ORIGINAL ARTICLE

Antinuclear Antibodies and Thyroid Autoantibodies in the Serum of Chinese Patients with Acute Psychiatric Disorders: A Retrospective Study

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ABSTRACT

Background: It has been shown that autoimmune diseases are associated with psychiatric disorders in epidemiological studies. The acute psychiatric disorder patients have higher frequency of autoantibodies in the blood, including antinuclear antibodies, anti-thyroid peroxidase, and thyroglobulin [thyroid antibody carriers]. However, large clinical studies with more relevant control groups in China are few.
Methods: This was a retrospective study. A total of 1669 sera were tested for autoantibodies in the clinical laboratory of the Fourth Affiliated Hospital, Zhejiang University School of Medicine from October 2016 to March 2021. All data available during this time period were analyzed. Only the first entry for each patient from inpatient care units was used for analysis. The clinical information and laboratory data of patients were retrospectively collected and analyzed.
Results: A significantly lower prevalence of antinuclear antibodies was observed in the healthy control group than in the patient group (21.7% vs 28.8%, $P < .05$). There was a significant difference in the prevalence of antinuclear antibodies between thyroglobulin-antibody carriers and thyroid peroxidase-antibody- and thyroglobulin-antibody-seronegative individuals in the unipolar depressive disorder group ($P < .05$). A positive anti-thyroid peroxidase test was significantly associated with patients having nonaffective psychoses ($P < .05$).
Conclusion: The results showed that psychiatric disorders were associated with antinuclear antibodies and thyroid autoantibodies in our large sample of patients admitted to acute psychiatric hospitalization, and autoimmune autoantibodies were potential biomarkers of psychotic disorders. The results might lead to new research directions for the study of psychiatric disorders in the future.

INTRODUCTION

An increasing amount of evidence and data suggest that the immune system has a role to play in a variety of psychiatric disorders. These findings are supported by more and more mechanism-based immunotherapy studies for subgroups of patients with psychiatric disorders. According to recent research, it is possible that immune dysregulation affecting function of central nervous system (CNS) may cause psychiatric disorders, including schizophrenia, major depressive disorder (MDD), and bipolar disorder (BD). However, the exact pathophysiology of psychiatric diseases is not completely understood to date. The aforementioned diseases are associated with multiple factors, including autoimmune factors such as alterations in autoantibodies. Psychotic disorders are believed to be pathophysiologized by autoimmune processes. The hypothesis that autoimmunity can affect psychiatric symptomatology is intriguing because it suggests that a subgroup of psychiatric patients might benefit from

immune-modulatory rather than traditional psychopharmacological treatment. In particular, autoimmune disorders associated with well-known autoantibodies such as thyroid and lupus antibodies seem to be associated with severe mental disorders. Interestingly, several studies have demonstrated that compared to healthy participants, autoantibodies associated with systemic autoimmune disorders are more prevalent in the blood of patients with acute psychiatric disorders, including antinuclear antibodies (ANAs), antithyroid peroxidase (anti-TPO), and thyroglobulin [thyroid antibodies (TG-Abs)], as shown by a recent systematic review.[1] Moreover, some studies have discussed shared genetic susceptibility between autoimmunity and psychiatric disorders recently.[2]

As an indicator for clinical diagnosis of multiple autoimmune disorders, the presence of ANAs can serve as a clinical biomarker of autoimmunity. The presence of ANAs in the serum of patients with psychiatric disorders has been

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proved by different studies, and it has been demonstrated that ANAs may participate in the pathogenesis of psychiatric disorders. In epidemiological studies, autoimmune thyroiditis has been associated with schizophrenia, MDD, and BD. As a result, these diagnoses are more likely to occur over the course of their lifetime by about 30%-45%.[3] The presence of diagnostically relevant antibodies (Abs) such as serum anti-TPO and TG-Abs has been reported in 90%-95% and 60%-80% of affected cases, respectively.[4] In this context, the association between autoimmune thyroiditis and psychiatric disorders has been established. There is a strong correlation between psychiatric disorders and autoimmune thyroiditis, according to several studies.[5] We performed thyroid-Ab testing in acute psychiatric disorders versus controls.

