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Concentrations of Thyroid Axis Hormones in Psychotic Patients on Hospital Admission: the Effects of Prior Drug Use

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Key words: *acute psychosis; schizophrenia; thyroid axis hormones; sex hormone-binding globulin; antipsychotics.*

Summary. *The aim of this study was to determine the concentrations of thyroid axis hormones in psychotic patients on hospital admission and to search for the associations between the concentrations of these hormones and prior drug use as well as mental symptoms.*

Material and Methods. Psychiatric diagnoses, psychotropic drug use, and the severity of psychoses were evaluated using the standard methods on admission. Venous blood from patients and healthy controls was drawn for the analysis of free thyroxin (FT_4), free triiodothyronine (FT_3), thyroid-stimulating hormone (TSH), and sex hormone-binding globulin (SHBG) concentrations.

Results. Eighty-one psychotic patients, free of a thyroid disorder, were enrolled into the study. Compared with the controls, they displayed the higher FT_4 concentrations in the general group (P=0.003) and the higher SHBG concentrations only in men (P=0.013). The FT_4 concentration was higher in the patients who were not taking an antipsychotic drug on admission (P=0.039). No significant correlation was found between the severity of psychosis and concentrations of thyroid axis hormones. However, the FT_3 concentration in the general group and TSH concentration in women correlated with the factor of the Brief Psychiatric Rating Scale expressing elevated mood.

Conclusions. Our study confirms the higher FT_4 concentrations in a significant proportion of acute psychotic patients. The concentrations of thyroid axis hormones were found to be associated with prior antipsychotic treatment on hospital admission.

Introduction

Dysfunction of the thyroid gland, hyperfunction or hypofunction, is frequently associated with mental disorders including psychoses that sometimes resemble schizophrenia (1). An increased prevalence of thyroid function abnormalities has been reported in families of patients with schizophrenia (2), suggesting a possible genetic linkage between the endocrine and mental disorders. Nevertheless, most schizophrenic patients are euthyroid with a basal concentration of thyroid stimulating hormone (TSH) within the reference range and normal TSH response to thyrotropin-releasing hormone (TRH) challenge (3, 4).

It is well known that illness, certainly including mental illness, may activate the thyroid axis, and this activation is often noted when patients are admitted to the hospital. Several studies have reported the elevated serum concentrations of thyroxine (T_4), but not triiodothyronine (T_3), in acute psychiatric disorders, an abnormality that usually resolves during recovery and is called transient hyperthyroxinemia (5, 6). The data on the frequency of this activation, the factors that may modify it, and associated findings are scarce.

Tissue responses to changes in thyroid hormone concentrations may be better indicators of the significance of thyroid axis activity than thyroid hormone concentrations themselves. Response of the anterior pituitary gland, evident by the changes in TSH concentrations, is a sensitive marker of thyroid dysfunction. The production of sex hormone-binding globulin (SHBG) in the liver is another sensitive tissue marker of thyroid activity (7). The hepatic synthesis of SHBG is stimulated by thyroid hormones (8). SHBG has a diagnostic value for detecting even mild changes in thyroid hormone concentrations and showing the biological effect of thyroid hormones at the tissue level (9, 10). However, there are no data pertaining to serum SHBG concentrations in patients with acute psychoses, though one study reported a decrease in SHBG concentrations after treatment with olanzapine, an atypical antipsychotic (11). Treatment with another atypical antipsychotic, quetiapine, may decrease the concentrations of thyroid hormone (12, 13). Therefore, the aim of this study was to determine the concentrations of thyroid axis hormones and SHBG in psychotic patients at the time of their hospital admission and to search for the associations between concentrations of these hormones and prior antipsychotic drug use as well as mental symptoms.

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Material and Methods

Study Population. From July 2006 to February 2008, the patients with acute psychosis admitted to the Acute Psychosis Department of Kaunas Hospital, Lithuania, were invited to participate in the study. The study protocol and informed consent form were approved by the Regional Committee for Biomedical Research of the Lithuanian University of Health Sciences, Kaunas, Lithuania.

