Autoimmune Encephalitis in Postpartum Psychosis

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Objective: Significant immunological alterations have been observed in women with first-onset affective psychosis during the postpartum period. Recent studies have highlighted the possibility that a subset of patients with first-onset severe psychiatric episodes might suffer from undiagnosed autoimmune encephalitis. Therefore, the authors performed a three-step immunohistochemistry-based screening for CNS autoantibodies in a large cohort of patients with postpartum psychosis and matched postpartum comparison subjects.

Method: Ninety-six consecutive patients with postpartum psychosis and 64 healthy postpartum women were included. Screening for antibodies in patient serum was performed using immunohistochemistry. Samples showing any staining were further examined by immunocytochemistry using live hippocampal neurons and cell-based assays to test for anti-*N*-methyl-D-aspartate (NMDA) receptor antibodies. Cell-based assays for all other known CNS antigens were performed in those samples with immunocytochemistry labeling but negative for NMDA receptor antibodies.

Results: Four patients (4%) with neuropil labeling suggestive for extracellular antigen reactivity were identified. Serum samples from all four patients showed clear extracellular labeling of live hippocampal neurons. Two women had the specific staining pattern characteristic for anti-NMDA receptor antibody positivity, which was confirmed by cell-based assays. Neither patient with anti-NMDA receptor antibody positivity had evidence of an ovarian teratoma. The other two patients tested negative by cell-based assays for all known CNS antigens. None of the matched postpartum comparison subjects had confirmed neuronal surface antibodies. The two patients with anti-NMDA receptor antibodies both showed extrapyramidal symptoms following initiation of treatment with low-dose haloperidol.

Conclusions: In patients with acute psychosis during the postpartum period, systematic screening for anti-NMDA receptor autoantibodies should be considered. The acute onset of severe atypical psychiatric symptoms in young female patients should raise the index of suspicion for anti-NMDA receptor encephalitis, particularly in the setting of neurological symptoms, including extrapyramidal side effects of antipsychotic treatment.

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Postpartum psychosis is the most severe form of pregnancy-related psychiatric illness, with a prevalence in the general population of 0.1% (1, 2). Given that postpartum psychosis is a severe, potentially life-threatening disorder during the acute phase, the prognosis is remarkably optimistic: nearly all women have a complete remission of symptoms within 6 months postpartum. However, women with a prior episode of postpartum psychosis are at a significantly elevated risk of relapse after a subsequent pregnancy, estimated to be approximately 30% and therefore approximately 300-fold higher than the general population risk. In addition, women with a previous postpartum psychosis also have an increased risk for severe affective episodes outside the postpartum period.

Postpartum psychosis occurs most frequently in primiparous women without a psychiatric history and generally manifests acutely within 4 weeks after delivery. The cardinal symptomatology is affective and severe, including acute mania, depression, or a mixed state. Psychotic symptoms almost exclusively occur within the setting of affective instability. Consequently, postpartum psychosis is generally considered a bipolar-spectrum mood disorder and not a primary psychotic disorder (3). However, unlike a classical bipolar-spectrum illness, postpartum psychosis is also notable for its delirium-like appearance. Women with postpartum psychosis frequently exhibit atypical cognitive symptoms such as disorientation, misrecognition of people, derealization, and depersonalization (4, 5).

During the acute phase, all patients require thorough physical and neurological examinations and comprehensive laboratory analyses to exclude known organic causes for acute psychosis and mania. In the vast majority of patients, the underlying pathophysiology remains unknown. For a subgroup of patients, postpartum activation of the immune system might be central to the pathogenesis of postpartum

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psychosis (6–8). Patients with postpartum psychosis have significantly elevated rates of autoimmune thyroiditis and pre-eclampsia, both of which have established autoimmune etiologies (9). Furthermore, abnormalities in monocyte activation and T-cell function have been observed in patients with postpartum psychosis during the acute phase (6).