Our analysis will enhance our understanding of the psychiatric associations with autoimmune diseases by taking these insights into consideration. According to previous studies, psychotic and affective disorder patients were more likely than healthy controls to have ANAs associated with systemic autoimmune disorders.[6-9] In addition, increased levels of anti-TPO and TG-Abs were found in the serum of patients with schizophrenia and BD compared with healthy controls.[10] However, not all studies consistently showed that autoantibodies had a positive correlation with psychiatric morbidity.[11-13] They found no association between ANAs and schizophrenia spectrum disorders or BD. Additionally, previous studies were limited by small sample sizes, the use of healthy volunteers as controls only, and the lack of correction for confounding factors (e.g., age, sex, and use of medications).[14,15] Large-sample clinical studies with more relevant control groups in China are few.

This study examined several of clinically relevant autoantibodies (associated with systemic autoimmune disorders) and revealed that psychiatric disorders are associated with autoimmune diseases in general.

As part of this study, we investigated the prevalence of the aforementioned autoantibodies in a large sample of acute psychiatric inpatients and examined the prevalence of ANAs and thyroid autoantibody among patients with nonaffective psychoses, unipolar depressive disorder, or BD (index groups) compared with patients admitted for other reasons (patient control group). Furthermore, we explored whether the ANA patterns were specifically related to the diagnosis of psychiatric disorders. Subsequently, we analyzed and discussed the association of the thyroid autoantibody status with ANAs.

MATERIAL AND METHODS

Study Design

A retrospective study was conducted. The 1669 sera were tested for autoantibodies in the clinical laboratory of the Fourth Affiliated Hospital, Zhejiang University School of Medicine from October 2016 to March 2021. All data available during this time period were analyzed. Only the first entry for each patient from inpatient care units was used for analysis. The laboratory data and clinical details of patients were retrospectively collected and analyzed. We focused on patients with schizophrenia, BD, and unipolar depression. Participation was voluntary; informed consent, including permission to publish the results of the research, was obtained. The confidential information and personal data of participants were protected. This study was conducted in accordance with the relevant guidelines and regulations and was approved by the Ethics Committee of Fourth Affiliated Hospital, Zhejiang University School of Medicine (Approval number: K2020140, 2020/09/22). In accordance with the Declaration of Helsinki, data collection and analysis were performed.

Participants

All patients admitted to the acute psychiatric inpatient department, who suffered from acute mental illness and needed hospitalization, from October 2016 to March 2021 were eligible for inclusion. A total of 834 participants were included in the study [216 male participants and 618 female participants; age range: 12-86 years; mean age = 46.4 ± 18.73]. Children younger than 18 years old were considered, and finally, 111 children were included (Table 1). The reasons for inclusion were as follows: (1) MDD and BD are among the most common psychiatric disorders of adolescence. The inclusion of adolescents made the reported results more realistic. (2) Autoantibodies have been reported to be associated with psychiatric disorders in adolescence, as in adults.[12] The only exclusion criterion for the patient group was a history of any autoimmune diseases or use of immune modulators. Two psychiatrists or senior clinical psychologists made the diagnosis. The psychiatric

MAIN POINTS

- The results showed that psychiatric disorders were associated with antinuclear antibodies and thyroid autoantibodies in our large sample of patients admitted to acute psychiatric inpatient care, and autoimmune autoantibodies seemed to be potential biomarkers of psychotic disorders.
- The nuclear speckled pattern of antinuclear antibodies was the most abundant one observed in all participants. All patients with bipolar disorder had a nuclear speckled pattern of antinuclear antibody. However, additional studies should be performed to further explore whether the antinuclear antibody patterns are specifically related to the diagnosis of psychiatric disorders.
- The presence of antinuclear antibodies in thyroid antibody carriers might be associated with unipolar depressive disorder.
- A significant difference in the positivity rates of thyroid autoantibodies was observed in patients with nonaffective psychoses compared with controls, and a positive anti-thyroid peroxidase test was significantly associated with nonaffective psychoses.

Table 1. Characteristics of Patients and Healthy Controls

	Patients (n=834)	Healthy Controls (n=835)	Group Comparison Test
Sex M/F (%males)	216/618 (25.9%)	243/592 (29.1%)	$P = .143$
Mean age in year	46.4 ± 18.73	47.3 ± 11.01	$P = .232$
Range	12-86	19-77	-
ANAs positive/negative	240 (28.8%)/594 (71.2%)	182 (21.8%)/653 (78.2%)	$P = .001$

ANA, antinuclear antibody.

patients were diagnosed according to the International Classification of Diseases-10 criteria and were divided into 4 categories: nonaffective psychoses (F20-29), bipolar

Table 2. Number of Patients in Each International Classification of Diseases-10 Diagnostic Category

