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Prevalence and Clinical Correlates of Autistic Features in Patients with Initial-Treatment and Drug-Naive Schizophrenia

ABSTRACT

Objective: A distinct subtype of schizophrenia (SCZ) is the one accompanied with autistic features (AF). This study aimed to determine the prevalence of AF in initial-treatment and drug-naive (ITDN) patients with SCZ and investigate its influencing factors.

Methods: The study recruited 710 ITDN patients with SCZ. Their sociodemographic data and general clinical information were collected, and a clinical psychological assessment was performed to quantify their psychopathology and disease severity. The severity of AF was calculated based on psychopathology scores.

Results: Overall, 19.01% (135/710) patients with SCZ showed AF. Patients with AF exhibited higher levels of thyroid-stimulating hormone (TSH) ($t = -4.54$, $P < .001$) and lower levels of free triiodothyronine (FT_3) and free tetraiodothyronine (FT_4) ($t = 2.38$, $P = .018$; $t = 3.19$, $P = .002$) than those with AF. Binary logistic regression analysis revealed waist circumference ($B = 0.03$, $P = .022$, odds ratio (OR) = 1.03) and TSH level ($B = 0.54$, $P < .001$, OR = 1.71) as risk factors for AF, and deemed low-density lipoprotein cholesterol ($B = -0.43$, $P = .025$, OR = 0.65), fasting blood glucose ($B = -0.72$, $P = .013$, OR = 0.49), FT_3 ($B = -0.32$, $P = .034$, OR = 0.73), and FT_4 ($B = -0.08$, $P = .025$, OR = 0.93) levels as protective factors. Multiple linear regression analysis identified FT_3 level ($B = -0.85$, $t = -2.22$, $P = .028$, 95%, Confidence Intervals (CI): −1.61- −0.09) as a protective factor influencing AF severity.

Conclusion: This study reports the prevalence of AF in the target SCZ population and identifies factors associated with its development and severity. The discernment of these distinctive clinical features may facilitate formulation of tailored prevention strategies and interventions for this precise subset of SCZ patients.

Keywords: Autistic features, drug-naïve, initial treatment, schizophrenia, thyroid function

Introduction

Schizophrenia spectrum disorder (SSD) and autism spectrum disorder (ASD) are clinically viewed as distinct diagnostic categories.[1] However, research-based scientific evidence has consistently emphasized the overlapping genetic and environmental factors associated with ASD and SSD.[2] Studies have demonstrated the key similarities in their clinical presentations,[3,4] in particular, the high degree of concordance between their symptoms.[5,6] About 20-50% of patients afflicted with childhood-onset schizophrenia (SCZ) and 27% of those with adult-onset SCZ fulfill the diagnostic criteria for ASD.[7,8] A recent report emphasized that 67% of cases of childhood-onset SCZ present clinical manifestations associated with ASD, including social and language impairment.[9] In addition, research has also proposed considerable genetic overlap between ASD and SSD,[10] consistent with numerous shared copy number variant deletions and duplications detected in both disorders, including 22q11.2 and 3q29 loci[11,12] and *PRKN* (the gene encoding parkin)[13] and *DNMT1* genes.[14]

The similarities in the clinical presentation and genetic overlap between the pathogenesis of SSD and ASD have made some scholars view patients with SCZ with autistic features (AF)

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as a distinct subtype that presents with peculiar clinical characteristics.[15] Accumulating evidence also suggests more severe social cognitive deficits and functional impairment in daily life among SCZ patients with AF[16-18] who face greater challenges in assessing their daily functioning and well-being.[19] A network analysis demonstrated the inverse correlation between AF and social functioning and found that individuals with AF are more likely to exhibit psychotic symptoms than those diagnosed with or at risk for psychotic disorders.[20] Further, individuals with SCZ who exhibit AF show less favorable responses to antipsychotic treatment and have poorer specific coping strategies.[21-23] Furthermore, a broader study on patients with SCZ found that those with significant AF performed poorly across various neurocognitive areas, social cognition, functional abilities, interpersonal relationships, and community participation.[24] Therefore, it is of utmost importance to explore AF among patients with SCZ and effectively differentiate them from SCZ patients without AF.

The published literature on the incidence of AF in patients with SCZ suffers from significant heterogeneity,[25-27] probably owing to different diagnostic criteria and evaluation systems used for AF assessment that negatively affect the consistency in reported rates of AF.[17,28] Further, there are no large-scale studies on initially treated and drug-naive (ITDN) patients. To this end, this study investigated the prevalence of AF in ITDN patients with SCZ and identified relevant factors that affect the development and severity of AF.