Over the last several years, multiple neuronal autoantibodies have been identified, leading to an emerging definition of "cell surface antibody-associated CNS disorders" in patients who might otherwise have been diagnosed as having a classical psychiatric illness (10). For example, anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis, an autoimmune disorder in which IgG antibodies are directed against the GluN1 subunit of the NMDA receptor, has been identified in young patients with first-onset psychiatric symptoms (11, 12). Against this background, we hypothesized that postpartum autoimmune encephalitis might be the primary pathophysiological mechanism for a subgroup of patients with postpartum psychosis. Accordingly, we performed an immunohistochemistry-based screening for CNS autoantibodies in a large cohort of patients with postpartum psychosis and matched postpartum comparison subjects.

METHOD

Patients

Ninety-six (N=96) consecutive patients with postpartum psychosis were recruited from the Mother-Baby Inpatient Unit of the Department of Psychiatry of the Erasmus University Medical Center between August 2005 and May 2012. All patients were diagnosed according to DSM-IV-TR using the Structured Clinical Interview for DSM-IV Axis I Disorders Patient Edition. We have included patients with any of the following diagnoses, including the specifier "onset postpartum": depressive disorder with psychotic features, mania with psychotic features, mixed episode with psychotic features, or brief psychotic disorder. Importantly, the specifier "onset postpartum" requires that the onset of symptoms must occur within 4 weeks postpartum. Physical examination and routine laboratory screening were performed at the time of study enrollment (median: 4 weeks postpartum). All patients were in an acute disease state at the moment of blood withdrawal.

Of 96 women, 21 had a diagnosis of mania and/or psychosis outside the perinatal period (bipolar disorder, psychosis not otherwise specified). Accordingly, 75 patients had mania and/or psychosis limited to the postpartum period, of which 62 patients were experiencing their first psychotic episode while 13 had at least one previous episode of postpartum psychosis.

The postpartum comparison cohort consisted of 64 healthy postpartum women recruited between 2008 and 2012 through the Department of Obstetrics and Gynecology (Erasmus Medical Center, Rotterdam). These women had no clinically significant psychiatric history and an Edinburgh Postnatal Depression Score <10 at the time of the 4-week postpartum blood sampling.

The study protocol was approved by the institutional review board of the Erasmus Medical Center, Rotterdam. After receiving a complete description of the study, all patients and their authorized legal representatives provided written informed consent.

Antibody Testing

Screening for antibodies in patients' serum was performed in all cases using immunohistochemistry with rat brain optimized for membrane-bound antibodies. To confirm the presence of neuronal surface antibodies, all samples showing any staining were tested by immunocytochemistry using live hippocampal neurons (13) and HEK cells recombinantly expressing GluN1/N2B to test for NMDA receptor antibodies (cell-based assay) (14). Serum samples with immunocytochemistry labeling but negative for NMDA receptor antibodies were screened with cell-based assays for all other known CNS antigens, including AMPA receptor (15), GABAA receptor (16), GABAB receptor (10), LGI1 (15), Caspr2 (10), DPPX (17), mGluR5 (10), D_2 receptor (18), and glycine receptor (19).

Immunohistochemistry. This methodology has been described previously (14). In brief, adult Wistar rats were sacrificed without perfusion, and brains were removed, mid-sagittally sectioned, fixed by immersion in 4% paraformaldehyde for 1 hour at 4 C°, cryopreserved in 40% sucrose for 48 hours at 4°C, embedded in freezing compound media, and snap frozen in isopentane chilled with liquid nitrogen. Seven micron-thick sections were then incubated with 0.3% hydrogen peroxide for 20 minutes, with 10% goat serum in phosphate-buffered saline for 1 hour, and then labeled with patient or comparison sample (dilution 1:200) at 4°C overnight. The next day, sections were washed and then incubated with a secondary biotinylated goat antihuman IgG (dilution 1:2,000, Vector BA-3000 [Burlingame, Calif., Vector Laboratories]) for 1 hour at room temperature, and the reactivity was developed with the avidin-biotin-peroxidase method (Burlingame, Calif., Vector Laboratories).

Immunocytochemistry on neuronal cultures. Primary rat hippocampal neuronal cultures were prepared as previously reported (20). Live neurons grown on coverslips were incubated for 1 hour at 37°C with patient or comparison serum (dilution 1:200). After removing the media and extensive washing with cold phosphate-buffered saline, neurons were fixed with 4% paraformaldehyde, permeabilized with 0.3% Triton X-100, and immunolabeled with Alexa Fluor 488 goat antihuman IgG (diluted 1:1,000, Invitrogen A11013 [Waltham, Mass., Invitrogen]). Immunocytochemistry labeling was imaged using an epifluorescence microscope with Zeiss Axiovision software (Thornwood, N.Y., Zeiss).

