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# Comparisons between Psychiatric Symptoms of Patients with Anti-NMDAR Encephalitis and New-Onset Psychiatric Patients

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**Keywords**
Anti-N-methyl-D-aspartate receptor antibody · Anti-N-methyl-D-aspartate receptor encephalitis · Psychiatric symptom · Retrospective study

**Abstract**
***Background:*** Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a potentially lethal autoimmune disease. Early diagnosis and immunotherapy can improve prognosis; however, early prominent psychiatric symptoms have led to misdiagnosis in numerous cases, delaying diagnosis and treatment. This study aimed to explore the clinical features and psychiatric symptoms of anti-NMDAR encephalitis and the association between antibody titers and psychiatric symptoms. ***Methods:*** In this retrospective study, 43 patients with anti-NMDAR encephalitis and 70 new-onset psychiatric patients were enrolled. Psychiatric symptoms were assessed by trained psychiatrists using the Positive and Negative Syndrome Scale. ***Results:*** There were significant differences in psychiatric symptoms between the antibody-positive and antibody-negative groups. The item scores for poor rapport ($p < 0.01$), difficulty in abstract thinking ($p < 0.01$), lack of spontaneity and flow of conversation ($p < 0.01$), unusual thought content ($p < 0.01$), and disorientation ($p < 0.01$) were significantly higher in the antibody-positive group, while the item scores for delusions ($p < 0.01$) were significantly higher in the antibody-negative group. These differences all remained significant after Holm-Bonferroni correction. In the antibody-positive group, scores for each item, subscale, and factor increased with increases in antibody titer, particularly for delusions ($p < 0.05$) and hallucinatory behavior ($p < 0.01$). Thereafter, only hallucinatory behavior remained significant. ***Conclusions:*** Patients with anti-NMDAR encephalitis with initial psychiatric symptoms may have the following characteristics: poor rapport, difficulty in abstract thinking, lack of spontaneity and flow of conversation, unusual thought content, and disorientation. Furthermore, antibody titer may be associated with psychiatric symptom severity, especially in hallucinatory behavior. 

## Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disease and a type of limbic encephalitis that was first identified in 2007 by Dalmau et al. [1]. This disorder was first discovered in young female patients with ovarian teratomas who presented with psy-



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chiatric symptoms, memory problems, decreased consciousness, and central hypoventilation [2, 3]. It can occur in both women and men with and without tumors [2]. Patients affected by this disease may initially present with multiple psychiatric symptoms [4], and they can later progress to multiple neurological deficits that require support from intensive care [3]. Detection of the anti-NMDAR antibody in cerebrospinal fluid (CSF) and/or serum confirms the diagnosis of this disease, which responds to immunotherapy [5]. Immunoglobulin G antibodies targeting the NR1 subunit of NMDAR can decrease the number of NMDARs, which leads to NMDAR hypofunction [3]. NMDAR hypofunction is associated with psychiatric symptoms [6]. Although it carries a risk of fatality, a majority of anti-NMDAR encephalitis patients have a good prognosis, especially in patients with early diagnosis and early treatment. However, owing to the prominent psychiatric symptoms in the early stage of this disease, a high percentage of patients seek help at first from a psychiatrist, which often leads to misdiagnosis of mental illness, delaying crucial early diagnosis and treatment for anti-NMDAR encephalitis [5–7]. It has been reported that approximately 77% of patients with anti-NMDAR encephalitis are initially evaluated by psychiatrists and receive antipsychotic treatment [3, 4, 8]. Furthermore, patients presenting with only psychiatric symptoms have been reported. Kayser et al. [9] reported that 4% of patients with anti-NMDAR encephalitis developed purely psychiatric symptoms, and that their number is increasing [10].

More than 300 studies have investigated anti-NMDAR encephalitis since its initial identification [4]. Surprisingly, despite the prominent psychiatric symptoms and the importance of psychiatric involvement in its treatment, the psychiatric literature on the disease is relatively scarce [5, 6]. Even more surprisingly, there are few reports on anti-NMDAR encephalitis from the perspective of psychiatrists in China [11–13]. It is largely unknown whether there are differences in psychiatric symptoms between patients with anti-NMDAR encephalitis who initially present with psychiatric symptoms and new-onset psychiatric patients. Further, whether this disease has characteristic clinical features in terms of psychiatric symptoms is still unknown.