Men and women with acute psychosis, aged 18 to 70 years, were considered eligible if they had no serious or unstable medical conditions, had not received treatment with thyroid medication, and were physically healthy as judged by physical examination, medical history, and results of routine blood and urine tests. The control group for biochemical comparisons consisted of consecutive blood donors from the Blood Donor Center in Kaunas, Lithuania.

Ninety-seven psychotic patients (44 men and 53 women) provided blood samples for the assessment of thyroid axis hormone and thyroid antibody concentrations in the morning after admission. The blood samples of 104 blood donors (57 men and 47 women) were used for control evaluations. Because thyroid disorders are common and their presence may skew the data, all the patients and controls were screened for autoimmune thyroid disease and frank thyroid dysfunction. Thirteen psychotic patients and 10 controls had thyroid peroxidase antibody (TPOAb) concentrations higher that 20 IU/mL, indicating autoimmune thyroid disease; 2 psychotic patients and 1 control subject had TSH concentrations higher than 4.05 μIU/mL, indicating hypothyroidism; and 1 psychotic patient had TSH concentrations less than 0.17 μIU/mL, indicating hyperthyroidism. All patients and controls with thyroid dysfunction and/or with autoimmune thyroid disease were excluded from the study. Thus, the data of 81 psychotic patients (42 men and 39 women; mean age, 36 years) and 93 controls (54 men and 39 women; mean age, 36 years) were included into analysis. There were no significant differences between patients and controls regarding gender or age.

Psychiatric diagnoses were made according to the standard diagnostic criteria using a structured clinical interview, and the severity of psychosis was evaluated using a standard clinical scale (see below) in the morning after admission. All 81 patients were considered to present indications for treatment with antipsychotic drugs.

No attempt was made to measure the serum concentrations of psychotropic drugs either in patients or controls. Instead, all patients were questioned about the use of psychotropic medications at the time of admission. Information from patients, referring psychiatrists, and patients' relatives was collected. A patient was considered as receiving psychotropic drug treatment on hospital admission if a referring psychiatrist documented such prescription and if a patient or a relative confirmed its use. If such information was lacking, the patient was considered as not receiving psychotropic drug treatment.

On hospital admission, 27 psychotic patients used the following antipsychotics: 4 patients, haloperidol; 7, olanzapine; 6, risperidone; 2, amisulpiride; 3, ziprazidone; 3, quetiapine; 1, clozapine; and 1, tiapride. Fifty-four patients did not use antipsychotics, but 12 of them used benzodiazepines or antidepressants. Thirty-nine patients did not use any psychotropic drug.

Psychiatric Evaluation. Psychiatric diagnoses were established according to the DSM-IV-TR diagnostic criteria (14) using the MINI-Plus 5.0.0 structured clinical interview (15). The MINI is a brief instrument that establishes DSM-IV-TR Axis I diagnoses. The MINI-Plus is comparable to other standard diagnostic instruments such as the Structured Clinical Interview for DSM-IV (SCID) (16), but can be administered in a much less time. The MINI- Plus is divided into 26 modules identified by letters, each corresponding to a diagnostic category, pertaining to past and current diagnoses. At the beginning of each diagnostic module (except for the module of psychotic disorders), screening questions corresponding to the main criteria of the disorder are presented. At the end of each module, a diagnostic box permits a clinician to indicate whether diagnostic criteria for a specific mental disorder have been met.

Three modules of the MINI-Plus, allowing diagnoses for major depressive episode (module A), (hypo)manic episode (module D), and psychotic disorder (module M), were used. Diagnostic algorithms for psychotic disorders were used to specify a psychotic disorder. It is important to note that only patients who met criteria for a current psychotic disorder on module M were enrolled into the study. Forty-four patients were diagnosed as having schizophrenia; 11 patients, schizoaffective disorder; 5 patients, schizophreniform disorder; 16 patients, brief psychotic disorder; 2 patients, major depressive disorder with psychotic features; and 3 patients, bipolar I manic episode with psychotic features.