Cell-based assay. The cell-based assay consisted of HEK293 cells transfected with plasmids expressing GluN1/N2B in equimolar ratios as described previously (14). Cells were grown for 24 hours after transfection and in the presence of ketamine (500 μM) to prevent cell death after transfection. Transfected cells were then fixed with 4% paraformaldehyde (5 minutes at room temperature), permeabilized with 0.3% Triton X-100 (5 minutes at room temperature), incubated with serum diluted 1:

40 (2 hours at room temperature), then washed with phosphate-buffered saline and incubated with a mouse monoclonal antibody against a noncompeting GluN1 epitope located in the extracellular loop at amino acid 660–811 (dilution 1:20,000; MAB363, Billerica, Mass., Millipore) for 1 hour at room temperature, followed by the corresponding fluorescent secondary antibodies (Alexa Fluor 488 goat antihuman IgG, Invitrogen A11013, diluted 1:1,000; Alexa Fluor 594 goat antimouse IgG, Invitrogen A11032, diluted 1:1,000) for 1 hour at room temperature. Cell-based assays for AMPA receptor, GABAA receptor, GABAB receptor, mGluR5, LGI1, Caspr2, DPPX, D_2 receptor, and glycine receptor were performed as previously described.

TABLE 1. Patient Demographic and Clinical Characteristics

Characteristic	Postpartum Psychosis Group (N=96)		Healthy Postpartum Comparison Group (N=64)	
	Mean	SD	Mean	SD
Age (years)	31.2	5.6	32.8	4.2
Days postpartum blood was drawn	32.3	28.5	29.5	17.2
	N	%	N	%
Caucasian	79	82	48	75
Primiparity	75	78	41	64
Primigravidity	59	61	38	59
Caesarean section	15	16	16	25
Psychiatric history				
Bipolar disorder	16	17	0	0
Psychosis	5	5	0	0
Previous postpartum episodes	13	14	0	0
Phenomenology				
Manic features	55	57	NA	—
Depressed features	11	12	NA	—
Mixed features	22	23	NA	—
Psychosis with no affective features	8	8	NA	—

RESULTS

The demographic and overall clinical characteristics of the study cohort are shown in Table 1. Using the combination of immunohistochemistry, immunocytochemistry with live hippocampal neurons, and cell-based assay, we identified four patients with neuropil labeling suggestive of extracellular antigen reactivity (N=4/96, 4%; Figure 1A, Figure 1C). Of these four patients, two (N=2/96, 2%) had the specific staining pattern characteristic for anti-NMDA receptor antibody positivity, which was confirmed with cell-based assay. The other two patients showed clear extracellular labeling of live hippocampal neurons (Figure 1A, Figure 1C) but tested negative for all known CNS antigens. The target antigen for the two non-NMDA receptor patients could not be identified. None of the other postpartum psychosis patients, nor any of the postpartum comparison subjects, had neuropil labeling suggestive of extracellular antigen reactivity.