In addition, owing to the overlap of psychiatric symptoms between anti-NMDAR encephalitis and schizophrenia, schizophrenia needs to be considered in the differential diagnosis [9, 10]. Previous studies have shown that NMDAR hypofunction is also associated with schizophrenia [14]. Over the past 2 decades, NMDAR hypofunction has been proposed as a potential mechanism underlying schizophrenia, which challenges the most widespread explanatory mechanism for schizophrenia – the "dopamine hypothesis" [6, 15]. Some researchers have described NMDAR dysfunction as the "final common pathway" for the mechanisms underlying the pathogenesis of schizophrenia and have associated it with both positive and negative symptoms [16]. Very interestingly, a few studies have reported that antibodies against NMDAR were also found in patients with schizophrenia [17–19]. Thus, some researchers have proposed that anti-NMDAR encephalitis and schizophrenia could be on the same spectrum and have a common underlying mechanism [6]. However, there is not enough evidence to date to determine whether they are disorders on the same spectrum or 2 different conditions.

In the present study, a total of 113 patients with new-onset psychiatric symptoms were enrolled, including 43 patients with anti-NMDAR encephalitis initially presenting with psychiatric symptoms and 70 new-onset psychiatric patients without anti-NMDAR encephalitis. Focusing on psychiatric symptoms, the present study aimed to explore the clinical features of anti-NMDAR encephalitis, expecting to aid clinicians in early diagnosis. In addition, we aimed to explore the association between antibody titer and psychiatric symptoms, hoping to provide some clues for understanding this disease.

## Materials and Methods

*Patients*

This is a retrospective study performed at West China Hospital and the Shangjin branch of West China Hospital from January 2015 to February 2017. A total of 113 patients with new-onset psychiatric symptoms were finally enrolled, including 43 patients with anti-NMDAR encephalitis who initially presented with psychiatric symptoms and 70 new-onset psychiatric patients without anti-NMDAR encephalitis. Target cases were chosen by the authors from the new patients with autoantibody tests completed by the neurology and psychiatry departments. CSF and blood serum samples were obtained from each patient during hospitalization and were used for antibody tests. All patients with a definitive diagnosis of anti-NMDAR encephalitis initially presenting with psychiatric symptoms were included in this study, and patients suspected of viral or any other infectious encephalitis or those for whom key clinical data were lacking were excluded. Ultimately, 43 patients with anti-NMDAR encephalitis who initially presented with psychiatric symptoms were enrolled. Due to the positive results for anti-NMDAR antibodies, this group of patients is referred to as the antibody-positive group. To investigate differences between anti-NMDAR encephalitis with psychiatric symptoms and psychiatric symptoms without anti-NMDAR encephalitis, we included a comparison group. All new-onset psychiatric patients

with a definitive diagnosis of mental illness with autoantibody tests completed by the psychiatry departments were included, and patients suspected of viral or other infectious encephalitis or other organic disorders or mental disorders due to psychoactive substances or mental disabilities were excluded. Ultimately, 70 new-onset psychiatric patients were enrolled in the present study, including 65 patients with a definitive diagnosis of schizophrenia, 2 patients with a definitive diagnosis of bipolar disorder, 1 patient with a definitive diagnosis of acute stress disorder, and 2 patients with a definitive diagnosis of depression. Due to the negative findings for anti-NMDAR antibodies, this group of patients is referred to as the antibody-negative group. Psychiatric symptoms were assessed simultaneously by 2 trained psychiatrists using the Positive and Negative Syndrome Scale (PANSS) according to patient medical records and information obtained from patients' families and referring physicians. Psychiatric symptoms were compared between the 2 groups. The present study was approved by the Ethics Committee of Sichuan University (No. 2016119) and conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each patient or their family members.

*Antibody Test*

All patients were examined after hospital admission. CSF and blood serum samples obtained simultaneously from each patient were sent to the Chinese Academy of Medical Sciences, Peking Union Medical College Hospital, to detect autoantibodies against NMDAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 1 (AMPA)-1, AMPA2, contactin-associated protein-2 (CASPR2), γ-aminobutyric acid receptors b1 and b2 (GABAbR1, GABAbR2), and leucine-rich glioma inactivated 1 (LGI1). Indirect immunofluorescence, which used EU 90 cells transfected with the NMDAR1 subunit (NR1) of the NMDAR complex and immobilized on BIOCHIPs (Euroimmun AG, Lübeck, Germany) as previously described [20], was used to evaluate all specimens (CSF and serum) for anti-NMDAR immunoglobulin G antibodies. The dilution starting points were 1:1 (undiluted) for CSF and 1:10 for serum. Samples were categorized as negative or positive based on the intensity of surface immunofluorescence of transfected cells compared to nontransfected cells. Similarly, indirect immunofluorescence of specifically transfected cells was also used to examine the antibodies against AMPA1, AMPA2, LGI1, CASPR2, and GABAbR1 and -2.

