. Serum of 3 subjects (2%) bound nonspecifically to HEK-293 cells expressing NMDA receptor protein. This reactivity was abrogated when the sera were preabsorbed with bovine liver powder (eFigure 1). Antibody values were low in 12 of the 16 seropositive controls. Overall, autoantibody values in the Group 1 patients with high likelihood of encephalitis were significantly higher than in healthy control subjects (3 of 12 low positive vs 12 of 16 low positive, $p = 0.025$) or in group 1 patients with an uncertain diagnosis (3 of 12 low positive vs 19 of 24 low positive, $p = 0.003$).

DISCUSSION

Despite increasing recognition of autoimmunity as a potential pathophysiologic basis for a subset of patients with psychiatric illness,²⁹ autoimmune neuropsychiatric disorders may not always be diagnosed. Classic limbic encephalitis is familiar to psychiatrists,³⁰ but more subtle phenotypes of autoimmune encephalopathy are likely under-recognized.^{10,21,31,32} Similarly, autoimmune cases of dementia²² and epilepsy²³ are often not detected in the absence of delirium.

Testing for neural autoantibodies was rarely undertaken by psychiatrists in this retrospective study (just 1.7% of all hospitalized patients), and thus it is not possible to comment on the appropriateness of case selection or prevalence. Also, given the case mix at our tertiary referral center, the findings may not be generalizable to all psychiatric practices. To improve our specificity of what we considered to be autoimmune, in addition to antibody seropositivity, patients had to have neuropsychiatric symptoms of subacute onset and at least one of the following factors: new-onset movement disorder, encephalitic-appearing MRI, encephalopathic or epileptiform EEG, inflammatory CSF, a paraneoplastic disorder, or past episode of immunotherapy-responsive encephalitis. Some notable autoimmune cases were detected. Among the 12 acutely hospitalized patients (group 1) whom we retrospectively judged to have an autoimmune psychiatric disorder, only 5 (42%) were identified at the time of hospitalization, and only 3 received immunotherapy (25%). None was seropositive for NMDA receptor IgG. Collapsin response mediator protein-5 IgG strongly predicts a coexisting cancer, most commonly small cell carcinoma and thymoma; breast adenocarcinoma was found in patient 7.³³

The study's retrospective design precluded determining the psychiatric significance of serologic findings in the remaining group 1 patients who had chronic psychiatric and cognitive symptoms. Cognition was difficult to assess retrospectively because of comorbid mood and thought disorders. Some of those 24 patients may indeed have had an autoimmune cause for psychiatric symptoms. Future, prospective studies should address the frequency of neuropsychiatric autoimmunity in well-defined clinical cohorts and evaluate for novel antibody biomarkers in those

TABLE 3. NMDA Receptor IgG-seropositive Patients, Clinical Symptoms, and Course

Patient no/ sex/age	Psychiatric symptoms	Psychiatric hospitaliza- tion	Neurologic symptoms	Speech or language symptoms	Encephalitis diagnosis	Cancer diagnosis	Follow-up period (months)	Immunotherapy response	Relapse
1/F/14	Anxiety, depressed mood, and disinhibited and disorganized behavior	N	Learning difficulty, transient arm numbness, and difficulty with complex motor tasks	Reduced verbal output, word-finding difficulty, slow speech, and long speech latency	Y	N	11	Improved	N
2/F/17	Depressed and labile mood, severe anxiety, agitation, disorganization, hallucinations, insomnia, and catatonic symptoms	N	Seizures and confusion	Word-finding difficulty. Rapid but infrequent speech, frequent omission of final syllable of words, echolalia, and mutism	Y	N	44	Improved	Y (initial episode 2 years before current episode)
3/F/20	Withdrawn, dysphoric, anxious, with suicidality, insomnia, restlessness, markedly reduced verbal output, agitation, catatonic symptoms, and hallucinations	N	Seizures, confusion	Decreased verbal output, 1-2-word responses only. Monotone. Long speech latency.	Y	N	5	Improved	N
4/F/21	Withdrawn, dysphoric, with disorganized behavior, paranoia, hallucinations, agitation, and catatonic symptoms	Y	Episode of posturing concerning for possible seizure; memory impairment	Decreased verbal output and mutism during acute episode.	Y	N	29	Improved	Y (6 months later)
5/F/22	Unspecified behavioral changes, with agitation	Y	Seizures, respiratory failure, and confusion	Mutism	Y	N	4	Progressive decline and death	N/A
6/F/24	Mood swings, dysphoria, crying spells, agitation, decreased need for sleep; later, and catatonic symptoms	Y	Confusion, memory difficulty, and seizure	Very limited verbal output, mutism, and occasional grunting in response to questions	Y	N	17	Progressive decline	N/A
7/F/27	Anxiety	N	Seizure and confusion	Aphasia, long pauses, and word-finding difficulties. Low average confrontation naming. Markedly impaired lexical fluency. Severely impaired comprehension of commands with increasingly complex syntax.	Y	N	35	Improved	N
8/F/30*	Depressed mood, anxiety, social withdrawal, suicidal behavior, then with increasingly disorganized behavior, disinhibited, hypersexual, decreased need for sleep, agitation, delusions, hallucinations, and catatonic symptoms	Y	Flailing movements of upper extremities	Echolalia. Perseverative, repetitive speech, and chanting. Long speech latency. Periods of mutism.	Y	N	6	Improved	N

