

Hypothyroidism and Bipolar Affective Disorder: Is There a Connection?

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ABSTRACT


Context: Hypothalamic-pituitary-thyroid axis dysfunction in the pathophysiology of bipolar disorder has received less attention as compared with that in depressive disorder. **Aims:** To study the prevalence of hypothyroidism in patients diagnosed with bipolar disorder and compare it with a population norm. **Settings and Design:** The setting was the psychiatry inpatient unit of a tertiary care hospital. The design was retrospective and observational. **Subjects and Methods:** A retrospective observational study was performed, referring to the case records of 84 cases of bipolar disorder admitted to the Department of Psychiatry in a Tertiary Referral Center during the year 2010-2012. The prevalence of hypothyroidism both subclinical as demonstrated by elevated thyroid stimulating hormone (TSH) levels (cut-off value 4.2 μ U/ml) and overt hypothyroidism (fasting T4 <0.92 ng/dl and TSH >4.2 μ U/ml) was calculated. This was compared with the population prevalence of hypothyroidism as determined by an epidemiological study carried out in the year 2009, in the same region. The correlation between hypothyroidism, gender, lithium prophylaxis and family history of mood disorder was computed. **Statistical Analysis:** Percentage prevalence of hypothyroidism in the sample was calculated and compared to a population norm. The correlation between hypothyroidism, gender, lithium prophylaxis and family history of mood disorder was computed using the odds ratio (OR). **Results:** The total prevalence of hypothyroidism in both males and females in the bipolar group was comparable with that in the general population. There is a significant association between family history of mood disorder in first degree relatives and patients having hypothyroidism (OR 5.504 and $P = 0.012$). There were no statistically significant associations between thyroid abnormalities and age, duration of illness and lithium prophylaxis. **Conclusions:** There is no significant association between hypothyroidism and bipolar disorder. Family history of mood disorder and hypothyroidism show significant association. (OR 5.504 AND $P = 0.012$).

Key words: Bipolar disorder, hypothalamic-pituitary-thyroid axis, hypothyroidism

INTRODUCTION

A great deal has been said about the hypothalamic-pituitary-thyroid (HPT) axis dysfunction in mood disorders, especially depression. Thyroxin is

often used as an augmenting agent for refractory depression.^[1] The most common psychiatric symptoms related to hypothyroidism are depression and cognitive dysfunction.^[2] Mania associated with hypothyroidism has rarely been reported in literature.^[3,4] Psychiatric symptoms in hyperthyroidism seem to be mediated by beta adrenergic receptor hyperactivity. The mechanism underlying mood disorder in hypothyroidism is less clear. These could include dysregulation of the central nervous system catecholamine receptor sensitivity, associated thyroiditis and thyrotoxicosis or circadian rhythm disruption.^[4]

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Animal studies have provided considerable data on the reciprocal interaction between thyroid hormones and neurotransmitter systems believed to play a role in the genesis of mood disorders.^[5]

Clinical wisdom seems to indicate that there is a connection between mood disorder and thyroid function, but this has not been proved unequivocally in studies on this condition. Resistant depression has been said to be associated with subclinical hypothyroidism (SCH); and this condition may in fact reduce the threshold for depression to occur.^[6] However very few studies have been performed on bipolar disorder and thyroid dysfunction.^[7] A Danish epidemiological study demonstrated a strong link between thyroid disease and mood disorder especially bipolar disorder.^[8] There are conflicting reports about the relationship with SCH and rapid cycling bipolar disorder.^[9-12]

In the present study, 84 cases records of bipolar disorder admitted to the Department of Psychiatry in a Tertiary Referral Center in Ernakulam District, Kerala during the year 2010-12 were examined. The prevalence of hypothyroidism both subclinical as demonstrated by elevated thyroid stimulating hormone (TSH) levels (cut off value 4.2 µg/dl) with or without in T3 or T4 as well as frank hypothyroidism were calculated. This was compared with the prevalence of hypothyroidism as determined by an earlier epidemiological study.^[13] (This was a two phase study performed on a population of central Kerala [Ernakulam] in 2009. A total of 971 subjects were screened for thyroid abnormalities. Frank hypothyroidism was present in 3.9% and SCH was identified in 9.4%). The correlation between hypothyroidism and family history of mood disorder was computed using the odds ratio (OR).

