A STUDY ON THE PREVALENCE AND RISK FACTORS FOR HYPOTHYROIDISM IN LITHIUM TREATED BIPOLAR DISORDER PATIENTS

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ABSTRACT

BACKGROUND

Lithium is a novel mood stabilizer in the treatment of bipolar disorders. Toxic effects are frequently encountered in clinical practice due to its narrow therapeutic index. Thyrostatic effects especially clinical hypothyroidism, is a well-known side effect of long term lithium treatment and has been reported in medical literature. However, Indian studies on this major issue is sparse.

The aim of the study was to evaluate the prevalence and risk factors for the onset of hypothyroidism (overt and subclinical) in bipolar disorder patients treated with lithium.

MATERIALS AND METHODS

110 patients who fulfilled the study criteria were taken from inpatient and outpatient departments of Institute of Mental Health and assessed for prevalence of hypothyroidism (clinical and subclinical) based on thyroid function test taken from case records (T3, T4, TSH). Retrospective analysis of risk factors like age, sex, weight gain during lithium intake, family history of thyroid disease, dose and duration of lithium intake and onset of hypothyroidism was done.

RESULTS

In our study, the prevalence of overt and subclinical hypothyroidism in bipolar patients treated with lithium was 32.7% and 15.5% respectively. Strong association was present between the risk factors (female sex, age group of 51-60 years of age, positive family history, and weight gain during lithium intake) and onset of overt hypothyroidism. Subclinical hypothyroidism developed within 1-3 yrs. at a dose of 900mg of lithium per day and overt hypothyroidism took >3 yrs. to manifest at a dose of 1200mg of lithium after the start of treatment.

CONCLUSION

Hypothyroidism in bipolar patients worsens the mood symptoms, leads to cognitive impairment and alters the response to psychotropic drugs. It calls for a mandatory drug review, along with baseline and periodic thyroid function test especially in high risk cases. Early intervention with thyroxin supplementation improves the patient mood and wellbeing.

KEYWORDS

Hypothyroidism, Lithium, Bipolar disorder, Thyroid function test.

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BACKGROUND

Lithium remains the drug of choice for bipolar disorders worldwide. It is used in acute management and as prophylaxis in mania, bipolar and unipolar depression. It reduces the suicide rate also.[1,2] Despite its effectiveness, its side effect profile and narrow therapeutic window demands for careful monitoring of the therapeutic concentrations of lithium at regular intervals.[2] Among its side effect profile, thyroid dysfunction associated with lithium treatment have been reported widely in literature till date. This includes goiter, hypothyroidism, thyrotoxicosis and autoimmune thyroiditis.[3,4] This study mainly focuses on the hypothyroidism (overt and subclinical) caused by lithium in bipolar disorder patients.

Lithium exerts multiple effects on the physiological function of thyroid gland. It causes hypothyroidism in various ways: 1) by inhibiting the synthesis and release of thyroid hormones 2) causing iodo-tyrosine coupling defects 3) by decreasing the activity of type-I 5' de-iodinase enzyme. All these ultimately result in compensatory elevation of thyroid stimulating hormone (TSH).[2,5,6]

Hypothyroidism in bipolar patients worsens the mood symptoms especially depression, leads to cognitive impairment and alters the response to psychotropic drugs.[5,7] As it remains to be elucidated why some individuals and not all develop hypothyroidism when treated with lithium, this study is aimed at identifying possible predisposing risk factors for development of hypothyroidism.

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Aim

To study the prevalence and risk factors for onset of hypothyroidism (overt and subclinical) in bipolar disorder patients treated with lithium.

Objectives

1. To determine the prevalence of lithium associated hypothyroidism in bipolar disorder patients
2. To determine the risk factors for development of hypothyroidism in bipolar disorder patients on lithium treatment.
3. To evaluate the association between the dose of lithium and onset of hypothyroidism.
4. To evaluate the association between the duration of lithium treatment and development of hypothyroidism.

MATERIALS AND METHODS

This study was carried out between the months of July 2017 and September 2017 in both inpatient and outpatient departments of Institute of Mental Health, Chennai. Our study protocol was reviewed and approved by the ethics committee of Madras Medical College Chennai. 150 patients diagnosed to have bipolar disorder according to ICD-10 were taken up as study subjects.

Inclusion Criteria

1. Patients aged 18-60 years (of both sexes) who fulfilled the criteria for Bipolar Disorder according to ICD-10 and were on lithium treatment.
2. Those who gave informed consent.

Exclusion Criteria

1. Those who had thyroid dysfunction prior to the lithium treatment
2. Patients in whom baseline thyroid functions tests were not done.
3. Patients who were not willing / uncooperative.