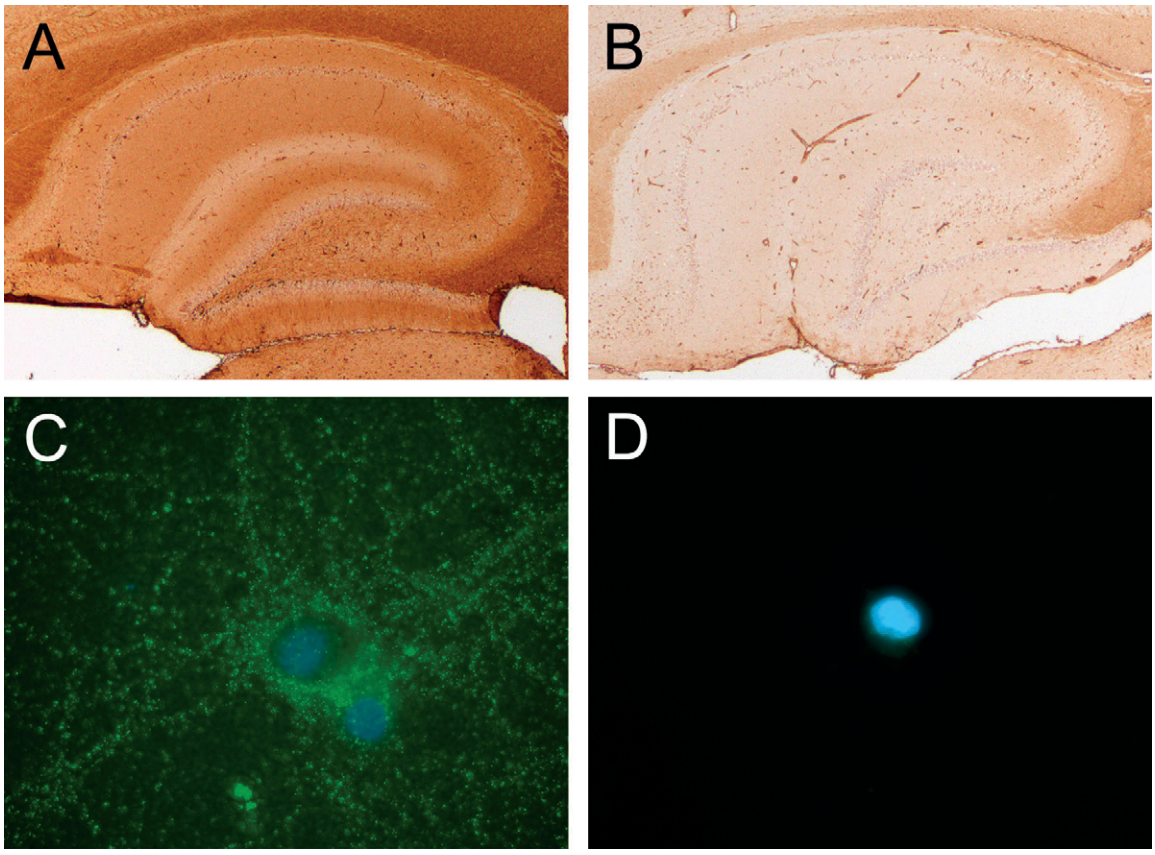
The clinical details of the four patients with cell surface antibody-associated CNS disorder are presented in Table 2 and described below. Importantly, no distinguishing clinical characteristics were identifiable that segregated the four antibody-positive patients from the remaining 92 patients within the postpartum psychosis cohort. From the overall postpartum psychosis cohort, 66 women were treated with haloperidol, of which 17 were switched to atypical antipsychotics because of clinically significant extrapyramidal side effects. Notably, however, both patients with anti-NMDA receptor antibodies showed extrapyramidal side effects with low doses of haloperidol (Table 2).

Case Vignettes of Patients With Anti-NMDA Antibody Positivity

Patient 1. "Mrs. H" is a 31-year-old primiparous primigravid woman with no prior psychiatric history, who delivered a healthy daughter at home following an unremarkable pregnancy. After 1 week, she confessed to her husband a belief that she had special gifts. She developed increasingly progressive confusion, leading to psychiatric admission at day 12 postpartum. On admission, she wrapped a blanket and a towel around her head and right arm, explaining to the psychiatrist, "This has everything to do with my special daughter and the beautiful, colorful world and prime numbers." She was diagnosed with manic and psychotic features. Physical examination and routine laboratory investigations, including thyroid screening, were normal. On admission, Mrs. H was treated with lorazepam and haloperidol. However, because of extrapyramidal side effects, haloperidol was switched to olanzapine. After 2 weeks, she required addition of lithium according to our structured treatment protocol (21). Over the next month, she developed a subclinical hypothyroiditis, which was diagnosed as thyroid peroxidase antibody-positive autoimmune thyroiditis. On a combination of lithium, olanzapine, and lorazepam, her psychiatric symptoms fully remitted, with the total duration of her episode being 34 days. Olanzapine and lorazepam were slowly titrated to discontinuation, after which she was discharged home from the hospital on lithium monotherapy, 2 months after delivery. Lithium was discontinued at 9 months postpartum, with no recurrence of symptoms following inpatient discharge.