Schizophrenia spectrum disorders F20-29 (n=50)	n
Schizophrenia F20	39
Delusional disorders F22	8
Acute and transient psychotic disorders F23	1
Schizoaffective disorders F25	2
Depressive disorders F32-33 (n=293)	
Depressive episode F32	
Mild F32.0	1
Moderate F32.1	11
Severe F32.2	16
Severe with psychosis F32.3	15
Severity unknown	142
Recurrent depressive disorder, current episode F33	
Mild F33.0	7
Moderate F33.1	34
Severe F33.2	10
Severe with psychosis F33.3	13
In remission F33.4	2
Severity unknown	42
Bipolar disorders F30-31 (n=60)	
Bipolar disorders, current episode F31	
Hypomania F31.0	13
Mania F31.1	2
Psychotic mania F31.2	1
Mild or moderate depression F31.3	13
Severe depression F31.4	5
Psychotic depression F31.5	2
Mixed episode F31.6	6
In remission F31.7	3
Other or unspecified F31.8-9	15
Patient control group (n=431)	
Organic mental disorders F00-09	62
Mental disorders due to substance use F10-19	1
Other affective disorders F34-39	3
Neurotic, stress-related, and somatoform disorders	335
F40-49	30

affective disorders (F30-31), unipolar depressive disorders (F32-33), and other diagnoses (for a detailed overview of the specific psychiatric diagnoses in each category, see Table 2). The healthy controls were obtained from a physical examination population in the International Health Care Center of the Fourth Affiliated Hospital, Zhejiang University School of Medicine. To be eligible, healthy controls had to meet the following criteria: no history of psychotic disorders during their lifetime and no first- or second-degree relative with psychosis. All participants with a previous history of any autoimmune diseases or use of immune modulators were excluded from this study.

Autoantibody Analyses

Venipuncture was used to collect peripheral venous blood samples (5 mL) without anticoagulants between 7:00 and 9:00 AM. The serum samples were centrifuged at 3000 rpm for 10 minutes and immediately separated, aliquoted, and stored at −80°C in a refrigerator until analysis. Blood tests were performed only once for each patient and control participant. The frozen samples were sent at the same time for analysis. Antinuclear antibody in serum was detected using an indirect immunofluorescence assay coated with HEp-2 cells (EUROIMMUN, Lubeck, Germany) using serial dilutions starting at 1:100. A fluorescence microscope was used to observe samples (EUROStarIII Plus, Lubeck, Germany). Antinuclear antibody profiles, which included anti-Jo-1, anti-nuclear ribonucleo-protein (nRNP), anti-Scl70, anti-Sm, anti-SS-A (R052), anti-SS-A, anti-SS-B, and anti-ds-DNA antibodies, were detected by line immunoassays (EURO Blot ONE, Lubeck, Germany). The sample was considered ANA positive if any of these antibodies were detected. The serum levels of anti-TPO and TG-Ab were measured with Abbott Architect I2000 (Abbott Diagnostics, Ireland). All analyses were performed following the instructions from the manufacturer, and recommended cut-off values were used. Borderline values were considered negative.

Data Analysis and Statistical Tests

Autoantibody variables were presented as dichotomous (positive–negative) and noncontinuous (titers) variables. The t-test was used for comparison of ANA prevalence between the diagnostic categories and the healthy control group. We assessed the differences in baseline characteristics and autoantibody prevalence between diagnostic categories using the Chi-square test or Fisher's exact test for categorical variables. The single-factor analysis of variance

Table 3a. Characteristics of Patients with Acute Psychiatric Disorders

	Nonaffective Psychoses (n=50)	Unipolar Depressive Disorder (n=293)	Bipolar Disorder (n=60)	Patient Control Group (n=431)	Group Comparison Test
Sex: M/F (males%)	11/39 (22%)	64/229 (21.8%)	21/39 (35%)	120/311 (27.8)	$P = .096$
Mean age in year	41.9 ± 18.02*#	42.18 ± 20.53*#	32.92 ± 17.29*	51.60 ± 15.77	$P < .001$
Range	13-70	12-76	12-68	12-86	-
ANAs positive/negative	15 (30%)/35 (70%)	88 (30%)/205 (70%)	12 (20%)/48(80%)	125 (29%)/306 (71%)	$P = .471$
Sex of ANAs positive: M/F	4 (36.4%)/11 (28.2%)	10 (15.6%)/78 (34.1%)	3 (14.3%)/9 (23.1)	24 (20%)/101 (32.5%)	$P = .194$[a]

ANA, antinuclear antibody.
*Versus patient control group, $P < .05$; #versus bipolar disorder, $P < .05$.
[a]Fisher's exact test.

was used for comparison between groups. The influence of the diagnostic group, gender, and age on ANA status was examined using a multiple logistic regression model. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) v22.0 (IBM SPSS Corp., Armonk, NY, USA). The significance level was set at $P < .05$, and the least significant difference test was used for post hoc analysis. To control for multiple comparisons, we calculated false discovery rate-adjusted P values.