*Symptom Assessment Tool*

The PANSS is a widely used medical scale for measuring psychotic symptom severity and changes in patients with psychosis. It was developed by Kay et al. [21] in 1987. It consists of a positive scale including 7 items, a negative scale including 7 items, and a general psychopathology scale including 14 items, comprehensively reflecting the patient's mental and pathological picture. It uses a scale of 1–7 points and has good credibility and validity. The α-coefficient of each scale is 0.73–0.75, the retest reliability index of each scale is 0.77–0.89, and the split-half reliability of the general psychopathology scale is 0.80. The scale has a clear definition of each item and a standardized evaluation, greatly improving the operability and consistency of the assessment. China's PANSS Collaborative Research Panel tested 150 patients with schizophrenia, and 5 factors were revealed via factor analysis, which included positive factors, negative factors, cognitive factors, excitatory factors, and anxiety and depression factors [22, 23].

**Table 1.** Demographic characteristics of study participants

| Characteristics | Positive group, *n* (%) | Negative group, *n* (%) | *p* value |
|---|---|---|---|
| Sex | | | |
| Male | 18 (41.86) | 32 (45.71) | 0.689 |
| Female | 25 (58.14) | 38 (54.29) | 0.689 |
| Age | | | |
| <20 years | 11 (25.59) | 26 (37.13) | 0.204 |
| 20–29 years | 13 (30.23) | 17 (24.29) | 0.487 |
| 30–39 years | 7 (16.28) | 10 (14.29) | 0.774 |
| 40–49 years | 8 (18.60) | 9 (12.86) | 0.407 |
| 50–59 years | 2 (4.65) | 5 (7.14) | 0.895 |
| 60–65 years | 2 (4.65) | 3 (4.29) | 0.704 |
| Ethnicity | | | |
| Han | 41 (95.35) | 66 (94.29) | 0.851 |
| Minority | 2 (4.65) | 4 (5.71) | 0.851 |
| Total | 43 (100) | 70 (100) | |

*Statistical Analysis*

As mentioned above, the patients were divided into antibody-positive and antibody-negative groups. The antibody-positive group was further divided into low and high antibody titer groups on the basis of antibody titer in CSF. The low antibody titer group included 9 cases with titers of 1:10, 2 cases of 1:32, and 1 case of 1:1. The high antibody titer group included 27 cases with titers of 1:100 and 4 cases of 1:320. The item, subscale, and factor scores were considered as continuous variables. Subsequently, a *t* test was performed for comparison of continuous variables between the 2 groups. In addition, a $\chi^2$ test was conducted on constituent ratios of sex, age, and ethnicity between the antibody-positive and antibody-negative groups. All data were analyzed using SPSS software (version 17.0; IBM Corporation, Armonk, NY, USA). All tests were 2-tailed, and the threshold for significance was set to $p < 0.05$. To correct for multiple comparisons, the Holm-Bonferroni correction was applied to all comparisons.

## Results

*Characteristics of Study Subjects*

A total of 113 patients were enrolled, including 43 patients in the antibody-positive group and 70 patients in the antibody-negative group. The mean ages of patients in the antibody-positive and antibody-negative groups were 30.28 ± 12.96 and 29.03 ± 14.56 years, respectively. There were no significant differences in age between the 2 groups ($t = 0.462$, $p = 0.645$). The proportions of female patients were 58.14% in the antibody-positive group and 54.29% in the antibody-negative group. The mean disease durations of the antibody-positive and antibody-negative groups were 19.28 ± 14.51 and 36.33 ± 44.95 days, respec-

