RESADES
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Original article

Functional alterations of the thyroid area and their clinical correlation with psychiatric entities

Alteraciones funcionales del ámbito tiroideo y su correlación clínica con entidades de índole psiquiátrica

Alterações funcionais da esfera tireoidiana e sua correlação clínica com entidades de natureza psiquiátrica

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Abstract

Abnormalities of thyroid hormone status are common in severe psychiatric disorders. The purpose of this study was to stratify and compare thyroid hormone levels associated with schizophrenia and bipolar disorder and to evaluate their changes in the Latin American population. The study was retrospective. Statistical results were based on systematic analysis. A descriptive analysis of thyroid tests and clinical characteristics was performed. Thyroid function data were obtained from the records of 343 patients, 18 of whom were positive for anti-TPO. Abnormal thyroid hormone status in general and the presence of hypothyroidism and hyperthyroidism, in particular, were found in 29,3 %, 25,17 %, and 4,08 % of schizophrenia patients, respectively. There were no gender differences. Conclusions: Thyroid changes were found in patients with schizophrenia and bipolar affective disorder. These results highlight the importance of studying special populations with organic mental illnesses, such as schizophrenia, rather than focusing only on bipolar disorders, to achieve better characterization.

Key words: autoimmune thyroiditis, hyperthyroidism, hypothyroidism, mood disorder, schizophrenia.

Resumen

Las anomalías en el estado hormonal de la tiroides son comunes en los principales trastornos psiquiátricos. El objetivo de este estudio fue estratificar y comparar las tasas del estado hormonal

tiroideo en el contexto de la esquizofrenia y el trastorno bipolar, evaluándose sus alteraciones en una población latinoamericana. El estudio fue retrospectivo. Los resultados estadísticos se basaron en análisis sistemáticos. Se realizó un análisis descriptivo de las pruebas tiroideas y las características clínicas. Los datos sobre la función tiroidea se obtuvieron de los registros de 343 pacientes, 18 pacientes eran anti-TPO positivo. El estado hormonal tiroideo anormal, en general, y la presencia de hipotiroidismo e hipertiroidismo, en particular, se observaron en el 29,3 %, el 25,17 % y 4,08 % de aquellos con esquizofrenia, respectivamente. No hubo diferencias en cuanto al género. Conclusiones: Las alteraciones tiroideas se encontraron en los pacientes con esquizofrenia y trastorno afectivo bipolar, dichos hallazgos señalan la importancia de evaluar a poblaciones especiales con enfermedad mental orgánica, como lo serían aquellos que padecen de esquizofrenia, y no solo limitarse a los trastornos del espectro afectivo bipolar para así lograr una mejor caracterización.

Palabras clave: tiroiditis autoinmune, hipertiroidismo, hipotiroidismo, trastorno del estado de ánimo, esquizofrenia.

Resumo

Anormalidades no estado hormonal da tireoide são comuns nos principais transtornos psiquiátricos. O objetivo deste estudo foi estratificar e comparar as taxas de status do hormônio tireoidiano no contexto da esquizofrenia e do transtorno bipolar, avaliando suas alterações em uma população latino-americana. O estudo foi retrospectivo. Os resultados estatísticos foram baseados em análises sistemáticas. Uma análise descritiva dos testes de tireóide e características clínicas foi realizada. Dados sobre a função tireoidiana foram obtidos dos registros de 343 pacientes, 18 pacientes eram anti-TPO positivos. O estado anormal do hormônio tireoidiano, em geral, e a presença de hipotireoidismo e hipertireoidismo, em particular, foram observados em 29,3 %, 25,17 % e 4,08 % daqueles com esquizofrenia, respectivamente. Não houve diferenças quanto ao gênero. Conclusões: Alterações da tireóide foram encontradas em pacientes com esquizofrenia e transtorno afetivo bipolar, esses achados indicam a importância de avaliar populações especiais com doença mental orgânica, como os que sofrem de esquizofrenia, e não apenas limitados a transtornos do espectro afetivo bipolar, a fim de alcançar uma melhor caracterização.

Palavras-chave: tireoidite autoimune, hipertireoidismo, hipotireoidismo, transtorno de humor, esquizofrenia.

Introduction

The effect of hormones produced in the thyroid gland plays an important role in neurodevelopment, specifically in neurogenesis, myelination, dendritic cell proliferation, and synapse formation (Williams *et al.*, 2009). Thyroid hormones are directly involved in working memory performance in schizophrenia. Levels of thyroid-stimulating hormone have been shown to correlate with performance on attention tasks. The role of thyroid hormones in regulating dopamine D2 receptors is also important for treatment. Hypothyroidism leads to increased sensitivity of dopamine receptors.