The severity of psychosis was assessed by the Brief Psychiatric Rating Scale (BPRS). The BPRS comprises 18 items rated from 0 (not present) to 6 (extremely severe) and includes symptoms of psychoses, depression, and anxiety. Some items (e.g., mannerism and posturing) are rated based on observation of the patient; other items (e.g., anxiety) involve self-reporting by the patient. It takes 15 to 30 minutes to complete. The severity of psychosis is measured by the total score ranging from 0 to 108. Scores below 10 are considered as normal variation. For later analyses, the total BPRS scores and 3 factors derived from the data (a factor for mood symp-

toms, psychotic symptoms, and anxiety symptoms) were used. All diagnostic evaluations were made by a trained psychiatrist (V.S.).

Endocrine Measurements. Venous blood samples were drawn from patients in the morning after admission to the hospital and after an overnight fast. Blood samples from the control group were collected at the Blood Donor Center. Blood samples were centrifuged, and then serum samples were stored at –40°C. All samples were analyzed for each biochemical variable as a batch to avoid interassay variability.

The serum concentrations of thyroid-stimulating hormone (TSH), free thyroxine (FT_4), free triiodothyronine (FT_3), TPOAb, and SHBG were assessed by radioimmunoassay, using commercial IMULITE kits (Czech Republic). The sensitivity of the assays was as follows: TSH, 0.025 μIU/L; FT_4, 0.4 pmol/L; FT_3, 0.5 pmol/L; TPOAb, 2 IU/mL; SHBG, 0.2 nmol/L. Table 1 gives the reference ranges for these variables.

Statistical Analysis. Continuous data are expressed as means (SD). To compare differences in hormone concentrations between the patient and control groups and between patients receiving or not receiving psychotropic drug treatment, analysis of variance was used. For two-group comparisons, ANOVA will give results identical to a *t* test. Differences between two proportions were calculated using the Fisher exact test. The factor structure of the BPRS was examined using principal component analysis with the varimax procedure to rotate factors. Principal component analysis (specifying the number of factors to extract) resulted in 3 interpretable factors. Sample size calculation was made according to the assumption about minimal 5% estimated prevalence of patients with FT4 >+2SD (17). As a result, an estimate of 73 patients per treatment group would provide a power of at least 0.80 to detect this prevalence with a 2-sided α=0.05. Data analysis was performed using the SPSS statistical software (version 17.0). All tests are based on a two-tailed α significance of 0.05.

Results

As shown in Table 1, the FT_3 and TSH concentrations were similar comparing the patient and control groups. However, there were statistically significant differences in the FT_4 concentration. The patients, whether as the general group (F=9.1, *P*=0.003) or subdivided by gender (F=6.0, *P*=0.016 for men, F=4.2, *P*=0.043 for women), had the higher FT_4 concentrations as compared with the control group. With FT_3 values for patients about like those for controls, the higher FT_4 values resulted in the diminished ratios of FT_3 to FT_4. This effect was statistically significant in the general group of patients (F=8.0, *P*=0.005). When the gender was considered, the effect was significant in women but not in men (F=4.5, *P*=0.037).

As the SHBG concentration normally varies substantially according to gender, the data from men and women were analyzed separately. The analysis revealed a novel finding: the SHBG concentrations were higher in men (F=6.4, *P*=0.013), but not women, as compared with the control group.

Having compared patients with controls, the comparisons between the subgroups of patients were performed. First, a group of 42 patients who were taking a psychotropic drug (whatever the specific drug) on admission was compared with a group of 39 patients who were not taking such a drug. No significant differences in any of the variables of interest were found (data not shown). Then, as

Table 1. Age and Thyroid Axis Hormone Concentrations in Acute Psychotic Patients on Hospital Admission and in Blood Donor Controls