Procedure of Study

Out of 150 patients, 110 fulfilled the inclusion criteria and were assessed for hypothyroidism (overt and clinical) using thyroid function test (T3, T4, and TSH) taken from the case records in whom baseline thyroid function test were done. Retrospective analysis of risk factors like age, sex, weight gain during lithium intake, family history of thyroid disease, dose and duration of lithium intake and onset of hypothyroidism was done. Patients on lithium dose of 300mg, 600mg, 900mg and ≥1200mg and patients taking lithium for <6 months, 6 months to one year, 1-3 years and more than 3 years were taken retrospectively.

Statistics

Data were analysed using Chi square test and Fisher Extract test. Chi-Square test was applied with 95% confidence interval (CI). P value of ≤0.05 was considered to be statistically significant.

RESULTS

Out of 150 patients (aged 18-60 years), 40 were excluded from the study based on exclusion criteria. The rest i. e. 110 bipolar disorder patients who were on lithium were taken into analysis. Sample population comprised of 53.6% females and 46.4% males. Majority belonged to the age group of 51-60 years (36.4%) and 54.5% had a positive family history. 45.5% of the patients were taking lithium at a dose of 900mg/day.

The prevalence of overt hypothyroidism was 32.7% and subclinical hypothyroidism was 15.5% among the study population (Figure 1).

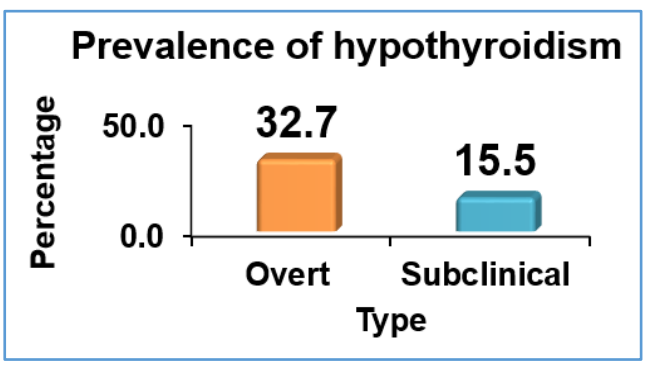

Figure 1

Overt hypothyroidism was present in 40.7% of females and 23.5% of males whereas subclinical hypothyroidism was present in 16.9% of the females and 13.4% of the males (Figure 2 and 3). The overall prevalence of hypothyroidism (overt and subclinical) was higher in females.

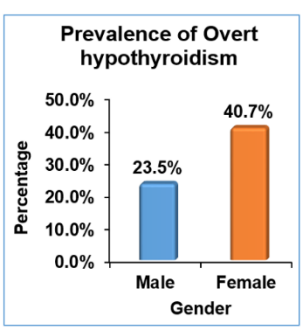

Figure 2

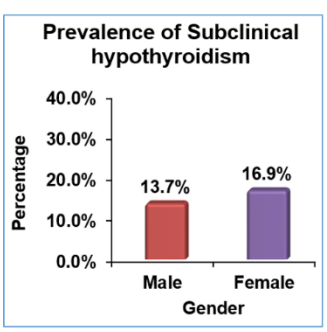

Figure 3

In our study, a higher occurrence of overt hypothyroidism was found in female sex (40.7%), in patients belonging to the age group of 51 to 60 years (63%), in subjects with a family history of thyroid disease (48.3%) and in those with increased weight gain during lithium intake (43%).

In age group of 51 to 60 years, out of 27 patients 17 (63%) developed overt hypothyroidism which was found to be statistically significant ($p<0.001$).

Among 59 female patients, 24(40.7%) developed overt hypothyroidism which was found to be statistically significant ($p=0.05$).

In 60 patients with positive family history of thyroid disease, 48.3% of patients developed overt hypothyroidism which was found to be statistically significant (($p<0.001$).

Of 79 patients gained weight during lithium intake, 43% of patients developed overt hypothyroidism which was found to be statistically significant (p<0.001) (Table 1).

Sl. No.	Parameters	Attributes	Overt Hypothyroidism						P-Value
			Absent		Present		Total		
			N	%	N	%	N	%	
1.	Age (Years)	18 – 30	14	82.4	3	17.6	17	100	<0.001
		31 – 40	23	88.5	3	11.5	26	100	
		41 – 50	27	67.5	13	32.5	40	100	
		51 – 60	10	37.0	17	63.0	27	100	
2.	Sex	Male	39	76.5	12	23.5	51	100	0.056
		Female	35	59.3	24	40.7	59	100	
3.	Family H\O Thyroid Disease	Present	31	51.7	29	48.3	60	100	<0.001
		Absent	43	86.0	7	14.0	50	100	
4.	Weight Gain During Lithium Intake	Yes	45	57.0	34	43.0	79	100	<0.001
		No	29	93.5	2	6.5	31	100	

Table 1. Test to Compare Proportions (Overt Hypothyroidism)

With respect to subclinical hypothyroidism, higher prevalence was seen in female sex (16.9%), in age group 41 to 50 years (22.5%), patients with family history of thyroid disease (20%) and those with increased weight gain during lithium intake (21.5%). Among 79 patients with increased weight gain, 17 (21.5%) developed subclinical hypothyroidism and 62(78.5%) not developed subclinical hypothyroidism which was found to be statistically significant (p 0.003) analysed using fisher's exact test as value was below 5. (Table 2).