Two years after her first delivery, Mrs. H gave birth to a second healthy daughter. Immediate postpartum prophylactic treatment with olanzapine was initiated to reduce the 30% relapse risk postpartum without medication (22). Olanzapine was recommended for mood stabilization instead of lithium, given the relative contraindication regarding the risk for thyrotoxicity in patients with thyroid peroxidase antibody positivity (9). Mrs. H remained psychiatrically stable throughout the postpartum period. During the past 7 years of outpatient follow-up since discharge, she has remained in full remission and maintained successful full-time work.

FIGURE 1. Demonstration of Uncharacterized Cell-Surface Antigens in a Cohort of Postpartum Psychosis Patients[a]



[a] The reactivity of a postpartum psychosis patient's serum antibodies is shown using immunohistochemistry of rat brain (brown staining in panel A) and cultured dissociated hippocampal neurons (green cell-surface neuronal labeling in panel C). The identity of the antigen is unknown. Panels B and D show the lack of reactivity of serum from a matched postpartum healthy comparison subject. In panels C and D, the nuclei of the neurons are shown with 4′,6-diamidino-2-phenylindole. In panels A–B, original magnification×2 is shown, counterstained with hematoxylin. In panels C–D, a 100X oil lens was used for immunofluorescence imaging.

Patient 2. "Mrs. A" is a 25-year-old multiparous woman who gave birth to her third child, a healthy daughter. She had experienced postpartum psychosis at the age of 16 in Middle East Asia. Because of traumatic events, she fled her home country and immigrated to the Netherlands with her husband and child. During her second pregnancy, she was referred to our hospital and agreed to use lithium for postpartum prophylaxis. She remained clinically stable throughout the entire postpartum period. Two years later, her third pregnancy was uneventful. After delivery, she declined lithium prophylaxis and relapsed. On admission, 3 weeks after her singleton delivery, she told the psychiatrist, "I gave birth to a twin, but someone has taken my other baby away." She had auditory hallucinations, and she was diagnosed with a psychotic episode, without manic features. She was treated with the sequential addition of lorazepam, haloperidol, and lithium, but haloperidol was tapered off because of extrapyramidal side effects. Her symptoms were in remission within 3 months. Over the past 5 years of outpatient follow-up since discharge, Mrs. A has been free of manic or clear psychotic symptoms, but she had minor mood instabilities and transient paranoid ideas. According to her husband, she has had these symptoms since her flight from her home country but has been able to take care of their three children.

Both patient 1 and patient 2 were identified retrospectively as anti-NMDA receptor antibody positive through this research study. We informed both women of this result and performed evaluations for ovarian teratoma by transvaginal ultrasound, which was negative. CSF analysis was not performed, given the remission of psychiatric symptoms without requiring maintenance pharmacotherapy and the absence of any known neurological or somatic symptoms.

Case Vignettes of Patients With Antibodies Against Unknown Cell Surface

Patient 3. "Mrs. V" is a 30-year-old primiparous primigravid woman with no prior psychiatric history, who delivered a healthy son after a 32-hour labor and delivery. Within 3 weeks postpartum, she developed increasingly severe depression and anxiety. Her family developed particular concern for her well-being because her mother had committed suicide within a few weeks after her birth.

Six weeks after delivery, Mrs. V experienced delusions of guilt and visual hallucinations and soon thereafter stopped

eating. On admission she reported, "I am bankrupt, and my son is ill," the reality of which was refuted by parallel history from the family. She was treated with lorazepam and quetiapine, without therapeutic benefit. Two weeks after admission, Mrs. V attempted suicide by hanging. Lithium was added to her medication regimen. On the combination of lorazepam, quetiapine, and lithium, she achieved full remission of her symptoms after 65 days. She was discharged home at 4 months postpartum. Lithium was discontinued at 9 months postpartum according to our structured treatment protocol, given the absence of any relapse episodes following discharge (21). Four years after discharge, Mrs. V became pregnant again and delivered a healthy daughter. She was given prophylactic lithium immediately following the delivery of her daughter and remained stable throughout the postpartum period. Over the past 6 years of outpatient follow-up since discharge, Mrs. V has remained in full remission.