RESULTS

Comparisons of Antinuclear Antibody Prevalence Between the Diagnostic Categories and the Healthy Control Group Using the *t* Test

A total of 834 patients admitted to the acute psychiatric inpatient department during the study period consented to participate in the study [mean age=46.4 ± 18.73, range, 12-86, 25.9% male] and 835 healthy controls [mean age=47.3 ± 11.01, range, 19-77, 29.1% male] (Table 2). No significant differences were observed in sex or age between patients and healthy controls. This study compared patients with healthy controls, and the prevalence of ANAs in the healthy control group was significantly lower than that in the patient group (21.7% vs 28.8%, $P < .05$). In the patient group, no significant differences were found in the prevalence of ANAs between the diagnostic categories and the patient control group in the univariate analyses (30% vs 30% vs 20% vs 29%, $P > .05$) (Table 3a and b).

Prevalence of Autoantibodies in Patients with Acute Psychiatric Disorders

One or more antibodies were detected in 44% of the patients. The prevalent autoantibodies were ANA (28.8%), anti-TPO (16.1%), and TG-Ab (15.2%). The anti-TPO was detected more frequently in patients with nonaffective psychoses compared with other groups of patients ($P < .05$). According to the univariate analysis, there was no significant difference in the prevalence of antibodies between the diagnostic categories and the patient control group ($P > .05$, Table 4a and b).

Association of the Thyroid Autoantibody Status with Antinuclear Antibody

Overall, TG-Ab carriers had an increased likelihood of ~38% (73 of 188 participants) as seropositive for ANAs compared with ~25% (167 of 646 participants) in TPO- and TG-Ab-seronegative individuals among patients admitted to the acute psychiatric inpatient department ($P < .05$, Table 5). We found significant differences in the prevalence of ANAs in thyroid Ab carriers based on diagnosis (nonaffective psychoses: n=6 of 19; unipolar depressive disorder: n=25 of 52; BD: n=4 of 13; patient control group 38 of 104 subjects; $P < .05$). In addition, a significant difference in ANA prevalence was also found between thyroid Ab carriers and TPO-Ab- and TG-Ab-seronegative individuals in the unipolar depressive disorder group (25+/27- vs 63+/178-, $P < .05$, Table 5).

Antinuclear Antibody Patterns of Patients with Acute Psychiatric Disorders

The IF-ANA staining patterns, including nuclear homogenous (H-ANA), nuclear speckled (S-ANA), centromere (C-ANA), nucleolar (N-ANA), nuclear dots (ND-ANA), cytoplasmic speckled (CS-ANA), and other patterns (o-ANA), correlated with both disease manifestations and laboratory measures. As shown in Figure 1, the prevalence of S-ANA in patients with acute psychiatric disorders was significantly higher (50%-100%) than in other staining patterns. Compared with other patient groups, participants with nonaffective psychoses had a higher incidence of nucleolar ANA pattern.

Table 3b. *P* Values of Pairwise Comparisons Among the Patient Groups

	Nonaffective Psychoses Versus Unipolar Depressive Disorder	Nonaffective Psychoses Versus Bipolar Disorder	Nonaffective Psychoses Versus Control Group	Unipolar Depressive Disorder Versus Bipolar Disorder	Unipolar Depressive Disorder Versus Control Group	Bipolar Disorder Versus Control Group
Age	.928	.003	<.001	.001	<.001	<.001

P value $< .05/6 = .0083$ indicates a statistically significant difference.