**Table 2.** Comparison of PANSS item scores between antibody-positive and antibody-negative groups

| PANSS item | Positive group ($n$ = 43) | | Negative group ($n$ = 70) | | $p$ value | Threshold after correction |
|---|---|---|---|---|---|---|
| | mean | standard deviation | mean | standard deviation | | |
| Delusions | 1.79 | 1.46 | 2.93 | 1.72 | 0.0003 | 0.0018 |
| Conceptual disorganization | 3.16 | 1.74 | 2.37 | 1.61 | 0.0155 | 0.0022 |
| Hallucinatory behavior | 2.42 | 1.79 | 2.03 | 1.63 | 0.2372 | 0.0042 |
| Excitement | 3.56 | 2.00 | 2.78 | 1.80 | 0.0331 | 0.0025 |
| Grandiosity | 1.12 | 0.63 | 1.21 | 0.85 | 0.5138 | 0.0083 |
| Suspiciousness/persecution | 1.88 | 1.50 | 2.61 | 1.76 | 0.0208 | 0.0023 |
| Hostility | 1.86 | 1.39 | 2.20 | 1.63 | 0.2410 | 0.0045 |
| Blunted affect | 2.51 | 1.72 | 1.79 | 1.41 | 0.0228 | 0.0024 |
| Emotional withdrawal | 1.58 | 1.47 | 1.61 | 1.30 | 0.9013 | 0.0250 |
| Poor rapport | 2.93 | 1.99 | 1.70 | 1.33 | 0.0006 | 0.0019 |
| Passive/apathetic social withdrawal | 1.74 | 1.42 | 1.64 | 1.31 | 0.6992 | 0.0100 |
| Difficulty in abstract thinking | 2.70 | 1.55 | 1.79 | 1.39 | 0.0016 | 0.0020 |
| Lack of spontaneity and flow of conversation | 2.98 | 2.22 | 1.74 | 1.44 | 0.0019 | 0.0021 |
| Stereotyped thinking | 1.26 | 1.07 | 1.27 | 0.85 | 0.9318 | 0.0500 |
| Somatic concern | 1.21 | 1.01 | 1.26 | 0.90 | 0.7937 | 0.0167 |
| Anxiety | 2.26 | 1.35 | 2.36 | 1.52 | 0.7207 | 0.0125 |
| Guilt feelings | 1.00 | 0.00 | 1.20 | 0.84 | 0.0515 | 0.0028 |
| Tension | 1.63 | 0.90 | 1.80 | 1.11 | 0.3933 | 0.0056 |
| Mannerisms and posturing | 1.19 | 0.70 | 1.40 | 1.18 | 0.2298 | 0.0038 |
| Depression | 1.14 | 0.64 | 1.89 | 1.42 | 0.0002 | 0.0017 |
| Motor retardation | 1.74 | 1.47 | 1.54 | 1.30 | 0.4489 | 0.0071 |
| Uncooperativeness | 2.67 | 1.76 | 2.40 | 1.71 | 0.4133 | 0.0063 |
| Unusual thought content | 2.72 | 1.50 | 1.83 | 1.12 | 0.0012 | 0.0019 |
| Disorientation | 3.91 | 1.72 | 1.57 | 0.99 | 0.0000 | 0.0017 |
| Poor attention | 2.81 | 1.56 | 2.26 | 1.33 | 0.0454 | 0.0026 |
| Lack of judgment and insight | 4.37 | 1.81 | 4.91 | 1.66 | 0.1061 | 0.0031 |
| Disturbance of volition | 1.00 | 0.00 | 1.03 | 0.17 | 0.1588 | 0.0036 |
| Poor impulse control | 2.02 | 1.63 | 2.30 | 1.60 | 0.3769 | 0.0050 |
| Preoccupation | 2.14 | 1.82 | 2.70 | 1.84 | 0.1169 | 0.0033 |
| Active social avoidance | 1.09 | 0.61 | 1.30 | 0.69 | 0.0988 | 0.0029 |

PANSS, Positive and Negative Syndrome Scale.

tively ($t$ = –2.934, $p < 0.01$). The demographic characteristics of enrolled subjects are summarized in Table 1; no significant differences in sex or ethnicity between the 2 groups were observed.

*Comparisons between Antibody-Positive and Antibody-Negative Groups*

The results of NMDAR antibody detection were positive in the CSF and/or serum of all 43 patients with anti-NMDAR encephalitis and negative in the CSF and/or serum of all 70 new-onset psychiatric patients. No autoantibodies against AMPA1, AMPA2, CASPR2, GABAbR, or LGI1 were detected in all 113 patients.