Variable	Gender	Patients Total, n=81 Men, n=42 Women, n=39	Controls Total, n=93 Men, n=54 Women, n=39	Univariate ANOVA	Reference Range
Age, years	Total	36 (11)	36 (12)	F=1.3, *P*=0.25	–
	Men	34 (11)	34 (12)	F=1.2, *P*=0.27	
	Women	38 (10)	40 (12)	F=0.0, *P*=0.96	
Free triiodothyronine, pmol/L	Total	5.1 (0.9)	5.2 (0.8)	F=0.8, *P*=0.36	2.5–6.8
	Men	5.4 (0.8)	5.3 (0.8)	F=0.0, *P*=0.98	
	Women	4.8 (1.0)	4.9 (0.6)	F=0.8, *P*=0.38	
Free thyroxine, pmol/L	Total	17.9 (2.9)	16.7 (2.2)	F=9.1, *P*=0.003	11.5–23.0
	Men	18.2 (2.5)	17.1 (2.1)	F=6.0, *P*=0.016	
	Women	17.6 (3.3)	16.2 (2.2)	F=4.2, *P*=0.043	
Ratio of free triiodothyronine to free thyroxine	Total	0.29 (0.06)	0.31 (0.05)	F=8.0, *P*=0.005	–
	Men	0.30 (0.05)	0.32 (0.05)	F=2.9, *P*=0.09	
	Women	0.28 (0.07)	0.31 (0.05)	F=4.5, *P*=0.037	
Thyroid-stimulating hormone, μIU/mL	Total	1.60 (0.86)	1.49 (0.85)	F=3.1, *P*=0.08	0.17–4.05
	Men	1.64 (0.89)	1.71 (1.00)	F=2.3, *P*=0.13	
	Women	1.57 (0.84)	1.33 (0.68)	F=0.7, *P*=0.42	
Sex hormone-binding globulin, nmol/L	Men	41 (17)	35 (14)	F=6.4, *P*=0.013	20–70
	Women	61 (29)	58 (33)	F=0.1, *P*=0.81	30–100

Values are mean (standard deviation).

displayed in Table 2, the patients were divided into two groups: those receiving an antipsychotic drug (n=27) and patients not taking an antipsychotic drug (n=54). Again, the comparison of these two groups revealed a difference to be significant only for FT_4: the patients using an antipsychotic had the lower FT_4 concentration than those not using an antipsychotic drug (F=4.4, P=0.039). When the gender was considered, women, but not men, showed a significant difference (F=4.7, P=0.037). The ratios of FT_3 to FT_4 changed accordingly. In this set of comparisons, no significant differences in the SHBG concentration were found. The severity of psychoses was similar in these two groups of patients.

All 93 control subjects and most of the 81 psychotic patients had the FT_4 concentrations within the reference ranges for the assays employed, but 1 woman had the FT_4 concentration below the lower reference limit and other 4 patients (5%) (2 men and 2 women) had the FT_4 concentrations above the upper reference limit. The TSH concentration was within the reference range in all study subjects, indicating euthyroidism.

When normal ranges for thyroid axis hormone values were considered arbitrarily as values that did not exceed SD above or below the mean of the control group, significant differences between patients and controls were found only for higher FT_4 concentrations. Of the 81 psychotic patients, 22 (27%) had the higher FT_4 concentrations, while only 5 (5%) of the 93 controls showed such changes indicating hyperthyroxinemia (P<0.001).

Factor analysis revealed 3 factors of the BPRS. One factor pertained to mood symptoms (somatic concern, guilt, grandiosity, depressive mood, hostility, motor retardation, and excitement); a second factor pertained to psychotic symptoms (emotional withdrawal, conceptual disorganization, mannerisms and posturing, suspiciousness, uncooperativeness, unusual thought content, and blunted affect); a third factor pertained to anxiety symptoms (anxiety, tension, and disorientation). We sought to discover correlations between endocrine measurements and mental symptoms in the patient population. In fact, there were no correlations between the concentrations of any endocrine hormone and the total BPRS score. However, certain correlations did emerge between certain endocrine measurements and BPRS factors. In the general sample of patients, higher FT_3 concentration correlated with elevated mood (r=0.26 and P=0.02). In the female patients, lower TSH concentration correlated with elevated mood (r=–0.39 and P=0.01). In the male patients, lower SHBG concentration correlated with the severity of psychotic symptoms (r=–0.41 and P=0.007).