SUBJECTS AND METHODS

The study design was retrospective. The case records of 84 patients with bipolar disorder admitted in a Tertiary Care Hospital in the Department of Psychiatry during the period from 2010 to 2012 were examined. Although clinically, there were no symptoms or signs of thyroid dysfunction in any of the patients, thyroid function test had been done as part of a routine screening in all except nine patients. 10 out of the 12 hypothyroid patients had been earlier diagnosed to have hypothyroidism and were on thyroxin replacement. The thyroid hormone estimations were performed using Electrochemiluminescence immunoassay method.

Hypothyroidism was defined as free T4 values <0.92 ng/ml with TSH levels >4.2 µU/ml; SCH was defined as elevation of TSH level above 4.2 µU/ml with normal T3 and T4 values.^[14]

Inclusion criteria

- In-patients diagnosed as having bipolar affective disorder by a psychiatrist using International Classification of Diseases-10th revision- Classification of Mental and Behavioural Disorders^[15] criteria admitted during the period from 2010 to 2012.
- Age 18 and above.

Analysis

There were 49 females and 35 male patients belonging to age groups ranging from 18 to 71 years.

Three patients were first episode mania with symptoms duration of 1-3 months while 54 patients had the illness for more than 10 years. The largest number had the diagnosis of bipolar 1 current episode mania (74), two with current episode depression and three had been diagnosed with mixed episodes. Seven patients had bipolar 2 (other bipolar disorder) [Table 1].

Of the cases with recurrent episodes, only 21 were on lithium prophylaxis (25%). None of the subjects in the study had a history of or lab results suggesting hyperthyroidism.

Other psychiatric and medical comorbidity

Alcohol and tobacco dependence-9

Seizure disorder-2

Parkinsons disease-1

Non-thyroid carcinomas (in remission after treatment)-3

Prolactinoma-1

Rheumatoid arthritis-1

RESULTS

- The prevalence of hypothyroidism in both males and females in the in-patient bipolar group was though comparable with that in the general population, there is a reversal in the ratio of overt to subclinical hypothyroidism in our study when compared to the population prevalence [Tables 2 and 3].
- There were no statistically significant correlation between thyroid abnormalities and age, duration of illness and lithium prophylaxis [Table 4].
- There is a significant correlation between family history of mood disorder in the first degree relatives and patients with hypothyroidism (OR 5.05; $P = 0.012$) [Table 4].

Table 1: Subtypes of bipolar patients in the study

Diagnosis	No. of patients n=84	%
BP-1 current episode mania	72	85.70
BP-1 current episode depressed	2	2.30
BP-1 mixed episode	3	3.50
BP-2	7	8.30

BP – Bipolar disorder

Table 2: Percentage of hypothyroid patients in the sample

Thyroid status	No. of patients-total 84	%
Subclinical hypothyroidism	4	4.76
Hypothyroid	8	9.52
Total hypothyroid	12	14.28
Euthyroid goiter	5	5.90

Table 3: Population prevalence of thyroid abnormalities according to a previous prevalence study in the community (Usha Menon et al. 2009) adapted with permission

Total population-n=971			
Thyroid status	Male (%)	Female (%)	Total (%)
Normal TFT	332	449	781 (80.4)
Hypothyroidism	3	35	38 (3.9)
SCH	24 (2.5)	67 (6.9)	91 (9.4)