With regard to PANSS items, we observed significant differences between the 2 groups in the categories of delusion ($p < 0.01$), conceptual disorganization ($p < 0.05$), excitement ($p < 0.05$), suspiciousness/persecution ($p < 0.05$), blunted affect ($p < 0.05$), poor rapport ($p < 0.01$), difficulty in abstract thinking ($p < 0.01$), lack of spontaneity and flow of conversation ($p < 0.01$), depression ($p < 0.01$), unusual thought content ($p < 0.01$), disorientation ($p < 0.01$), and poor attention ($p < 0.05$). We found that delusion, suspiciousness/persecution, and depression were less severe in the antibody-positive group, while conceptual disorganization, excitement, poor rapport, blunted affect, difficulty in abstract thinking, lack of

**Table 3.** Comparison of each subscale score and factor score between antibody-positive and antibody-negative groups

| | Positive group ($n$ = 43) | | Negative group ($n$ = 70) | | $p$ value | Threshold after correction |
|---|---|---|---|---|---|---|
| | mean | standard deviation | mean | standard deviation | | |
| Total score | 64.40 | 19.95 | 59.41 | 11.37 | 0.1402 | 0.0100 |
| Positive scale score | 15.79 | 6.43 | 16.13 | 5.80 | 0.7737 | 0.0500 |
| Negative scale score | 15.70 | 8.19 | 11.54 | 7.77 | 0.0080 | 0.0063 |
| General psychopathology scale score | 32.91 | 9.31 | 31.74 | 6.38 | 0.4727 | 0.0125 |
| Positive factor | 8.81 | 4.71 | 9.40 | 4.47 | 0.5088 | 0.0167 |
| Negative factor | 16.70 | 8.32 | 13.57 | 7.42 | 0.0402 | 0.0083 |
| Cognitive factor | 17.16 | 5.49 | 13.36 | 4.61 | 0.0001 | 0.0012 |
| Excitatory factor | 10.12 | 5.46 | 9.67 | 5.02 | 0.6593 | 0.0250 |
| Anxiety and depression factor | 11.60 | 3.81 | 13.41 | 3.95 | 0.0182 | 0.0071 |

spontaneity and flow of conversation, unusual thought content, disorientation, and poor attention were significantly severer in the antibody-positive group. After Holm-Bonferroni correction, delusions, poor rapport, difficulty in abstract thinking, lack of spontaneity and flow of conversation, depression, unusual thought content, and disorientation remained significant. Details of these comparisons are shown in Table 2.

Regarding scale and factor scores, there were significant differences in the negative scale ($p < 0.01$), negative factor ($p < 0.05$), cognitive factor ($p < 0.01$), and anxiety and depression factor ($p < 0.05$) scores between the 2 groups. Negative scale score, negative factor score, and cognitive factor score were significantly higher in the antibody-positive group, while the anxiety and depression factor score was significantly lower for this group than for the antibody-negative group. However, only the cognitive factor score remained significant after Holm-Bonferroni correction. As far as the PANSS total scores were concerned, no significant difference was observed between the 2 groups ($p = 0.140$); however, there was a trend toward a higher total score in the antibody-positive group compared to the antibody-negative group (64.40 ± 19.95 vs. 59.41 ± 11.37, $t = 1.495$, $p = 0.140$). Details are shown in Table 3.

*Comparisons between Low and High Antibody Titer Groups*

With regard to PANSS items, the data suggested that delusions and hallucinatory behavior were severer in the high antibody titer group than in the low antibody titer group, with significant differences being observed between the 2 groups ($p < 0.05$ or $p < 0.01$). After Holm-Bonferroni correction, only hallucinatory behavior remained significant. No significant differences in any other items were observed between the low and high antibody titer groups. Details are shown in Table 4.

Regarding scale and factor scores, only positive factors ($p < 0.05$) showed a significant difference between the 2 titer groups, but this significance disappeared after Holm-Bonferroni correction. Positive factors were severer in the high antibody titer group than in the low antibody titer group. In terms of total PANSS score, although there was no significant difference between groups, a trend toward a higher score in the high antibody titer group than in the low antibody titer group was observed (66.29 ± 20.07 vs. 59.50 ± 19.59, respectively; $t = -1.001$, $p = 0.323$). Notably, there was also a trend toward higher scores in each item, subscale, and factor with the increase in antibody titer in CSF. Details are presented in Table 5.