Animal studies have shown that treatment with antipsychotics such as clozapine and haloperidol is associated with changes in the expression of nuclear receptors and genes involved in thyroid hormone function (Kokkosis & Tsirka, 2020). Most antipsychotic medications block dopaminergic transmission and result in elevated levels of thyroid-stimulating hormone (quetiapine is an exception). Lithium concentrates in the thyroid gland and can lead to inhibition of iodine uptake in follicular cells, structural changes in thyroglobulin by interfering with the conjugation of residues to form iodothyronines, and inhibition of thyroid hormone secretion (Mpango *et al.*, 2023). It has also been observed that the conversion of T4 to active triiodothyronine is decreased in both animal and human models (Rasool *et al.*, 2021). Lithium use has also been associated with hyperthyroidism due to mechanisms such as thyroid hormone excess due to increased intrathyroidal iodine pool, Jod-Basedow phenomenon, and release of thyroglobulin due to direct toxicity to thyroid follicles. Lithium exacerbates pre-existing thyroid autoimmunity by activating lymphocytes rather than inducing thyroid peroxidase (TPO) alone.

If TPO antibodies are present, continued administration of thyroxine is required even if lithium is discontinued. Another possibility is that thyroid hormone abnormalities may represent a non-thyroidal condition, such as «euthyroid sick syndrome» and «euthyroid hyperthyroxinemia, » which are a response to chronic systemic disease. The prevalence of euthyroid sick syndrome

ranges from 7 % to 33 % in hospitalized psychiatric patients (Yıldız *et al.*, 2021; Møllehave *et al.*, 2022), whereas euthyroid hyperthyroxinemia may be more common in mood disorders. Although it is difficult to distinguish the nonthyroidal disease from true thyroid dysfunction in a sample of hospitalized patients, the level of thyroid-stimulating hormone in euthyroid sick syndrome pathology can reach 15-20 µUI/ml (Castro-de-Araujo *et al.*, 2022).

The association between thyroid pathology and bipolar affective disorder is well known. Epidemiologically, the prevalence of bipolar affective disorder is higher in patients with thyroid disease (van Trotsenburg *et al.*, 2021). Thyroid status predicts treatment response in depressive illness and bipolar disorder (Fukao *et al.*, 2019). Thyroid hormone supplementation is therapeutically effective in treatment-resistant depression (Liu *et al.*, 2021), and thyroid hormone receptors are localized in limbic structures involved in mood regulation (Jonklaas *et al.*, 2020).

However, the nature of the association between thyroid dysfunction and schizophrenia spectrum disorders has not been well-studied. Several studies have revealed a high prevalence of thyroid dysfunction in patients with schizophrenia (Eslami-Amirabadi & Sajjadi, 2021; Uchida & Suzuki, 2021; van Vliet *et al.*, 2021). There are reports on the association between autoimmune thyroid disorders and non-affective psychosis (Makarow-Gronert *et al.*, 2021; Mishu *et al.*, 2021; Schiera, 2021).

It should be noted that studies that have shown an association between thyroid pathology and bipolar affective disorder (BAD) have tended to select the disorder of interest (i.e., BAD) and group other psychiatric disorders together as a 'control group' (Baksi & Pradhan, 2021; McIntyre *et al.*, 2022). The very low prevalence rates in certain diagnosis groups within such a heterogeneous control group could potentially lower the overall prevalence in the control group, exaggerating the difference between the target diagnosis and the control group.

There is limited literature on the prevalence of endocrine thyroid disorders in individuals with severe psychiatric disorders from an epidemiological perspective. This study was undertaken to stratify and compare the extent of thyroid dysfunction in patients with mood disorders and schizophrenia spectrum disorders in a sample of hospitalized patients. The term *thyroid dysfunction*

refers to abnormalities in the laboratory parameters of thyroid hormone status, i.e., serum thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), and free thyroxine (FT4).

Materials and methods

Study design: a retrospective study conducted in 2018, in a Latin American hospital in Northwestern Colombia. The study protocol was approved by the Institutional Ethics Review Board. Data were obtained from medical records, and information on diagnosis, age, sex, medication status, thyroid function tests (serum thyroid-stimulating hormone, triiodothyronine, T4, free triiodothyronine, FT4), and thyroid antibody titers (anti-TPO levels) were collected.

Since the majority of admissions were substance-dependent patients and the focus of the analysis was to determine thyroid function status in patients with schizophrenia and bipolar affective disorder, a random sample of 30 individuals with chronic multiple substance use was drawn as a representative sample. For the other diagnostic groups (dissociative disorder, panic disorder, and other anxiety disorders), a consecutive sample was used.

Selection criteria included all patients who had thyroid function tests within the six months before the study; patients diagnosed with a mood disorder or schizophrenia during follow-up by psychiatrists; and patients or their responsible family members who voluntarily expressed a desire to participate in said study.