TFT – Thyroid function test; SCH – Subclinical hypothyroidism

Table 4: Correlation of age, gender, duration of illness, lithium prophylaxis and family history with the thyroid status as determined by T3, T4 and TSH levels

Variable	Hypothyroidism		
	OR	(95% CI)	P value
Family history (yes vs. no)	5.504	(1.464, 20.688)	0.012
Gender (female vs. male)	4.013	(1.013, 15.0892)	0.048
Diagnosis (yes vs. no)	1.144	(0.195, 6.70)	0.882
Total duration of illness			
0-5 versus 5-10	0.993	(0.162, 6.107)	0.994
0-5 versus 10-15	1.532	(0.260, 9.008)	0.637
0-5 versus >15	0.597	(0.090, 3.950)	0.593
Age			
18-38 versus 38-58	1.470	(0.283, 7.649)	0.647
18-38 versus >58	1.209	(0.183, 7.970)	0.844
Lithium	3.087	(0.745, 12.796)	0.120

TSH – Thyroid stimulating hormone; OR – Odds ratio; CI – Confidence interval

DISCUSSION

With regards to the HPT axis in bipolar disorder, there are a number of unanswered questions. Is there any significant correlation between thyroid dysfunction and bipolar disorder? If so, is the thyroid dysfunction prior to the onset of the disease; is it a state dependent consequence of the disease evolution or further still — is it treatment induced; a result of lithium prophylaxis? Could an HPT axis dysfunction be a heritable trait? This study is an attempt to address at least some of these questions. In the present study, there was no association between hypothyroidism and bipolar disorder. The prevalence in the study population though comparable with that in the general population, there is a reversal in the ratio of overt to subclinical hypothyroidism in our study when compared to the population prevalence. This is a curious finding. It could be because the detection

of thyroid abnormalities is more likely in a clinical population. There were no cases of hyperthyroidism in the sample though the organic mood disorder in hyperthyroid states has been often described to be mania.^[1,2,16] There is a significant correlation between family history of mood disorder in first degree relatives and patients having hypothyroidism. This may suggest a possible genetic connection, perhaps an inherited vulnerability as indicated by a genetic study in the Chinese population.^[17] In another study of the female offspring of bipolar parents, children of parents with bipolar disorder were found to be more vulnerable to develop thyroid autoimmunity, independently of their vulnerability to develop psychiatric disorders.^[18] In a similar vein, in a case-control association study,^[19] genetic variations of the type II deiodinase gene were shown to be associated with bipolar disorder. These findings suggest that genetic investigations are likely to eventually unravel the link between thyroid dysfunction and bipolar disorder. Lithium prophylaxis and thyroid abnormalities did not show any significant association. This could be because only 1/4th of our subjects were on prophylaxis with lithium reflecting the general trend to use newer mood stabilizers. It is likely that had there been many more patients been on lithium, the prevalence of hypothyroidism would have been greater.

Limitations and future direction

One of the major limitations of the study is its study design. Owing to the retrospective nature of the study we were not able to ascertain if the affected first degree relatives also had hypothyroidism, which would have been an exciting finding. In many patients, the thyroid functions were not performed as it is not part of the management protocol to do so. The study sample being an inpatient one, other factors could have influenced the thyroid hormone levels like the stress of hospitalization. Many patients also had medical comorbidity, which could have confounded the results. We were also not able to ascertain the relationship of different sub types of bipolar disorder to thyroid dysfunction as this would have required a much larger sample. A prospective study of a similar nature with a larger sample including outpatients might be more rewarding.

It might be useful in future to correlate family history of mood disorder and level of thyroid peroxidase antibody titers. This would help in identifying if there is an inherited vulnerability to both auto immune thyroiditis and bipolar illness.

Genetic studies to determine the sub types of deiodinase gene, especially the de-iodinase-2 and the correlation with bipolar disorder and its sub types would go further in establishing that thyroid axis dysfunction could be a trait marker for bipolar mood disorder and an endophenotype.

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