## Discussion

In the present study, 43 patients with anti-NMDAR encephalitis were enrolled, and all initially presented with psychiatric symptoms. The present study and previous ones [3, 17, 24] show that anti-NMDAR encephalitis, an inflammatory brain disease that often presents with prominent psychiatric symptoms, often occurs in young women. Similarly, a study [7] from China that included 51 patients (63% women) with anti-NMDAR encephalitis reported that 90% of the patients exhibited psychiatric symptoms. A considerable portion of patients with anti-

**Table 4.** Comparison of PANSS item scores between low antibody titer group and high antibody titer group

| | Low antibody titer group ($n$ = 12) | | High antibody titer group ($n$ = 31) | | $p$ value | Threshold after correction |
|---|---|---|---|---|---|---|
| | mean | standard deviation | mean | standard deviation | | |
| Delusions | 1.25 | 0.62 | 2.00 | 1.63 | 0.0349 | 0.0017 |
| Conceptual disorganization | 3.08 | 1.73 | 3.19 | 1.78 | 0.8552 | 0.0083 |
| Hallucinatory behavior | 1.25 | 0.87 | 2.87 | 1.86 | 0.0004 | 0.0017 |
| Excitement | 3.50 | 1.68 | 3.58 | 2.14 | 0.9074 | 0.0100 |
| Grandiosity | 1.33 | 1.15 | 1.03 | 0.18 | 0.3875 | 0.0022 |
| Suspiciousness/persecution | 1.58 | 1.38 | 2.00 | 1.55 | 0.4203 | 0.0024 |
| Hostility | 1.58 | 0.90 | 1.97 | 1.54 | 0.4226 | 0.0025 |
| Blunted affect | 2.25 | 1.76 | 2.61 | 1.73 | 0.5421 | 0.0029 |
| Emotional withdrawal | 1.75 | 1.60 | 1.52 | 1.43 | 0.6449 | 0.0038 |
| Poor rapport | 2.75 | 2.01 | 3.00 | 2.02 | 0.7169 | 0.0045 |
| Passive/apathetic social withdrawal | 2.00 | 1.48 | 1.65 | 1.40 | 0.4677 | 0.0026 |
| Difficulty in abstract thinking | 2.58 | 1.88 | 2.74 | 1.44 | 0.7676 | 0.0050 |
| Lack of spontaneity and flow of conversation | 2.75 | 2.49 | 3.06 | 2.14 | 0.6821 | 0.0042 |
| Stereotyped thinking | 1.00 | 0.00 | 1.35 | 1.25 | 0.1253 | 0.0019 |
| Somatic concern | 1.00 | 0.00 | 1.29 | 1.19 | 0.4059 | 0.0023 |
| Anxiety | 2.17 | 1.34 | 2.29 | 1.37 | 0.7908 | 0.0056 |
| Guilt feelings | 1.00 | 0.00 | 1.00 | 0.00 | 1.000 | 0.0250 |
| Tension | 1.58 | 0.79 | 1.65 | 0.95 | 0.8427 | 0.0071 |
| Mannerisms and posturing | 1.00 | 0.00 | 1.26 | 0.82 | 0.0882 | 0.0019 |
| Depression | 1.00 | 0.00 | 1.19 | 0.75 | 0.3796 | 0.0021 |
| Motor retardation | 1.67 | 1.37 | 1.77 | 1.52 | 0.8321 | 0.0063 |
| Uncooperativeness | 2.42 | 1.51 | 2.77 | 1.86 | 0.5555 | 0.0033 |
| Unusual thought content | 2.50 | 1.51 | 2.81 | 1.51 | 0.5546 | 0.0031 |
| Disorientation | 3.92 | 1.68 | 3.90 | 1.76 | 0.9819 | 0.0167 |
| Poor attention | 3.00 | 1.86 | 2.74 | 1.46 | 0.6328 | 0.0036 |
| Lack of judgment and insight | 4.42 | 1.51 | 4.35 | 1.94 | 0.9215 | 0.0125 |
| Disturbance of volition | 1.00 | 0.00 | 1.00 | 0.00 | 1.000 | 0.0250 |
| Poor impulse control | 1.67 | 1.37 | 2.16 | 1.71 | 0.3772 | 0.0020 |
| Preoccupation | 1.50 | 1.17 | 2.39 | 1.98 | 0.0790 | 0.0018 |
| Active social avoidance | 1.00 | 0.00 | 1.13 | 0.72 | 0.5403 | 0.0028 |

PANSS, Positive and Negative Syndrome Scale.