Methods

Subjects

In total, 710 ITDN patients with SCZ hospitalized at Nanyang No. 4 People's Hospital (located in Nanyang City, Henan Province, China) and Wuhan Mental Health Center (located in Wuhan, Hubei Province, China) between February 2017 and June 2022 were enrolled in the study.

The enrolled patients met the following inclusion criteria:

1. The 10th Revision of the International Classification of Diseases (ICD-10) criteria for the diagnosis of SCZ.
2. Psychopathology severity, as determined from a Positive and Negative Symptom Scale (PANSS) score ≥ 60.
3. Age range between 18 and 60 years for both sexes.
4. No history of antipsychotics, mood stabilizers, and antidepressants prior to admission but no restriction on benzodiazepine usage.
5. Individuals diagnosed with newly identified and untreated comorbid metabolic disorders such as hypertension, hyperlipidemia, diabetes mellitus, and obesity were included.

MAIN POINTS

- *The proportion of ITDN patients with SCZ that showed AF was 19.01%.*
- *SCZ patients with comorbid AF had lower thyroid functions than those without AF.*
- *Thyroid-stimulating hormone level can significantly and positively predict the development of AF.*
- *FT_3 level can negatively predict the severity of AF.*

Patients were excluded if they met any of the following exclusion criteria:

1. Age below 18 years.
2. Suffering from any other types of psychiatric disorders such as major depressive disorder, bipolar disorder, personality disorders, substance abuse and dependence, intellectual developmental disorders, etc.
3. Severe comorbid somatic diseases and autoimmune diseases.
4. Those who had undergone any type of surgery 6 months prior to study commencement.
5. Patients with co-morbid diabetes mellitus who were being treated with exogenous insulin.

Patients who met any of the following criteria were withdrawn from the study:

1. Patients who were unable to receive a diagnosis of SCZ within 2 weeks from admission.
2. Those whose SCZ diagnosis was subsequently ruled out within the same timeframe.

The study protocol was reviewed and approved by the Ethics Committee of the Fourth People's Hospital of Nanyang (reviewed 2017-SP001). Written informed consent was obtained from all participants and/or their guardians.

Research Design

The study design was cross-sectional, developed to report the prevalence of AF in ITDN patients with SCZ and determine factors influencing its occurrence and progression. As such, patient sociodemographic and general clinical information was collected. Excel was used to design targeted forms to extract the following information from the patient's electronic case system: current age, age at onset, duration of psychosis, gender, education, marital status, height, weight, and race.

In addition, data on clinical biochemical parameters and serologic tests were collected. All patients were instructed to fast after 8:00 pm the night before the tests were performed. Venous blood samples were obtained, and blood pressure and waist circumference were measured between 6:00 am and 8:00 am the following morning. All collected blood samples were immediately sent to the biochemistry laboratory of the attending medical institution and analyzed by 11:00 am. Indicators measured included blood cell count, renal function, lipid profile, fasting blood glucose, and thyroid function. The specific parameters are shown in Table 1.

Psychological assessment was carried out using PANSS and the Clinical Global Impression Scale—Severity of Illness (CGI-SI) to investigate psychiatric symptoms and the severity of illness, respectively, at the time of admission. Two attending psychiatrists completed assessments using both scales. They were trained to use these scales prior to the study. Repeated assessments after training showed correlation coefficients greater than 0.8 between the 2 scales.

The diagnosis and assessment of AF were performed after referring to previous studies that assessed autistic features using the PANSS Autism Severity Score (PAUSS).[25,15] It comprises 3 subscales made up of different PANSS items that measure difficulties in social activity