Patients with a history of cancer, including thyroid carcinoma, patients who had not received prior or ongoing chemotherapy, patients with a history of thyroidectomy, and patients who did not agree to participate in the study or were not supported by their family members were excluded.

Thyroid function tests were routinely performed for all patients during their initial admission and subsequent admissions if there was suspicion of thyroid disorder. Thyroid-stimulating hormone (TSH) was measured in nearly all patients, while triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4), and anti-thyroid peroxidase (anti-TPO) were performed when TSH levels were abnormal.

The aforementioned assays were performed using the *chemiluminescence* method, using automated systems from a recognized commercial company. The sensitivity and range of the assays were as follows: triiodothyronine = 0,1 ng/ml (range = 0,1-8 ng/ml); T4 = 0,5 µg/dl (range = 0,5-30 µg/dl); thyroid-stimulating hormone = 0,003 µIU/ml (range = 0,01-100 µIU/ml); free triiodothyronine = 0,88 pg/ml (range = 0,88-30 pg/ml); free thyroxine = 0,25 ng/dl (range = 0,25-6 ng/dl); and anti-thyroid peroxidase antibodies = 0,25 IU/ml (range = 0,25-1000 IU/ml).

The data were analyzed using IBM SPSS Statistics version 21.0, USA. Psychiatric disorders were grouped into schizoid disorders (schizophrenia, schizoaffective disorder, acute psychosis) in addition to affective disorders (major depression and bipolar disorder). Since serum levels of thyroid hormones have a wide range of normal variability, the data were analyzed with subjects classified as either normal thyroid function or abnormal thyroid function (thyroid-stimulating hormone < 0,34 µIU/ml or thyroid-stimulating hormone > 4,1 µIU/ml or thyroid-stimulating hormone = normal, but free thyroxine < 0,61 ng/dl), and positive versus negative thyroid peroxidase antibodies.

In the absence of data on physical manifestations of thyroid disease, a thyroid-stimulating hormone (TSH) level > 4,1 µIU/ml with T4 < 6,09 µIU/ml was considered clinically significant hypothyroidism, whereas a TSH level ≤ 0,02 µIU/ml was considered indicative of clinically significant hyperthyroidism (14).

Results

Thyroid hormone status data were available for 343 individuals [males = 173 (50,4 %), females = 169 (49,3 %), missing = 1 (0,3 %)]. The mean age of the study participants was 37,46 ± 13,56 years. The distribution of psychiatric diagnoses in the population is shown in Table 1. There were 147 individuals (42,86 %) who had schizoid disorders (schizophrenia = 108, schizoaffective type = 17, acute psychosis = 22), and 185 (53,94 %) with mood disorders (bipolar affective disorder = 122, major depression = 63).

Table 1

Distribution of the sample according to diagnosis and rates of thyroid dysfunction

Diagnosis	Individuals	%	Hyperthyroidism	%	Hypothyroidism	%	Abnormal thyroid function	%
Bipolar-type affective disorder	122	35,57	3	2,46	28	22,95	31	35,57
Schizophrenia	108	31,49	4	3,70	25	23,15	29	31,49
Major depressive disorder	63	18,37	0	0,00	12	19,05	12	18,37
Acute delirium	22	6,41	1	4,55	6	27,27	7	6,41
Schizoaffective disorder	17	4,96	1	5,88	6	35,29	7	4,96
Personality dissociation	2	0,58	0	0,00	0	0,00	0	0,58
Panic	1	0,29	0	0,00	0	0,00	0	0,29
Use of stimulant substances	4	1,17	0	0,00	2	50,00	2	1,17
Anxiety	4	1,17	0	0,00	0	0,00	0	1,17
Total	**343**	**100**	**9**	**2,62**	**79**	**23,03**	**88**	**25,66**

Distribution of the sample according to diagnosis and rates of thyroid dysfunction

Thyroid Dysfunction

Hypothyroidism was observed in 37 out of 147 patients (25,17 %) who had a diagnosis related to schizoid disorders (schizophrenia = 25/108, schizoaffective disorder = 6/17, acute psychosis = 6/22). This adds up to a total of 185 individuals with mood disorders, and 40 (21,62 %) had hypothyroidism (bipolar disorder = 28/122, major depressive disorder = 12/63).

Three individuals with schizophrenia and two with major depressive disorder had clinically significant hypothyroidism. Hyperthyroidism was observed in six out of 147 patients (4,08 %) with schizophrenia spectrum disorders (schizophrenia = 4/108, schizoaffective disorder = 1/17, acute psychosis = 1/22). Three out of 185 patients (1,62 %) had mood spectrum disorders of the bipolar disorder type = 3/122.