**Table 5.** Comparison of each subscale score and factor score between low antibody titer group and high antibody titer group

| | Low antibody titer group ($n$ = 12) | | High antibody titer group ($n$ = 31) | | $p$ value | Threshold after correction |
|---|---|---|---|---|---|---|
| | mean | standard deviation | mean | standard deviation | | |
| Total score | 59.50 | 19.59 | 66.29 | 20.07 | 0.3225 | 0.0071 |
| Positive scale score | 13.58 | 5.28 | 16.65 | 6.71 | 0.1640 | 0.0063 |
| Negative scale score | 15.08 | 9.34 | 15.94 | 7.86 | 0.7636 | 0.0250 |
| General psychopathology scale score | 30.83 | 8.59 | 33.71 | 9.59 | 0.3699 | 0.0083 |
| Positive factor | 6.58 | 3.50 | 9.68 | 4.87 | 0.0283 | 0.0056 |
| Negative factor | 16.50 | 8.77 | 16.77 | 8.29 | 0.9242 | 0.0500 |
| Cognitive factor | 16.08 | 5.09 | 17.58 | 5.67 | 0.4294 | 0.0100 |
| Excitatory factor | 9.17 | 4.20 | 10.48 | 5.90 | 0.4847 | 0.0125 |
| Anxiety and depression factor | 11.17 | 2.59 | 11.77 | 4.21 | 0.6443 | 0.0167 |

NMDAR encephalitis in this study initially visited a psychiatric clinic because of prominent psychiatric symptoms, and over half (56.86%) of these patients were misdiagnosed with psychosis. Another study [25] from China involving 33 patients with anti-NMDAR encephalitis showed that the average age was 29.7 years at disease onset. Therefore, clinical physicians, especially psychiatrists, should know more about this disease and consider it in their differential diagnosis when receiving new patients with psychiatric symptoms, particularly young female patients with new-onset psychiatric symptoms.

The NMDAR is an ionotropic glutamate receptor that plays an important role in synaptic transmission, brain plasticity, and neuronal maturation [24, 26]. NMDARs are heteromers of NR1 subunits, which bind with glycine, and NR2 subunits, which bind with glutamate [3]. Hyperfunction of NMDARs is proposed to be associated with epilepsy, while hypofunction of NMDARs is associated with psychosis [15, 27, 28]. As for anti-NMDAR encephalitis, it represents a state of NMDAR hypofunction caused by autoantibodies against NMDAR. Regarding schizophrenia, NMDAR hypofunction with glutamate dysregulation has been extensively studied as a potential mechanism over the past 2 decades [29]. Evidence for the involvement of NMDARs in schizophrenia has been obtained primarily from studies on NMDAR antagonists, which can lead to schizophrenia-like psychiatric symptoms [30]. Previous studies have suggested that NMDAR hypofunction is associated with schizophrenia and that NMDAR may play a central role in the development of schizophrenia [6, 16]. Highlighting the connection between NMDAR hypofunction and schizophrenia, Kantrowitz et al. [16] described NMDAR dysfunction as the "final common pathway" for the mechanisms underlying the pathogenesis of schizophrenia and associated it with both positive and negative symptoms. Interestingly, the overlap between NMDAR encephalitis and schizophrenia regarding NMDAR hypofunction and psychotic symptoms has led researchers to question whether autoantibodies against NMDAR are part of the pathogenesis of schizophrenia [17–19]. To date, there have been several studies examining the presence of anti-NMDAR antibodies in patients with schizophrenia, but the results are variable. Zandi et al. [17] reported that 3 out of 46 patients with first-episode psychosis were positive for anti-NMDAR antibodies in their blood serum. Similarly, Tsutsui et al. [18] found that 4 patients were positive for anti-NMDAR antibodies in their serum in a study of 51 patients with schizophrenia. Steiner et al. [19] also found that 9.9% of patients ($n$ = 121) diagnosed with schizophrenia and 2.8% of patients with depression ($n$ = 70) had NMDAR antibodies in their blood serum. Moreover, they reported interesting findings that the seropositive patients had immunoglobulin G antibodies not only directed against the NR1a subunit of the NMDAR (seen in anti-NMDAR encephalitis), but also against the NR1a/NR2b subunit. However, more recently, Timucin et al. [24] examined patients with schizophrenia ($n$ = 49) and healthy controls ($n$ = 48), and none of the subjects were positive for antibodies against the NR1 subunit of the NMDAR.