Discussion

Our findings, generated in a naturalistic setting but with careful attention to background thyroid illness and prior drug use, supported, modified, and extended the finding of earlier investigations. As a whole, acute psychotic patients compared with healthy controls showed an increase in the FT_4 concentrations, and male patients also showed the increased SHGB concentrations. No significant differences were found in the serum FT_3 or TSH concentrations.

The pattern of increase in FT_4 concentrations with normal TSH concentrations corresponds to

Table 2. Severity of Psychoses and Thyroid Axis Hormone Concentrations in Acute Psychotic Patients With and Without Current Antipsychotic Treatment on Hospital Admission

Variable	Gender	No Current Antipsychotic Use Total, n=54 Men, n=31 Women, n=23	Current Antipsychotic Use Total, n=27 Men, n=16 Women, n=11	Univariate ANOVA	Reference Range
Brief Psychiatric Rating Scale	Total	38 (9)	40 (6)	F=1.6, P=0.22	<10
	Men	41 (6)	41 (6)	F=1.3, P=0.27	
	Women	35 (10)	38 (8)	F=0.0, P=0.97	
Free triiodothyronine, pmol/L	Total	5.1 (0.9)	5.1 (0.9)	F=0.5, P=0.82	2.5–6.8
	Men	5.4 (0.8)	5.4 (0.7)	F=0.03, P=0.86	
	Women	4.7 (0.9)	4.9 (1.0)	F=0.51, P=0.48	
Free thyroxine, pmol/L	Total	18.4 (2.8)	17.0 (2.8)	F=4.4, P=0.039	11.5–23.0
	Men	18.3 (2.4)	18.0 (2.7)	F=1.4, P=0.71	
	Women	18.5 (3.4)	16.3 (2.7)	F=4.7, P=0.037	
Ratio of free triiodothyronine to free thyroxine	Total	0.28 (0.06)	0.31 (0.05)	F=3.2, P=0.077	
	Men	0.30 (0.05)	0.31 (0.05)	F=2.4, P=0.63	
	Women	0.26 (0.07)	0.31 (0.06)	F=4.8, P=0.035	
Thyroid-stimulating hormone, μIU/mL	Total	1.54 (0.87)	1.73 (0.85)	F=9.1, P=0.34	0.17–4.05
	Men	1.57 (0.94)	1.55 (0.50)	F=0.1, P=0.92	
	Women	1.49 (0.78)	1.86 (1.02)	F=1.7, P=0.21	
Sex hormone-binding globulin, nmol/L	Men	42 (17)	40 (16)	F=0.1, P=0.76	20–70
	Women	66 (31)	55 (24)	F=1.3, P=0.27	30–100

Values are mean (standard deviation).

the description of euthyroid hyperthyroxinemia that has been reported in acute psychotic patients and patients with mood disorders (5, 6, 18–21). We have demonstrated earlier in patients with major depression that concomitant autoimmune thyroiditis (22) or goiter (23) in psychiatric patients with normal TSH concentrations had significant effects on thyroid function assessed by the most sensitive method, the TRH test. Therefore, in the present study, the exclusion of patients and controls with autoimmune thyroid disease, as well as subjects with primary thyroid dysfunction, allowed us to evaluate thyroid axis hormone concentrations in association with psychoses without endocrine bias. Our study eventually indicated that an increase in FT_4 concentrations in acute psychotic patients might be mild, usually not exceeding the reference range.

In our study, free rather than total thyroid hormone concentrations were measured despite the fact that in psychiatric patients changes in the total hormone concentrations are more evident than changes in the free hormone concentrations (18, 19). However, free hormone concentrations better express thyroid axis activity and are less influenced by carrier proteins, which in turn are affected by many other factors, including inflammation (24). In this regard, inflammation has been considered as a possible factor in the pathogenesis of schizophrenia (25).