Patient 4. "Mrs. M" is a 21-year-old primiparous primigravid woman with no prior psychiatric history, who delivered a healthy son after an unremarkable pregnancy. One week after delivery, her husband noticed that she was getting more and more depressed and anxious. At 2 weeks postpartum, she was involuntarily admitted to the Erasmus Medical Center. She was crying and screaming that people were following her, and she had auditory hallucinations. She was diagnosed with postpartum psychosis with depressive features and treated with benzodiazepines and antipsychotics. Because of anemia, ferrous fumarate was started. Within 2 weeks, her psychotic and depressive symptoms were in remission, but she was still highly irritable. Upon her request, she was transferred to a mother-baby unit in her own geographic region. Over the past 12 months of outpatient follow-up since discharge, Mrs. M has remained in full remission.

Patients 3 and 4 were diagnosed with "CNS disorders associated with antibodies against unknown neuronal cell surface antigens" through this research study. The target antigen remains unknown. Monocyte gene expression and T-cell data previously collected from these two patients were retrospectively analyzed (6). No difference in inflammatory gene expression was observed in comparison with the other first-onset postpartum psychosis patients examined in parallel. In contrast, patients 3 and 4 showed notable differences in their lymphocyte counts. Natural killer cells were moderately elevated in patients 3 and 4 (20.3% and 13.8%, respectively) compared with the overall group with first-onset postpartum psychosis (10.9% [SD=4.7%]) and postpartum comparison subjects (8.8% [SD=3.4%]). Furthermore, we previously showed that these patients exhibit a blunted postpartum elevation of T-cells (74.4% [SD=8.4%]) compared with healthy postpartum comparison subjects (81.1% [SD=6.0%]) (6). Patients 3 and 4 had particularly low T-cell counts (57.4% and 66.8%, respectively). In addition, percentages of $CD4^{+}CD25^{high}FoxP3^{+}$ natural T-regulatory cells were lower in patients 3 and 4 (1.5% and 1.6%, respectively) compared with postpartum psychosis patients and postpartum comparison subjects (2.1% [SD=0.61%] and 2.2% [SD=0.76%]). Regulatory T-cells have a primary role in maintaining tolerance to self-antigens, for which T-regulatory cell deficiencies have been increasingly associated with autoimmune disorders (23).

DISCUSSION

Out of 96 consecutive patients with postpartum psychosis screened for CNS surface antibodies, four patients showed neuronal cell surface antibodies suggestive for encephalitis (4%). Two of these patients were identified as having anti-NMDA receptor encephalitis, while for the other two patients the antigen remains unknown. Notably, none of the 64 healthy postpartum comparison subjects had confirmed neuronal surface antibodies.

Two patients (2%) out of the total cohort of 96 were identified as anti-NMDA receptor antibody positive. Notably, anti-NMDA receptor encephalitis was not initially considered during the acute clinical presentation because of the absence of classical features of autoimmune encephalitis, including seizures, decreased consciousness, dyskinesia, and autonomic instability. Importantly, however, and only in retrospect, it is notable that both of the patients with anti-NMDA receptor antibody positivity had extrapyramidal symptoms with only a low dose of haloperidol, a clinical sign frequently seen among patients with autoimmune encephalitis (personal observations by M.J.T. and J.D.).

Both patients recovered after treatment with lithium, and remission was sustained, despite the absence of any steroid or immunosuppressive treatment. In general, immunotherapy and removal of an identified ovarian teratoma are the definitive treatments for anti-NMDA receptor encephalitis, both during the acute phase and for relapse prevention (24). The effectiveness of this treatment strategy has been described in the postpartum period (25–27). In contrast to previous case reports of postpartum anti-NMDA receptor encephalitis, our patients displayed only a few of the classical neurological symptoms. A partial, or attenuated, anti-NMDA receptor encephalitis syndrome with predominantly psychiatric symptoms and few, if any, classical neurological features of anti-NMDA receptor encephalitis has been described in approximately 4% of all patients with NMDA encephalitis (28, 29). Moreover, some of these patients might have antibodies with a distinct affinity and/or antigen location within the NMDA receptor complex (13, 30). Lastly, the dynamic immunological changes of the postpartum period could also provide an explanation for the full recovery of both patients without immunotherapy in the present study.