Table 1. Differences in Clinical Variables Between Subgroups

Index	Totally (n = 710)	AF (n = 135)	Non-AF (n = 575)	t/χ^2	*P*
Age (years)	28.98 ± 7.18	29.78 ± 7.68	28.80 ± 7.06	−1.36	.175
Onset age (years)	24.33 ± 6.32	23.63 ± 5.17	24.50 ± 6.55	1.66	.098
Course of disease (years)	2.92 ± 1.84	3.05 ± 1.90	2.89 ± 1.82	−0.95	.343
Gender, (n, %)				3.86	.050
Female	257, 63.80%	39, 28.89%	218, 37.91%		
Male	453, 36.20%	96, 71.11%	357, 62.09%		
Marital status (n, %)				2.35	.125
Spousal	326, 45.92%	54, 40.00%	272, 47.30%		
Others	384, 54.08%	81, 60.00%	303, 52.70%		
Educational level (n, %)				0.53	.468
Junior school and below	466, 65.63%	85, 62.96%	381, 62.26%		
High school and above	244, 34.37%	50, 37.04%	194, 33.74%		
TC (mmol/L)	3.84 ± 0.71	3.79 ± 0.66	3.85 ± 0.72	0.94	.350
TG (mmol/L)	1.09 ± 0.56	1.15 ± 0.64	1.08 ± 0.54	−1.22	.222
LDL-C (mmol/L)	2.17 ± 0.58	2.08 ± 0.52	2.19 ± 0.59	2.10	.037*
HDL-C (mmol/L)	1.18 ± 0.23	1.19 ± 0.23	1.18 ± 0.23	-0.23	.821
WC (cm)	78.42 ± 8.93	79.96 ± 7.54	78.06 ± 9.19	-2.52	.012*
FBG (mmol/L)	5.75 ± 0.31	5.68 ± 0.38	5.76 ± 0.29	2.19	.030*
SBP (mmHg)	113.06 ± 12.51	113.36 ± 14.09	112.99 ± 12.12	-0.28	.782
DBP (mmHg)	75.14 ± 8.77	75.27 ± 9.68	75.11 ± 8.55	-0.20	.843
BUN (mmol/L)	4.49 ± 1.78	4.51 ± 1.74	4.49 ± 1.79	-0.11	.913
CRE (mmol/L)	58.03 ± 12.55	59.78 ± 12.16	57.62 ± 12.61	-1.80	.072
UA (mmol/L)	412.69 ± 123.21	402.82 ± 109.67	415.00 ± 126.16	1.03	.302
TSH (uIU/mL)	1.72 ± 0.71	1.93 ± 0.58	1.66 ± 0.73	-4.54	<.001*
FT_3 (pmol/L)	4.84 ± 0.68	4.71 ± 0.64	4.87 ± 0.69	2.38	.018*
FT_4 (pmol/L)	16.88 ± 3.15	16.17 ± 2.75	17.04 ± 3.22	3.19	.002*
CGI-SI	5.36 ± 0.62	5.27 ± 0.52	5.38 ± 0.64	1.98	.049*
PANSS	88.87 ± 11.35	87.7 ± 10.61	89.14 ± 11.51	1.33	.186
PAUSS	24.71 ± 5.71	33.53 ± 2.86	22.64 ± 3.97	-36.73	<.001*
Social activity	11.45 ± 2.91	15.27 ± 1.71	10.55 ± 2.36	-26.65	<.001*
Communication	6.50 ± 2.32	9.83 ± 1.34	5.71 ± 1.73	-25.95	<.001*
Stereotyped behavior	6.77 ± 2.04	8.44 ± 1.51	6.37 ± 1.94	-13.44	<.001*

AF, autistic features; BUN, blood urea nitrogen; CGI-SI: Clinical Global Impression Scale - Severity of Illness; CRE: blood creatinine; DBP: diastolic blood pressure; FBG: fasting blood glucose; FT_3: free triiodothyronine; FT_4: free tetraiodothyronine; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; PANSS: Positive and Negative Syndrome Scale; PAUSS: PANSS Autism Severity Score; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; TSH: thyroid- stimulating hormone; UA: blood uric acid; WC: waist circumference.
*$P < .05$.

(N1, N3, N4), communication (N5, N6), and stereotyped behavior (N7, G5, G15). The higher the total scores on the 3 subscales, the greater is the severity of autistic traits. A cut-off score of 30 indicates AF.[29]

Data Analysis

Categorical variables were reported as frequencies. Continuous variables that followed a normal distribution were expressed as means and SDs, whereas those following a non-normal distribution were summarized using percentile intervals. An independent sample *t*-test was used to compare continuous variables across groups, while a chi-squared test was employed to compare proportions. To examine the factors influencing the development of AF, a binary logistic regression model was constructed using AF as the dependent variable. The variables that exhibited significant differences in the univariate analysis served as independent variables. Subsequently, multivariate linear regression models were developed using PAUSS as the dependent variable and the predictors identified as factors affecting AF severity in the binary logistic regression. Statistical analysis was performed using (IBM SPSS Corp.; Armonk, NY, USA) version 27, and a *P*-value < .05 indicated statistical significance (2-tailed).