9/F/33	Decreased need for sleep, elevated energy, hyperverbal, disinhibited speech (profanity), perseverative, with anxiety, depressed mood, paranoia, musical hallucinations, disorganization, agitation, and catatonic symptoms	Y	Confusion, paresthesias, and unsteady gait	Hyperverbal initially, with repetitive/perseverative speech, progressing to mutism.	Y	Ovarian teratoma	30	Improved	N		
10/F/47	Mood lability, depressed mood, severe agitation, decreased need for sleep, disorganized thought and behavior, catatonic symptoms, and hallucinations	Y	Seizure and cognitive impairment	Word-finding difficulty. Decreased verbal output during acute episode.	Y	N	36	Improved	Y (initial event 8 years before the current episode)		
11/F/47	Hyperverbal, inappropriate behavior and affect, hyperreligiosity, disorganization, agitation, anxiety, hallucinations, decreased need for sleep, and catatonic symptoms	Y	Dystonia, dyskinesia, tremor, and confusion	Hyperverbal, neologisms, elevated volume, progressing to nonverbal, noncommunicative	Y	Small cell lung cancer, metastatic, diagnosed 8 months later	28	Improved	N		
12/M/35	Depressed mood with marked lability and inappropriate affect, anxiety, flight of ideas, decreased need for sleep, suicidal ideation, disorganization, agitation, and catatonic symptoms	Y	Cognitive decline from baseline (unable to balance numbers at work).	Word-finding difficulty, hyperverbal, neologisms, repetitive/perseverative speech, progressing to decreased verbal output, and mutism	Y	N	16	Improved	Y (8 months later)		
13F/49	Depressed mood, anxiety, concentration and attention difficulties	N	Subjective cognitive complaints	Difficulty with word retrieval and recall	N	N	17	n/a	n/a		

F = female patient; M = male patient; N = No; N/A = not available; Y = Yes; NMDA-R = N-methyl-D-aspartate receptor.

* Previously published case report.⁴²

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cohorts. In several patients, there was a history or subsequent evidence of cancer. In those patients, the serologic findings may have had an oncologic basis without psychiatric significance.²⁷ Low positive neural autoantibody values, as defined in our previous publications, are sometimes encountered in patients with nonneurologic autoimmune diseases, or as false-positive phenomena in patients with polyclonal and monoclonal gammopathies.^{25–28}

Autoimmune NMDA receptor encephalitis cases are an increasingly well-known entity among psychiatrists. As illustrated in this study, testing of both serum and CSF is recommended when that diagnosis is suspected. In half of the cases, CSF evaluation proved more sensitive than serum for confirming the diagnosis (i.e., serum testing showed negative finding), or for refuting the diagnosis where serum testing had yielded a suspected false-positive result.^{20,34} There is growing consensus that specificity is compromised when serum alone is tested for NMDA receptor antibody using cell-based assays. Hammer et al. reported detecting NMDA receptor antibodies of IgG, IgM, and IgA isotypes in serum of patients with primary psychiatric disorders and in healthy controls.³⁵ IgA and IgM NMDA-R antibody isotypes are unlikely to have clinical significance.³⁶ Caution is advised in interpreting a positive serum result for NMDA receptor antibody detection by cell-based assays in the absence of CSF inflammatory findings or autoantibody detection in CSF.³⁷

We have described in this article a spectrum of autoantibodies and coexisting psychiatric, neurologic, and speech phenotypes encountered in patients with autoimmune psychiatric disorders. Catatonic symptoms and speech disorders were more common in patients with autoimmune NMDA receptor encephalitis, but they were not unique to that diagnosis. Kayser et al. similarly reported a predominance of delusional thinking (74%) and mood disturbances (70%)¹⁷ in patients with autoimmune NMDA receptor encephalitis, and speech disorders were observed in more than 70% of patients in another large cohort with NMDA receptor encephalitis.¹⁵ In our cohort, mood symptoms were the most common early manifestation of autoimmune NMDA receptor encephalitis. Psychosis (hallucinations or delusions) usually followed, and later disorders of speech and language were universal. Decreased verbal output and periods of mutism developed in all patients. In many instances hyperverbal speech, echolalia,