Table 4a. Prevalence of Autoantibodies of Patients with Acute Psychiatric Disorders

Autoantibody	Nonaffective Psychoses (n=50)			Unipolar Depressive Disorder (n=293)			Bipolar Disorder (n=60)			Patient Control Group (n=431)			Total (n=834)			Group Comparison Test
	Ab+(n)	Total	%	Ab+(n)	Total	%	Ab+(n)	Total	%	Ab+(n)	Total	%	Ab+(n)	Total	%	
ANA	15	50	30	88	293	30	12	60	20	125	431	29	240	834	28.8	P=.470
Anti-TPO	17	50	34#△	36	293	12.3	7	60	11.7	74	431	17.2	134	834	16.1	P=.001
TG-Ab	12	50	24	42	293	14.3	10	60	16.7	63	431	14.6	127	834	15.2	P=.336
≥1 Autoantibody	28	50	56	120	293	41	22	60	36.7	197	431	45.7	367	834	44	P=.112
Specific antinuclear																
Anti-Jo-1		2			0			0			3			5		
Anti-nRNP		0			1			2			4			10		
Anti-SS-A (RO52)		4			6			1			20			31		
Anti-SS-A		2			11			2			17			32		
Anti-SS-B		0			1			0			2			3		
Anti-ds-DNA		0			2			1			2			5		

ANA, antinuclear antibody; TG, thyroglobulin; TPO, thyroid peroxidase.
*Versus control group, $P < .05$; #versus bipolar disorder, $P < .05$; △versus unipolar depressive disorder, $P < .05$.

Moreover, all patients with BD (50/50, 100%) had a nuclear speckled pattern of ANA.

Multiple Logistic Regression Analysis of Autoantibodies

The independent variables of autoantibodies are shown in Table 6. The logistic regression models were designed for ANA, anti-TPO, TG-Ab, and positivity to one or more antibodies. Antinuclear antibody was more frequently present in women than in men (odds ratio=1.923, 95% CI: 1.310-2.822, $P < .05$). Similar results were obtained for anti-TPO and TG-Ab (odds ratio=2.018, 95% CI: 1.223-3.329, $P < .05$, and odds ratio=2.684, 95% CI: 1.544-4.664, $P < .001$, respectively). For every 10-year increase in age, the odds ratio for the presence of one or more antibodies increased with an odds ratio of 1.168 (95% CI: 1.080-1.264, $P < .05$). Age and sex were independent influencing factors of the prevalence of autoantibodies. A positive anti-TPO test was significantly associated with nonaffective psychoses (odds ratio=2.728, 95% CI: 1.415-5.258, $P < .05$). Other than that, none of the psychiatric diagnostic groups were significantly associated with the presence of any autoantibodies.

DISCUSSION

This study was one of the largest studies on blood autoantibody profiles in people with psychotic disorders in China to date. The strengths of the study were adequate sample size, including all psychiatric patients with 4 types of psychiatric disorders, and the high inclusion rate, which allowed correction for confounding factors (age, sex, and pharmacological treatment). Further, the addition of a healthy control group strengthened the study. The patient control group, consisting of patients with nonpsychotic conditions, was more relevant clinically.

In this study, the prevalence of ANAs was significantly higher in acutely admitted psychiatric patients than in healthy controls (28.8% vs 21.7%, $P < .05$). Moreover, since the age and male-to-female ratio were not significantly different between the groups, there was no influence of these factors on grouping. Additionally, 367 of 834 patients (44%) tested positive for one or more serum autoantibodies. It was shown that autoimmune processes played an important role in psychotic disorders. However, no significant differences were found in the prevalence of ANAs between the diagnostic groups and the patient control group ($P > .05$). The prevalence of ANAs at admission to an acute psychiatric inpatient care unit in our cohort did not differ significantly between the diagnostic groups. Thus, we concluded that autoimmune autoantibodies were potential biomarkers of psychotic disorders but would not be useful biomarkers for the differential diagnosis of psychotic disorders. According to the findings, there was no evidence that certain psychiatric disorders were associated with specific autoantibodies. The reason for

Table 4b. *P* Values of Pairwise Comparisons Among the Patient Groups

	Nonaffective Psychoses Versus Unipolar Depressive Disorder	Nonaffective Psychoses Versus Bipolar Disorder	Nonaffective Psychoses Versus Control Group	Unipolar Depressive Disorder Versus Bipolar Disorder	Unipolar Depressive Disorder Versus Control Group	Bipolar Disorder Versus Control Group
ANA	.996	.225	.883	.116	.765	.145
Anti-TPO	<.001	.005	.004	.894	.072	.282
TG-Ab	.083	.338	.083	.642	.916	.676
≥1 Autoantibody	.047	.043	.167	.537	.206	.187

P value < .05/6 = .0083 indicates a statistically significant difference.
ANA, antinuclear antibody; TG, thyroglobulin; TPO, thyroid peroxidase.