Results

Sociodemographic and General Clinical Characteristics of Patients from Different Subgroups

In total, 135 patients from our target population met the diagnostic criteria for AF, which accounted for a prevalence of 19.01% (135/710). The PAUSS was 33.53 ± 2.86 for the AF subgroup and 22.64 ± 3.97 for the non-AF subgroup. In comparison with the non-AF subgroup, the AF subgroup had significantly higher levels of thyroid-stimulating hormone (TSH), waist circumference (WC), and PUASS and the 3 factors as well as lower levels of low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), free triiodothyronine (FT_3), free

Table 2. Binary Logistic Regression Model of Factors Influencing AP in All Included Patients

	Coefficients				95% CI for Exp (*B*)		
	B	Std. Error	Wald	*P*	Exp (*B*)	Lower	Upper
Constant	3.24	2.15	2.27	.132	25.49		
LDL-C - mmol/L	−0.43	0.19	5.03	.025*	0.65	0.45	0.95
WC - mmol/L	0.03	0.01	5.28	.022*	1.03	1.00	1.05
FBG - mmol/L	−0.72	0.29	6.20	.013*	0.49	0.28	0.86
TSH - uIU/mL	0.54	0.14	14.12	<.001*	1.71	1.29	2.27
FT_3 - pmol/L	−0.32	0.15	4.51	.034*	0.73	0.54	0.98
FT_4 - pmol/L	−0.08	0.03	5.03	.025*	0.93	0.87	0.99

CI: Confidence Intervals; FBG: fasting blood glucose; FT_3: free triiodothyronine; FT_4: free tetraiodothyronine; LDL-C: low density lipoprotein cholesterol; TSH: thyroid stimulating hormone; WC: waist circumference.
*$P < .05$.

tetraiodothyronine (FT_4), and CGI-SI (Table 1). All *P*-values were less than .05.

Correlates Affecting AF, as Determined Using Binary Logistic Regression Models

We examined the relevant factors influencing the development of AF by constructing binary logistic regression models (backward: Wald) using AF as the outcome variable. The clinical variables identified as "different" in the univariate analysis served as independent variables (excluding PAUSS and its 3 factors). The results revealed WC ($B = 0.03$, $P = .022$, odds ratio (OR) = 1.03) and TSH ($B = 0.54$, $P < .001$, OR = 1.71) levels as risk factors for AF and LDL-C ($B = -0.43$, $P = .025$, OR = 0.65), FBG ($B = -0.72$, $P = .013$, OR = 0.49), FT_3 ($B = -0.32$, $P = .034$, OR = 0.73), and FT_4 ($B = -0.08$, $P = .025$, OR = 0.93) levels as protective factors (Table 2).

Correlates Affecting AF Severity, as Determined Using Multiple Linear Regression Models

Next, we constructed a multiple linear regression model (backward) to identify factors that are associated with the severity of AF. PANSS Autism Severity Score was the outcome variable, while the clinical variables found to impact the development of AF in the binary logistic regression were used as independent variables. The results showed that FT_3 level (B = −0.85, $t = -2.22$, $P = .028$, 95% CI: −1.61 - −0.09) was a protective factor affecting the severity of AF (Table 3).

Discussion

The results of our study showed that 19.01% (135/710) of the ITDN patient population with SCZ met the diagnostic criteria for AF. The SCZ subgroup with AF had higher TSH and lower FT_3 and FT_4 levels than the non-AF subgroup, which is indicative of a certain degree of hypothyroidism. We identified various factors that affected the development of AF, including risk factors such as abdominal circumference and TSH levels and protective factors such as LDL-C, FBG, FT_3, and FT_4. Lastly, the FT_3 level was identified as a risk factor determining the severity of AF.

Table 3. Correlates that Influence the AP Score: A Multiple Linear Regression Model

	Coefficients	Std.			95% CI	
	B	error	*t*	*P*	Lower	Upper
LDL-C - mmol/L	−0.90	0.46	−1.95	.054	−1.81	0.02
FT_3 - pmol/L	−0.85	0.38	−2.22	.028*	−1.61	−0.09
FT_4 - pmol/L	0.17	0.09	1.88	.062	−0.01	0.34

FT_3: free triiodothyronine; FT_4: free tetraiodothyronine; LDL-C: low density lipoprotein cholesterol.
$P < .05$.