Two patients (N=2/96, 2%) showed neuronal cell surface antibodies suggestive for encephalitis, but the corresponding antigen has remained unknown after comprehensive screening with cell-based assays. Levels of antibodies were insufficient to identify the antigen. Our hope is that with ongoing screening of additional cases, we might find additional patients with similar staining patterns and provide an opportunity for more sophisticated antigen identification approaches. In contrast

TABLE 2. Characteristics of Four Patients With CNS Disorders Associated With Antibodies Against Neuronal Cell Surface Antigens

Patient Parity/Gravidity, Pregnancy Outcome (Sex), and Age	CNS Antibody	Predominant Psychiatric Symptoms Postpartum	Treatment	Episode (Days)
P1G1, healthy daughter, 31 years old	Anti-*N*-methyl-D-aspartate receptor	Mania; delusions of grandeur; bizarre behavior	Antipsychotic, lithium	34
P3G3, healthy daughter, 25 years old	Anti-*N*-methyl-D-aspartate receptor	Auditory hallucinations; paranoid delusions	Antipsychotic, lithium	30
P1G1, healthy son, 30 years old	Unknown neuronal surface antibody	Depression; delusions; visual hallucinations; suicidal ideation	Antipsychotic, lithium	65
P1G1, healthy son, 21 years old	Unknown neuronal surface antibody	Depression; auditory hallucinations; paranoid	Antipsychotic	25

to patients with anti-NMDA receptor encephalitis for whom the estimated relapse risk is 15%, the relapse risks for these two patients with unknown antigens remains unknown. We intend to closely monitor all four patients identified with cell surface antibody-associated CNS disorder and have advised them to contact us immediately if they experience any remarkable neurological or psychiatric symptoms.

A major caveat in CNS autoantibody testing has been false positivity, as previously shown in patients with a presumed diagnosis of schizophrenia who tested positive for NMDA receptor antibodies using only cell-based assay screening (31). Among healthy cohorts, anti-NMDA receptor antibodies can often be detected in serum using cell-based assays, although IgG antibodies are rarely present (0.4%) (32). Therefore, we previously recommended that detection of serum antibodies to neuronal cell surface antigens, including anti-NMDA receptor, should involve at least two of three antigen-binding assays: 1) immunohistochemistry with rat brain sections optimized for antigen presentation, 2) live dissociated primary neuronal cultures, or 3) a recombinant cell-based assay using transfected cells expressing the antigen of interest or confirmation by CSF testing (10, 13, 14). Accordingly, if a patient's serum demonstrates autoantibody positivity by cell-based assay, then at least one additional assay should be performed to verify the result. Using this confirmatory method, no false positives have yet been identified by our group, together including over 10,000 samples (unpublished observations). In addition, this method of confirmatory screening has also been shown to provide significantly higher sensitivity for detecting CNS cell surface antibodies (10, 33).

In the present study, CSF was not sampled at the time of acute symptom onset, given the lack of any overt neurological symptoms suggestive of classical anti-NMDA receptor encephalitis. CSF has been previously shown to provide a higher sensitivity and specificity for detecting CNS autoantibodies, and therefore our analysis using serum may underestimate the frequency of autoimmune encephalitis in postpartum psychosis (14). Importantly, however, all four patients with positive immunohistochemistry labeling were confirmed using live neuron immunocytochemistry, thereby proving the presence of an antibody binding to an extracellular antigen.

To date, systematic screening for anti-NMDA receptor encephalitis in psychiatric case/control cohorts has been reported in five studies. Zandi et al. (28) exclusively used cell-based assay and concluded that three out of 46 schizophrenia patients had GluN1 and/or GluN2 serum antibodies. Of these patients, two had decreased verbal fluency, and the remaining third had antibody titers that would fall below the currently accepted threshold for positivity (34). Three follow-up studies did not confirm these findings using cell-based assay, among a total of 206 schizophrenia patients and 70 affective disorder patients, for which a subset of 80 subjects also tested negative by immunohistochemistry (32, 35, 36). In the most recent study, IgG anti-GluN1 serum cell-based assay positivity was reported in eight of 1,378 schizophrenia patients (0.6%) and six of 310 affective disorder patients (1.9%); however, no additional confirmatory antibody testing or clinical follow-up was performed (36). Taken together, the current best evidence suggests that most patients with well-established chronic psychiatric disorders are unlikely to have anti-NMDA receptor encephalitis (24, 30).