Table 5. Association of the Thyroid Autoantibody Status with ANA

		Thyroid Autoantibody Status			
		TPO-Ab+and/or Tg-Ab+ (n=188)	TPO-Ab- and Tg-Ab- (n=646)	Test	*P*
ANAs positive/negative	Nonaffective psychoses (n=50)	6+/13−	9+/22−	Pearson's Chi square test	.849
	Unipolar depressive disorder (n=293)	25+/27−	63+/178−	Pearson's Chi square test	.002
	Bipolar disorder (n=60)	4+/9−	8+/39−	Pearson's Chi square test	.481
	Control group (n=431)	38+/66−	87+/240−	Pearson's Chi square test	.052
	Total (n=834)	73+/115−	167+/479−	Pearson's Chi square test	.001

ANA, antinuclear antibody; TG, thyroglobulin; TPO, thyroid peroxidase.

this difference is unclear. Further, significant differences in age between the different diagnostic groups might account for this disparity. This question will be addressed in future work. The study showed that the prevalence was closely associated with age and sex, similar to the prevalence previously reported.[8,15]

According to this comparison among different nations,[16] autoantibody-positive frequency in adults differs by geography. Autoantibody positivity was believed to be influenced by age and gender. On the whole, ANA prevalence was positively correlated with age and sex in our study, implying that estrogen may be involved. Therefore, some
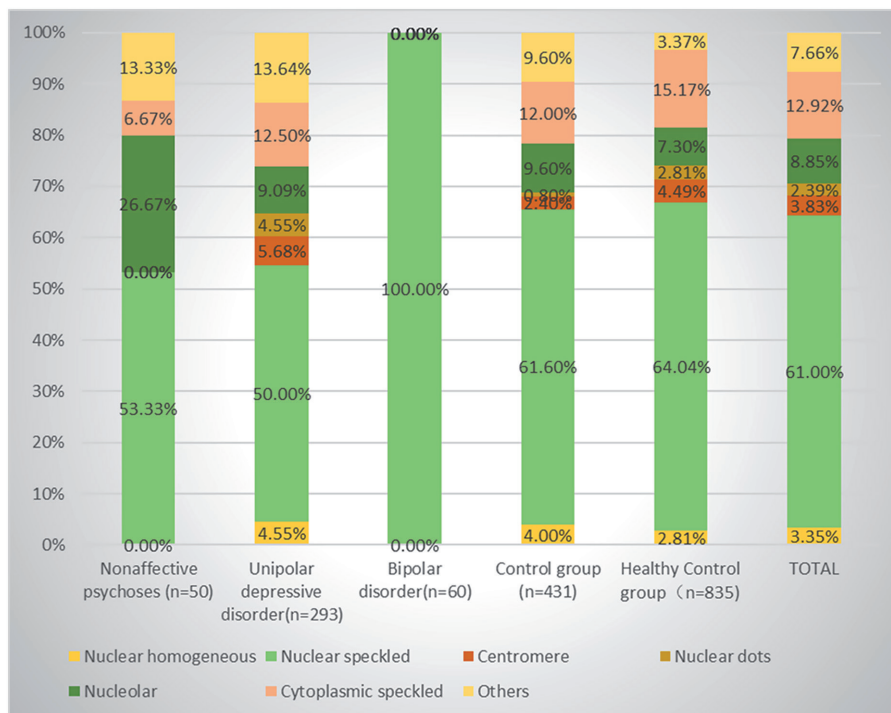

Figure 1. Antinuclear antibody patterns of patients with acute psychiatric disorders.