Baumgartner et al. concluded that the high serum concentrations of T_4, with T_3 and TSH concentrations within the reference limits, might be specific for acutely ill schizophrenic patients (6). They reported that the elevated serum T_4 concentrations were caused by a disturbed T_4 uptake and/or metabolism in the central nervous system. In fact, transient euthyroid hyperthyroxinemia is not specific for schizophrenia and occurs across a range of acute psychiatric and medical conditions. Euthyroid hyperthyroxinemia may be considered an early manifestation of nonthyroidal illness syndrome (NTIS), which is sometimes referred to as euthyroid sick syndrome or so-called "low T_3 syndrome." This unspecific syndrome manifests as a decrease in T_3 concentration, occurring in severe medical conditions and fasting. In the early presentation of NTIS, a marginal increase in the serum FT_4 concentration with no change in the FT_3 concentration may indicate a deceased conversion of T_4 to T_3 in tissues, including the brain (26), as well as the suppression of TRH secretion in the hypothalamus (27).

Other authors (5, 28) suggest that the elevations of peripheral thyroid hormone concentrations in psychiatric inpatients may result from a centrally mediated hypersecretion of TSH. However, in our study, no differences in the TSH concentrations in psychotic patients compared with controls were found.

SHBG secretion by the liver is controlled by several factors, including thyroid hormones (7). Increased SHBG concentrations in parallel with increased FT_4 concentrations in psychotic patients indicate a possible interaction between euthyroid hyperthyroxinemia and SHBG secretion. Thyroid axis function in mental disorders (29) is gender-specific, and, it, at least in part, may explain our novel findings on gender differences in SHBG concentrations. SHBG is a sensitive biomarker of insulin resistance and the metabolic syndrome (7) and should be taken into consideration prescribing atypical antipsychotics, such as olanzapine. Moreover, it has been recently demonstrated that treatment with olanzapine decreases SHBG concentrations in psychotic patients (11).

In our group of psychotic patients, the severity of psychoses, measured by the total BPRS score, was not related to the FT_4 concentrations; however, the symptoms of mood elevation correlated positively with the FT_3 concentrations. Moreover, in female patients, mood elevation correlated with the lower TSH concentrations. Earlier studies reported an association between thyroid axis function and the severity of psychiatric symptoms in acute psychiatric patients (5) and patients with mood disorders (30).

Moreover, our study revealed an association between the severity of psychotic symptoms and SHBG concentrations in the male patients. This finding is preliminary and needs further evaluations.

Our study has demonstrated that the use of antipsychotic drugs, but not other psychotropic drugs, prevented an increase in FT_4 concentrations in acute psychotic patients on hospital admission. Many psychotropic drugs, including lithium, carbamazepine, and antidepressants, may cause diverse effects on thyroid function (28). Antipsychotic drugs may also cause such effects (6, 12). Antipsychotics may affect thyroid axis function by several mechanisms. Like antidepressants (6), antipsychotics may enhance type 2 deiodinase activity in certain brain regions resulting in an increased conversion of T_4 to T_3 in the brain and diminished concentration of the substrate T_4 in serum. Antipsychotics may also affect thyroid axis function by diminishing the inhibitory effects of dopamine on TSH secretion in the anterior pituitary.

Conclusions

Our study confirms the presence of hyperthyroxinemia in a significant proportion of acute psychotic patients. An alteration in thyroid dynamics in psychotic patients may have consequences on the functions of other tissues, such as liver function evident by the differences in the SHBG concentrations. The effects on SHBG concentrations appear to be influenced by gender. Thyroid hormone concentrations are associated with severity of mood symptoms of psychosis. Treatment with antipsychotics may also affect thyroid function; however, our cross-sectional study could not determine the cause of the endocrine changes we found. Future cohort studies of pa-

tients treated with antipsychotics may improve our knowledge of the interplay among mental illness, thyroid state, and the effects of antipsychotic drugs.

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Statement of Conflict of Interest

The authors state no conflict of interest.

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