In the present study, patients were placed into the antibody-positive or antibody-negative group based on the presence or absence of anti-NMDAR antibodies. We found that patients in the antibody-negative group exhibited severer positive symptoms, particularly in the category of delusions. In comparison, the patients in the antibody-positive group exhibited severer negative symptoms. Our findings support the following speculations. First, the results of the present study do not support the "final common pathway" point, because many significant differences in psychiatric symptoms between the 2 groups should not be observed if anti-NMDAR encephalitis and schizophrenia are the same kind of disease with the common underlying neurobiological basis of NMDAR dysfunction. There may be 2 ways to interpret the relationship between NMDAR dysfunction and schizophrenia considering the results of the present study. Psychiatric symptoms are not adequately manifested with disease progression. Furthermore, they are 2 different conditions with few links between them, to some extent. The dopamine hypothesis may still be the main neurobiological basis of schizophrenia. Obviously, the association between NMDAR and dopamine dysfunction is largely unknown, thereby warranting further investigation in future studies. Second, concurrent with the findings of Timucin et al. [24], the present study did not find NMDAR antibodies in the CSF or serum of patients diagnosed with schizophrenia, suggesting that antibodies against the NR1 subunit of the NMDAR may not play a role in schizophrenia. From this point of view, it is again suggested that anti-NMDAR encephalitis and schizophrenia may be 2 different conditions. Nevertheless, owing to the inconsistent findings, further studies involving larger samples to investigate the role of the NMDAR in anti-NMDAR encephalitis and schizophrenia, as well as the role of autoimmunity, are needed in the future. Third, NMDAR hypofunction may also play an important role in the presence of negative symptoms in patients with anti-NMDAR encephalitis. The role of NMDARs in negative symptoms is

not very clear [6, 16], but its presence is supported by genetic studies. O'Tuathaigh et al. [31] found a relationship between neuregulin-1 (NRG1; a growth and differentiation factor involved in the regulation of the NMDARs) dysfunction and negative symptoms of schizophrenia through reduced NMDAR expression. In addition, patients in the antibody-positive group in the present study exhibited severer cognitive impairment, suggesting that NMDAR hypofunction may play a role in cognitive impairment. Evidence for this comes from studies on NMDAR antagonists reporting that they can lead to the development of psychotic symptoms and cognitive impairment [30].

Furthermore, because CSF titers are indicative of intrathecal antibody production and may correlate with disease severity [32], the antibody-positive group was further divided into low antibody titer and high antibody titer groups regarding CSF antibody titers. Compared with the low antibody titer group, the high antibody titer group presented with severer positive symptoms, particularly delusions and hallucinatory behavior. Dalmau et al. [3] reported that a decrease in serum antibody titers was associated with symptom improvement. Similarly, Ando et al. [10] reported that psychiatric symptoms resolved or were ameliorated with the serum antibody titer changing from positive to negative at follow-ups. These findings show that anti-NMDAR antibody titers may be associated with psychiatric conditions. However, these studies only discussed the relationship between serum antibody titer and psychiatric symptoms. The present study may be the first to systematically compare psychotic symptoms between different CSF antibody titer groups using the PANSS to explore the relationship between antibody titers and psychiatric symptoms.

According to previous studies [4, 5, 33, 34], psychiatric symptoms, such as hallucinations, agitation, delusion, anxiety, aggression, etc., are observed in patients with anti-NMDAR encephalitis. In the present study, compared to new-onset psychiatric patients, we found that patients with anti-NMDAR encephalitis initially presenting with psychiatric symptoms may have the following characteristics: poor rapport, difficulty in abstract thinking, lack of spontaneity and flow of conversation, unusual thought content, and disorientation. When encountering new-onset patients with these characteristics, especially young female patients, the possibility of anti-NMDAR encephalitis should be considered. Obviously, combined with other neuropsychiatric symptoms, a definitive diagnosis of anti-NMDAR encephalitis should be confirmed via detection of antibodies against the NMDAR.

The present study has the following limitations. First, there was a possible selection and recall bias, and the study used a relatively small sample size. Second, we did not record or analyze other clinical manifestations such as prodromal symptoms and neurological symptoms, which may reinforce the study limitations. Therefore, the present findings need to be cautiously interpreted and to be further validated in future studies with larger sample sizes.

## Conclusions

Patients with anti-NMDAR encephalitis initially presenting with psychiatric symptoms may have the following characteristics: poor rapport, difficulty in abstract thinking, lack of spontaneity and flow of conversation, unusual thought content, and disorientation. More attention should be paid to young female patients with new-onset psychiatric symptoms, as anti-NMDAR encephalitis is more likely to occur in young women. Further evidence suggests that antibody titer is associated with psychiatric symptoms. With elevation of antibody titer, psychiatric symptoms seem to be severer, especially regarding hallucinatory behavior.

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## Disclosure Statement

The authors have no conflicts of interest to declare.

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