Table 6. Multiple Logistic Regression Analysis of Auto-antibodies

Autoantibody and Independent Variable	Odds Ratio	95% CI	P
ANA			
Sex			
Male (Ref. cat.)	1.000		
Female	1.923	1.310-2.822	.001
Age[a]	1.159	1.063-1.264	.001
Group			
Patient control group (Ref. cat.)	1.000		
Nonaffective psychoses	1.162	0.603-2.238	.654
Unipolar depressive disorders	1.164	0.829-1.635	.380
Bipolar affective disorders	0.841	0.421-1.680	.624
Anti-TPO			
Sex (female vs male)			
Male (Ref. cat.)	1.000		
Female	2.018	1.223-3.329	.006
Age[a]	1.126	1.008-1.257	.035
Group			
Patient control group (Ref. cat.)	1.000		
Nonaffective psychoses	2.728	1.415-5.258	.003
Unipolar depressive disorders	0.722	0.464-1.124	.149
Bipolar affective disorders	0.836	0.354-1.973	.683
TG-Ab			
Sex			
Male (Ref. cat.)	1.000		
Females	2.684	1.544-4.664	<.001
Age[a]	1.100	0.986-1.228	.089
Group			
Patient control group (Ref. cat.)	1.000		
Nonaffective psychoses	1.941	0.945-3.988	.071
Unipolar depressive disorders	1.019	0.658-1.578	.934
Bipolar affective disorders	1.509	0.698-3.263	.295
≥1 Autoantibody			
Sex			
Male (Ref. cat.)	1.000		
Females	1.877	1.348-2.613	<.001
Age[a]	1.168	1.080-1.264	<.001
Group			
Patient control group (Ref. cat.)	1.000		
Nonaffective psychoses	1.710	0.930-3.145	.084
Unipolar depressive disorders	0.906	0.661-1.241	.538
Bipolar affective disorders	0.945	0.527-1.696	.850

TG, thyroglobulin; TPO, thyroid peroxidase.
[a]Data represent the odds ratio for every 10-year increase in age.

similarities of genetic deposition and hormone factors may play a role in the manifestation of diseases.

Antinuclear antibodies have been suggested to play an important role in psychiatric patients, but studies showed complex results.[13,17] This also applies to schizophrenia,[18] with an extensive study showing no differences in ANA occurrence. The prevalence of ANAs was significantly higher in this study compared with previous studies,[8,9,16,19] in both the patient groups and the healthy control group. We speculated that the discrepant results might be due to different study populations and ANA detection methods. The cut-off for ANA (1:100) used in our study was close to that suggested by the 2019 ACR/EULAR classification criteria (1:80) and lower than that in previous reports (1:320). This might be due to the characteristics of the patients. Satoh et al[20] found that the positivity rate of ANA with a titer of 1:100 in healthy people aged more than 12 years in the United States was 13.8%. Hayashi et al[21] reported that the positivity rate of healthy residents was 9.5% with a titer of 1:100 ANA in healthy Japanese residents. The incidence rate might be related to sex, age range, and regional differences of selected participants. Some studies found that the positivity rate of ANAs in the Chinese population was much higher.[16,22]

However, this study found that the prevalence of ANAs was significantly higher in the patient groups than in the healthy control group. Thus, we concluded that ANAs were closely associated with the nosogenesis of many acute psychiatric disorders. Also, the autoimmunity response of patients with psychiatric disorders was stronger than that of normal people, and they had the tendency of autoimmunity. At present we can speculate only about the possible biomolecular mechanisms. A previous study[23] indicated that some patients with psychiatric disorders who received immunotherapy have shown full or substantial recovery, indicating that their symptoms may have only been caused by the antibody. As a result, immunotherapy may be effective for certain subgroups of patients with psychiatric disorders. However, additional experiments will be required to justify these results.

In a few studies,[24] ANAs with anti-nucleosome specificity were detected both in serum and in cerebrospinal fluid (CSF), suggesting the CNS is affected. A number of autoantibodies can cross the blood–brain barrier (BBB) in some patients with psychiatric disorders and can be detected in the CSF. It is essential that autoantibodies reach the targets in the brain for manifesting neuropsychiatric symptoms. It may be due to the damage of BBB. These autoantibodies may arrive targets either by local (intrathecal) production or by crossing the BBB. As a consequence, neuronal injury and death may happen in the brain, and BBB permeability may be increased. As mentioned previously, compared with the autoantibodies in serum, the autoantibodies in CSF should be more closely related to mental diseases. Thus, in the future, the autoantibodies in CSF of autoantibodies-positive psychiatric patients could be used as markers for assessing the BBB integrity. This result shows that there are autoimmune abnormalities within the brain, but it is not clear if they play a pathological role or they are merely

bystanders. We believe that this would be a useful prompt for future researches.

All participants showed the nuclear speckled pattern of ANA more frequently and all patients with BD (50/50, 100%) had the nuclear speckled pattern of ANA. This might open up a new research direction for the study of BD. To date, studies on ANA patterns and diagnosis of psychiatric disorders are few. Chen et al[25] found that the homogenous pattern of ANA was more frequently observed in patients with schizophrenia and systemic lupus erythematosus, which was inconsistent with our findings. Due to the small sample size, whether the ANA patterns were specifically related to the diagnosis of psychiatric disorders could not be determined. Hence, the results of that study must be interpreted with caution. Additional studies should be conducted to further explore this issue.