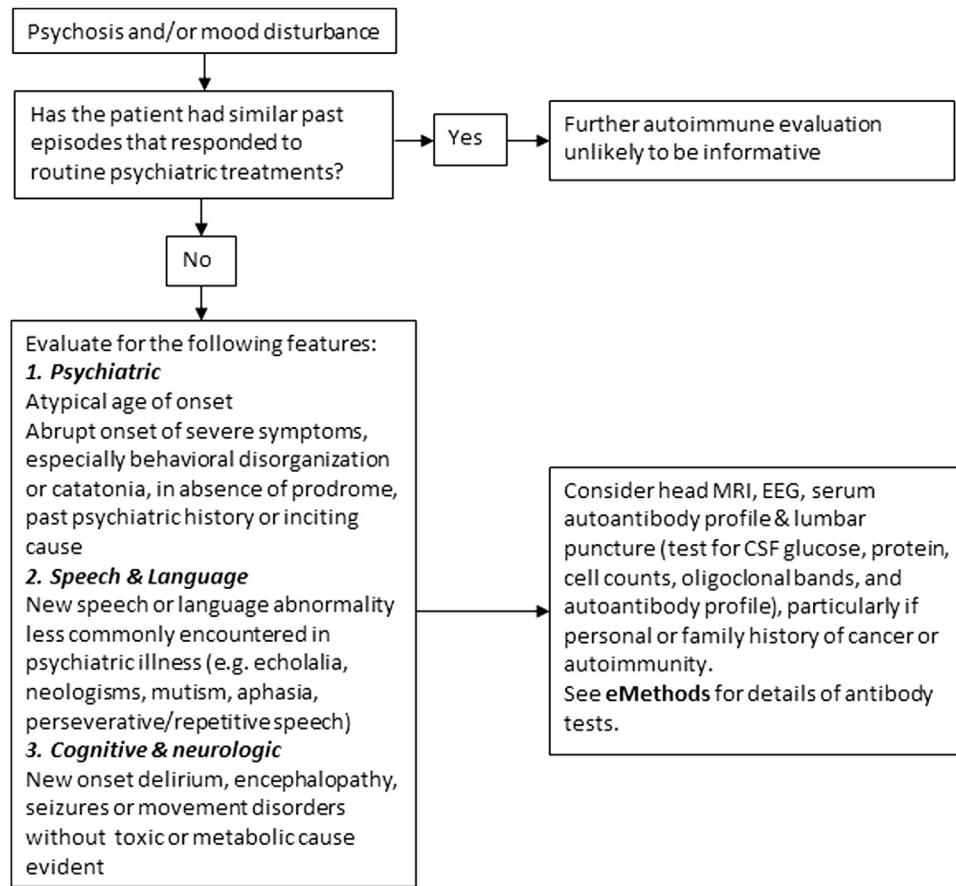
neologisms, and word-retrieval difficulties preceded mutism.

NMDA receptor IgG autoantibody was not detected in any older, hospitalized patient of this study, and it was detected in only 1% of patients for whom that specific testing was requested. A limitation of our study was that physician bias restricted autoimmune serologic testing in mostly older patients with perceived risk for cancer (median age = 68 years for the inpatient group vs 27 years for the NMDA receptor IgG-seropositive group). Psychiatric autoimmunity is now recognized to occur across the age range.^{38–40} The intergroup age and sex differences also mean that results of our comparisons should be interpreted with caution.

In summary, the patients we describe had psychiatric symptom-predominant presentations. Careful review of histories revealed comorbid neurologic symptoms (most commonly disorders of rapidly progressive cognitive change or movement) and sometimes a history of autoimmunity or cancer. Other features that may raise clinical suspicion for an autoimmune cause include an unusual age of symptom onset, an absence of history of psychiatric illness (personal or family), and relatively abrupt onset of severe symptoms.

Neurologic examination and cognitive screen at the time of psychiatric evaluation raised suspicion for a disorder beyond the spectrum of common primary psychiatric disorders. Evaluation of serum and CSF for neural autoantibodies aided confirmation of an autoimmune psychiatric disorder. Comprehensive testing of both serum and CSF has higher clinical sensitivity and specificity than physician-selected single-antibody testing in 1 specimen type only (see eMethods for complete listings). Some autoantibodies are detected more readily in CSF (e.g., NMDA receptor) than in serum, and others more readily in serum (e.g., VGKC complex IgGs). Low positive values of serum antibodies need to be interpreted with caution. Ancillary testing, including MRI of head and EEG, complements psychiatric evaluation to define the neuropsychiatric phenotype. These modalities also provide a quantitative baseline against which post-treatment parameters can be compared.

A timely diagnosis of an autoimmune neuropsychiatric disorder is important because patients may be responsive to immunotherapies (as well as standard psychiatric medications), including corticosteroids, intravenous immune globulin, plasma exchange, or immunosuppressive agents, such as

FIGURE 2. Suggested Algorithm to Evaluate for Psychiatric Autoimmunity.

rituximab or cyclophosphamide.⁴¹ Although additional research is required to determine the optimal approach for evaluating psychiatric autoimmunity, we provide a suggested algorithm (Figure 2) for identifying patients for whom there is increased clinical suspicion and the diagnostic approach.

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APPENDIX A. SUPPLEMENTARY MATERIALS

Supplementary material cited in this article is available online at <http://dx.doi.org/10.1016/j.psym.2015.01.003>.

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