Previous studies have highlighted varying rates of AF across different subclinical populations of SCZ.[25-27] Herein, we found that the prevalence of AF was 19.01%. Another large cross-sectional study conducted by *Pu Peng* et al. in Chinese patients with chronic SCZ reported an AF detection rate of 18.6%.[25] An Italian study conducted on 75 patients undergoing antipsychotic treatment reported an AF rate of 44%.[26] These findings highlight the variability in AF prevalence among distinct subclinical groups. These discrepancies in the reported prevalence of AF can be attributed to differences in the cut-off values used in assessments. This is evident from 80.05% of patients with SCZ in a stable phase showing ASD symptoms if a PAUSS >10 criterion was applied for AF diagnosis.[17] The variability in AF assessment and diagnostic tools can significantly contribute to the heterogeneity of AF prevalence, which can range from 2.8% to 27.8% in the same sample upon application of different diagnostic tools.[28] While definitive statements on AF prevalence are challenging owing to differences in evaluation methodologies and patient subpopulations, exploring the characteristics of the SCZ subgroup with AF is a key requisite for improved prognosis through their early identification and recognition.

Only a few studies have attempted to compare differences in thyroid functions among SCZ patients with and without AF. However, there is every indication that hypothyroidism may play an important role in the formation and development of ASD and AF in patients with SCZ. A large-scale meta-analysis confirmed the suggestive association of maternal hypothyroxinemia in early pregnancy with an increased risk of AF.[30] To this end, 2 national case-cohort studies conducted in Denmark revealed maternal hypothyroidism in early pregnancy as a risk factor for ASD in children.[31,32] Further exploration of the association between neonatal thyroid function and the plausible development of ASD revealed no direct evidence between neonatal TSH and overall ASD risk. However, one cannot completely dismiss the effect of thyroid hormones on ASD sub-phenotypes.[33,34] In comparison to healthy children, those with ASD exhibit higher serum TSH levels. Although within the physiologic range, this increase is reflective of the presence of thyroid dysfunctions in them.[35,36] While this may not serve as direct evidence of relatively reduced thyroid function in SCZ patients with concomitant AF, it enhances our certainty that thyroid function influences the onset and progression of AF in patients with SCZ.

While exploring the factors that influenced the development of AF and its severity in this population, we found that TSH and FT_3 levels contributed to the development of AF and more severe AF scores, respectively. However, reports available thus far have less frequently mentioned the effect of thyroid functions on AF in the SCZ diagnostic population. Considering ASD, Sarika Singh and colleagues revealed no direct association between TSH levels and overall ASD but reported its negative association with sub-phenotypes, such as social interaction, communication+social interaction, and stereotypic behaviors.[37] This result contradicts to a certain extent the findings of the present study in the domain of SCZ. As the vast majority of AF symptoms have a PANSS-negative symptom subscale component,[15] we expanded our exploration of the association between negative symptoms and thyroid function. A clinical study on a small sample of patients reported the involvement of thyroid autoimmunity in the development of more severe negative symptoms among patients with early SCZ.[38] Another small-sized clinical study demonstrated a weak negative correlation between PANSS negative subscale scores and TSH levels.[39] While this may not be clear evidence of the direct involvement of thyroid functions TSH and FT_3 in AF among patients with SCZ, they do shed light on the potential role of thyroid functions in the onset and development of AF.

The present study has several limitations. First, given its cross-sectional design, it is difficult to establish a causal relationship between risk factors and outcome variables. Second, prior research on the impact of thyroid functions on the initiation and advancement of AF in individuals with SCZ is scarce, leading to a lack of adequate literature for referencing and reviewing this mechanism. Third, the study only included adult patients; therefore, the findings may not be generalized to the population of juvenile schizophrenic patients. To address these limitations, future research endeavors should focus on designing more rigorous prospective studies.

Conclusion

Our study identified the prevalence of AF to be 19.01% among ITDN patients with SCZ. Hypothyroidism is a key factor potentially mediating the onset and progression of AF in this patient population. The identification of these clinical features of AF in patients with SCZ improves our understanding and knowledge of the specific clinical subtypes of SCZ and serves as a basis for the development of preventive and interventional measures in clinical practice.

Availability of Data and Materials: *The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.*

Ethics Committee Approval: *Ethical committee approval was received from the Ethics Committee of The Fourth People's Hospital of Nanyang (Approval no: 2017-SP001).*

Informed Consent: *Written informed consent was obtained from the subject guardians who agreed to take part in the study.*

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