We further examined the relationship between psychiatric disorders and thyroid autoantibody status. Large epidemiological studies have found associations between thyroid autoimmunity and psychiatric disorders, which led to this study.[5,26] Tylee et al[2] observed significant genetic correlations between immune-related disorders and several psychiatric disorders. Furthermore, compared with healthy controls, higher serum anti-TPO values have been found in depression patients. Depression has been reported to affect the hypothalamic-pituitary-thyroid axis whereby thyroid antibody secretion has shown to be affected. In this study, significant differences in positivity rates were observed in patients with nonaffective psychoses compared with patient controls, and a positive anti-TPO test was significantly associated with nonaffective psychoses. These results were inconsistent with the previous study by Steiner et al.[10] who observed that the seroprevalence of TPO- and/or TG-Abs was comparable in ill and healthy individuals (MD ~10%, schizophrenia ~7%, and controls ~9%). In comparison, the larger sample size in our study increased the statistical power and made our results more plausible. The previous studies on autoantibodies mainly focused on schizophrenia and were not directly comparable to the results of our nonaffective psychosis category. Further studies are needed to validate the findings. However, despite a strong association of thyroid Abs with psychiatric disorders, our findings of a similar prevalence of TG-Abs across diagnostic groups were consistent with previous findings of Ittermann et al[27] indicating no differences in seropositivity for TPO- and TG-Abs between patients with MD and BD and patient controls. Our study also had some interesting findings. The prevalence of ANAs in TG-Ab carriers was significantly dependent on diagnosis. Furthermore, our findings demonstrated that TG-Ab carriers were more likely to carry ANAs to TG-Ab-seronegative individuals, particularly in patients with unipolar depressive disorder. Thus, the presence of ANAs in TG-Ab carriers might be associated with unipolar depressive disorder.

To sum up, psychotic and affective disorders were associated with ANAs and TG-Abs in our large sample of patients admitted to acute psychiatric inpatient care. Our findings might be particularly important for patients with psychiatric disorders. With our study, we come to the following recommendations. (1) This subgroup of antibody-positive psychiatric patients requires immunosuppressive treatment, similar to other autoimmune diseases, especially when usual antidepressants or neuroleptics are not effective. (2) Serum thyroid antibodies is the main indicator for considering the diagnosis of Hashimoto encephalopathy (HE). Therefore, HE should be considered in diagnostic procedures in cases of therapy-refractory depression or psychosis, especially in cases of good response to steroids. (3) Testing for ANAs should be performed in CSF as a marker of CNS involvement and autoantibodies in CSF could be used as markers for assessing the BBB integrity. The clinical practice would greatly benefit from this. (4) Autoimmune autoantibodies seemed to be potential biomarkers for the diagnosis of psychotic disorders.

Although multiple lines of evidence support the conclusion that autoantibodies are present in psychiatric disorders, their clinical significance and potential role in immune regulation are less certain.

Therefore, studies on the role of each associated autoantibody should open new avenues to understand the molecular mechanisms of psychiatric disorders. Future studies should have standardization of methods and sufficient numbers of subtypes to improve the comparability of studies. They should also have a longitudinal design to control for several important potential confounding factors.

To sum up, our findings aimed to shed more light on the relationship between autoimmune autoantibodies and psychiatric disorders. The results presented showed that autoimmune processes played a role in the pathophysiology of psychotic disorders. A significant difference in the positivity rates of thyroid Abs was observed in patients with nonaffective psychoses compared with controls. Further, the presence of ANAs in TG-Ab carriers might be associated with unipolar depressive disorder. All patients with BD had nuclear speckled pattern of ANAs. The results showed that psychiatric disorders were associated with ANAs and TG-Abs in our large sample of patients admitted to acute psychiatric inpatient care unit, and autoimmune autoantibodies seemed to be potential biomarkers of psychotic disorders. The findings might open up a new research direction for the study of psychiatric disorders in the future.

This study had some limitations. (1) The participants in this study were recruited from only one hospital, without additional data from other provinces and other hospitals. (2) Despite the large sample size, the sample sizes in some subgroup analyses were small, leading to some bias in the results. (3) The autoimmune history of patients was based on the results of the self-report questionnaire

survey. The low prevalence of autoantibodies could reduce the power to detect minor differences between diagnostic groups. (4) The underlying mechanisms involved in the dysregulation and its long-term complications and association with other psychiatric comorbid conditions need to be further elaborated.

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