Two individuals with schizophrenia had thyroid-stimulating hormone ≤ 0,02 µUI/ml, indicative of clinically significant hyperthyroidism. Overall, an abnormal thyroid hormone status was observed in 43 out of 147 individuals (29,3 %) with schizoid pathology (schizophrenia = 29/108, schizoaffective type = 7/17, acute psychosis = 7/22); and in 23,24 % of individuals (43/185) with mood disorders (bipolar affective disorder = 31/122, major depression = 12/63).

Anti-TPO Positivity

Data on anti-TPO status were available for 210 patients (schizophrenia = 52, schizoaffective disorder = 13, acute psychosis = 16, major depressive disorder = 44, bipolar disorder = 81, dissociative disorder = 2, anxiety disorder = 2). Eighteen patients tested positive for anti-TPO. Among these, 11 had a schizophrenia spectrum disorder (schizophrenia = 8, schizoaffective disorder = 0, acute psychosis = 3), while seven had a mood-related pathology (bipolar affective disorder = 5, major depressive disorder = 2).

The rate of anti-TPO positivity in the schizophrenia spectrum disorder group was 13,58 % (11/81) compared to 5,6 % (7/125) in the mood disorder group.

Gender effect

Overall, there was no difference in abnormal thyroid hormone levels (M = 40/166; F = 46/165), hypothyroidism (M = 35/166; F = 42/165), or hyperthyroidism (M = 5/166; F = 4/165) between males and females. There was no gender difference in individual psychiatric diagnostic categories.

Effect of medications

Limited data were available for the following antipsychotic and mood-stabilizing medications: Lithium (n = 32), valproate (n = 27), risperidone (n = 68), olanzapine (n = 13), quetiapine (n = 9), haloperidol (n = 6), clozapine (n = 6).

There were no significant differences in the level of thyroid-stimulating hormones between patients receiving different classes of antipsychotics; however, the level of thyroid-stimulating hormones was lower under quetiapine (2,09 ± 1,74) and higher under olanzapine (7,29 ± 20,05).

Patients receiving lithium had higher levels of thyroid-stimulating hormone (5,37 ± 8,71 μUI/ml, n = 32) compared with patients receiving valproate (3,79 ± 3,21 μUI/ml, n = 27), although the difference was not statistically significant.

Discussion

The results indicated that thyroid abnormalities were present in individuals with schizoid pathology and mood disorders in individuals attending a level III psychiatric facility. Autoimmune thyroid disorders were more common in schizoid pathology than in abnormal mood states. There was no gender difference. There was no significant effect of medication on levels of thyroid-stimulating hormones in this study population, although data on medication status were limited.

In this study, 29,3 % of individuals with schizoid pathology were found to have abnormal thyroid hormone status. This is consistent with the results of previous studies that have shown a high prevalence of thyroid dysfunction in patients with schizophrenia (Jurado-Flores *et al.*, 2022; Winder *et al.*, 2022). They found that a sample of consecutive patients with schizophrenia had positive serum markers for autoimmune thyroiditis, which is comparable to the results of the present study. In the general population of other countries, thyroid dysfunction has been associated with bipolar disorder (Joseph *et al.*, 2023).

In the study sample, the observed thyroid dysfunction in bipolar disorder was 25,41 %, lower than the 32 % reported by Bartalena *et al.* (1990), and higher than the 11,51 % reported by Cassidy *et al.* (2002). While some studies have shown an association between autoimmune thyroid disorders and bipolar disorder (Ettleson & Papaleontiou, 2022; Lekurwale *et al.*, 2023), others have failed to find an association. Eller et al. (2010) and Schneider *et al.* (2023) reported an autoimmune thyroiditis rate of 8,9 % in depressive disorders, comparable to the 5,6 % in the study sample hereby shown.

The mean levels of thyroid-stimulating hormone in the schizophrenic spectrum and affective disorders groups were above the range of 15-20 microIU/ml in the studied population. In addition, the presence of autoimmune markers in some cases of this population sample suggests that non-thyroidal disease cannot explain all findings.

Limitations of this study include the retrospective study design, inpatient sample, lack of control for medication status, and lack of data on clinical signs of hypothyroidism or comorbid medical conditions.

Conclusions

The main finding of this study was the high rate of thyroid dysfunction in schizophrenia spectrum disorders, which warrants screening and has implications for cognition and response to treatment. Despite these limitations, the study highlights the fact that thyroid dysfunction is common in this patient population with schizoid pathology and is not exclusive to bipolar disorder.

The implications regarding the detection/treatment of abnormal thyroid hormone levels and the cost-effectiveness in the treatment of schizoid disorders warrant further studies, as this will allow for more accurate characterization of these patients and facilitate a balance in terms of monitoring and appropriate therapeutic management of these psychiatric conditions.

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Conflict of interest

The authors declare that they have no conflict of interest.

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