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REVIEW ARTICLE

What is the real significance and management of major thyroid disorders in bipolar patients?☆

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Abstract Thyroid dysfunction affects negatively emotional stability and worsens the clinical course of bipolar affective disorder. The main stabiliser used in this illness, lithium carbonate has numerous effects on the physiology of the thyroid, with the most significant being the inhibition of thyroid hormone release that may occur at therapeutic levels. These dysfunctions have also been reported most frequently in bipolar patients not undergoing treatment with lithium, and were not completely explained by the effects of this drug. Apart from the numerous medical complications and mood disturbances, the cognitive or perceptual system may also be affected. In fact, the presence of thyroid disease increases the rates of obsessive–compulsive disorder, phobias, panic disorder, major depressive disorder, cyclothymia, or bipolar disorder. In severe cases of hypothyroidism, the clinical symptoms and signs can be similar to a melancholic depression or dementia.

It is therefore important to know well all these possible complications in daily clinical practice. This review will cover the main thyroid dysfunctions present in bipolar patients, whether or not produced by treatment with lithium carbonate, and will provide a series of recommendations for clinical management.

PALABRAS CLAVE
Litio;
Tiroides;
Hipotiroidismo;
Trastorno bipolar;
Bocio;
Hipertiroidismo;
Autoinmunidad tiroidea

¿Cuál es la relevancia real y el manejo de las principales alteraciones tiroideas en los pacientes bipolares?

Resumen Las alteraciones del funcionamiento de la glándula tiroidea influyen en la estabilidad afectiva repercutiendo negativamente en el curso clínico de la enfermedad bipolar. El principal estabilizador utilizado en este trastorno, las sales de litio, ejerce numerosos efectos sobre la fisiología del tiroides. La inhibición del recambio de la hormona tiroidea, que puede producirse con niveles terapéuticos de sales de litio, es el que tiene mayor relevancia clínica. Por otro lado, la disfunción tiroidea también parece ser más frecuente en pacientes bipolares no tratados con litio. Al margen de las numerosas complicaciones médicas y afectivas, también el

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sistema perceptivo o el cognitivo pueden verse afectados. De hecho, la presencia de una enfermedad tiroidea aumenta las tasas de trastorno obsesivo compulsivo, fobias, trastorno de pánico, trastorno depresivo mayor, ciclotimia o trastorno bipolar (TB). En casos de hipotiroidismo grave, la clínica puede ser semejante a una depresión melancólica o a una demencia.

Por ello, en la práctica clínica diaria, es importante conocer bien los efectos de las sales de litio sobre la función tiroidea. En esta revisión abordaremos las principales disfunciones tiroideas presentes en los pacientes bipolares, generadas o no por el tratamiento con sales de litio, y aportaremos una serie de recomendaciones para su manejo clínico.

Introduction

Greater prevalence of alterations in the hypothalamus–pituitary–thyroid (HPT) axis have been found in patients with mood disorders compared to the general population.[1] However, in most of the studies published an important number of patients in treatment with lithium or carbamazepine were included, which may explain the elevated prevalence found. At any rate, the association between bipolar disorder (BD) and thyroid dysfunction is not completely explained by the effects of these drugs. In a study carried out on patients with bipolar disorders not previously treated with these stabilisers, 9% of patients were found to have thyroid hypofunction, while the rate of primary hyperthyroidism in the general population reaches 3%.[2]

Hypothyroidism can mimic depressive symptoms and, in turn, some patients with affective disorders respond favourably to coadjuvant thyroid treatment. For that reason, some authors suggest that these patients could present anomalies in their thyroid metabolism not detected by standard tests normally used.[3] In fact, up to 90% of patients with primary affective disorders have thyroid hormone levels in the eurothyroid range.[4] Elevation of serum concentrations of total and free thyroxine (T4) with normal levels of triiodothyronine (T3) is the most frequent thyroid alteration found during the depressive phase of the disease, in comparison with controls and healthy subjects. The fact that more affective episodes and more serious depression are suffered during treatment with lithium has been associated in some studies with low levels of free T4 in bipolar patients.[5]

The mechanisms that underlie the association between thyroid pathology and affective disorders continue to be uncertain. The current hypothesis is that it could be due to the disruption of circadian rhythms or deregulation of the sensitivity of the catecholaminergic receptor associated with thyroiditis and hyperthyroidism.[6]

Consequently, the thyroid hormones seem to modulate the seriousness and development of depression, more than specific pathogenic role. This hypothesis is reinforced by the relationship found in some studies between thyroid function and the clinical course of BD, especially in cases of rapid cycling.[7]

Materials and methods

We carried out a systematic search in the databases Pubmed, Medline and Embase (1965, April 2013). The search terms were: *bipolar disorder OR Lithium*, *Thyroid*, *Hypothyroidism*, *Goitre* and *Hyperthyroidism*. At the same time we performed a manual search and located additional articles using the references of the articles obtained. We obtained 578 studies that complied with the search criteria. The abstracts were reviewed and 125 were excluded for not being written in English or Spanish, or for involving other pathologies or objectives.

We have divided this article into various subsections, which appear as indicated below.

Thyroid autoimmunity and lithium salt

Lithium affects many aspects of cellular and humoral immunity, both *in vitro* and *in vivo*. However, controversy exists over whether it is capable of inducing thyroid autoimmunity on its own. It is known that lithium affectation of the thyroid can occur without the presence of thyroid autoimmunity, and that the prevalence of specific thyroid antibodies among patients treated with lithium varies in different studies. In fact, there are 2 important factors, age and gender, that influence the incidence of thyroid autoimmunity. This is greater in women and the range of greatest risk is middle age.[8]

Some studies have found high prevalence of antithyroid antibodies in patients with affective disorders that receive treatment with lithium. It seems that this salt can speed up the development of existing thyroiditis, as can be seen in the increase in the rate of circulating antibodies. Lithium is thought to be incapable of stimulating the production of *de novo* antibodies in humans, but it has been demonstrated that administering lithium salt can be associated with an increase in the antibody rate in patients that already had elevated antibodies at the commencement of treatment.[9] This situation may imply a greater risk of developing hypothyroidism while this treatment is received. However, the study of this matter is complex, given that prevalence of antiperoxidase antibodies varies depending on the sensitivity and specificity of the measurement method used, as well as gender and age, as already commented.