Previous cohort studies of patients with anti-NMDA receptor encephalitis have shown that the majority of patients were women (N=468/577, 81%; median age: 21 years) (24). Furthermore, several case reports and a larger cohort study described anti-NMDA receptor encephalitis in patients with first-episode psychosis (29). Compared with chronic patients, the likelihood of identifying carriers of CNS autoantibodies in patients with recent-onset severe psychiatric symptomatology is expected to be higher, especially when atypical psychiatric symptoms are present (29).

Compared with nonpuerperal psychosis, the characteristics of women with postpartum psychosis likely increases the a priori likelihood of NMDA receptor autoantibodies because these patients are female, generally young, and have first-onset episodes of atypical psychiatric symptoms, including delirium-like symptoms. In addition, following delivery, there is a well-described period of rebound immune activation, which has been widely implicated in the onset or exacerbation of multiple autoimmune disorders (37). For example, postpartum immune activation causes clinically significant increases in thyroid peroxidase antibody levels, with elevated rates of clinical thyroid dysfunction (38). The postpartum period is also a well-established period of

Neurological Symptoms	Comorbidity	Tumor	Remission	Follow-Up Antibody Screening	Psychiatric History	Family History
Extrapyramidal symptoms (after use of haloperidol)	Autoimmune thyroid disease	None	Full (84 months)	Negative	None	None
Extrapyramidal symptoms (after use of haloperidol)	None	None	Full (60 months)	Negative	Postpartum psychosis	Postpartum depression
None	None	None	Full (72 months)	Negative	None	Bipolar disorder
None	None	None	Full (12 months)	Positive	None	Autism

substantially elevated risk for both first-onset and relapse episodes of autoimmune CNS diseases, such as multiple sclerosis (39). Accordingly, a similar mechanism could underlie anti-NMDA receptor autoantibody pathogenesis during the postpartum period.

Patients with anti-NMDA receptor encephalitis often present with memory deficits, disorientation, and/or decreased consciousness. Furthermore, affective psychotic symptoms are relatively common. Postpartum psychosis is remarkable for having both features: an acute delirium-like appearance and prominent affective symptoms. Additionally, in the present study, both women with postpartum psychosis and anti-NMDA receptor autoantibodies exhibited extrapyramidal symptoms with low-dose haloperidol, a clinical response that is not particularly common among patients with postpartum psychosis. Interestingly, in patients with anti-NMDA receptor encephalitis, classical antipsychotics such as haloperidol seem to result in a high incidence of extrapyramidal symptoms, as well as the exacerbation of mild motor symptoms evident prior to antipsychotic treatment. Accordingly, we acknowledge the possibility that subtle neurological signs may have been unrecognized during the acute phase of the illness. Taken together, the acute onset of severe atypical psychiatric symptoms in young female patients should raise the index of suspicion for anti-NMDA receptor encephalitis, particularly when patients demonstrate neurological symptoms, including extrapyramidal side effects of low-dose antipsychotic treatment (40). Primary screening for anti-NMDA receptor encephalitis is most optimal when performed using CSF. The problem of false positives when using serum has been recently shown in several studies (34, 41, 42), thereby emphasizing the importance of confirming serum cell-based assay results with an independent methodology (e.g., immunohistochemistry with brain sections and/or live cultured neurons) (33, 42).

In conclusion, we recommend NMDA receptor autoantibody screening for all patients with the acute onset of a severe psychiatric illness comorbid with neurological symptoms, including seizures, decreased consciousness, dyskinesia, or overt motor symptoms. Furthermore, anti-NMDA receptor encephalitis should be considered within the differential diagnosis for any patient with first-onset psychosis or mania, especially if multiple risk factors are present. The present study suggests that anti-NMDA receptor autoantibody screening should be considered in particular for patients with postpartum psychosis.

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