Sl. No.	Parameters	Attributes	Sub Clinical Hypothyroidism						P –Value
			Absent		Present		Total		
			N	%	N	%	N	%	
1.	Age (Years)	18 – 30	14	82.4	3	17.6	17	100	0.583
		31 – 40	25	96.2	1	3.8	26	100	
		41 – 50	31	77.5	9	22.5	40	100	
		51 – 60	23	85.2	4	14.8	27	100	
2	Sex	Male	44	86.3	7	13.7	51	100	0.641
		Female	49	83.1	10	16.9	59	100	
3.	Family H\O Thyroid Disease	Present	48	80.0	12	20.0	60	100	0.149
		Absent	45	90.0	5	10.0	50	100	
4.	Weight Gain During Lithium Intake	Yes	62	78.5	17	21.5	79	100	0.003*
		No	31	100	0	0.0	31	100	

Table 2. Test to Compare Proportions (Sub Clinical Hypothyroidism)

Fisher's exact test used to compare proportions.

42.9% of patients developed overt hypothyroidism after 3 years of lithium treatment and 39.3% of patients developed overt hypothyroidism within 1-3 years of lithium treatment. Meanwhile, 17.9% of patients developed subclinical hypothyroidism in 1 to 3 years of lithium treatment and 14.3% of patients developed subclinical hypothyroidism after 3 years of lithium treatment.

Our analysis showed that, 48% of patients who developed overt hypothyroidism were taking more than 1200mg of lithium per day and 44% of patients were taking 900mg of lithium per day. We also noted that 18% of patients who developed subclinical hypothyroidism were taking 900mg of lithium per day and 16.7% of patients were taking 600mg of lithium per day.

We found that the association between the dose of lithium (p value 0.001) and duration of lithium treatment (p value 0.003) was statistically significant with the onset of overt hypothyroidism. (Table 3 and 4).

Sl. No.	Parameters	Attributes	Overt Hypothyroidism						P-Value	Sub Clinical Hypothyroidism						P-Value
			Absent		Present		Total			Absent		present		TOTAL		
			N	%	N	%	N	%		N	%	N	%	N	%	
1.	DOSE	300	11	100	0	0.0	11	100	<0.001	10	90.9	1	9.1	11	100	0.943
		600	22	91.7	2	8.3	24	100		20	83.3	4	16.7	24	100	
		900	28	56.0	22	44.0	50	100		41	82.0	9	18.0	50	100	
		>1200	13	52.0	12	48.0	25	100		22	12.0	3	12.0	25	100	

Table 3. Chi Square Test for Dose of Lithium Treatment and Onset of Hypothyroidism

Sl. No.	Parameters	Attributes	Overt Hypothyroidism						P Value	Subclinical Hypothyroidism						P Value
			Absent		Present		Total			Absent		Present		Total		
			N	%	N	%	N	%		N	%	N	%	N	%	
1.	Duration of Lithium Treatment	<6 Months	5	100	0	0.0	5	100	0.003	5	100	0	0.0	5	100	0.243
		6 Months – 1 Year	14	100	0	0.0	14	100		13	92.9	1	7.1	14	100	
		1 – 3 Years	51	60.7	33	39.3	84	100		69	82.1	15	17.9	84	100	
		>3 Years	4	57.1	3	42.9	7	100		6	85.7	1	14.3	1	100	

Table 4. Chi Square Test for Duration of Lithium and Onset of Hypothyroidism

DISCUSSION

This study was conducted to find out the prevalence and risk factors for development of hypothyroidism (overt and subclinical) in bipolar disorder patients treated with lithium. The association between the dose, duration of lithium treatment and onset of hypothyroidism (overt and subclinical) were also determined in this study.

In our study we found that overall prevalence rate of clinical and subclinical hypothyroidism in bipolar patients receiving lithium was 32.7% and 15.5% which is in concordance to study done by Bocchetta et al.[8] He conducted a study among 150 ambulatory Sardinian patients on lithium therapy and reported a prevalence rate of Subclinical hypothyroidism to be 19%.

Also, Kleiner et al.[7] estimated the prevalence of overt hypothyroidism as 8–19% and subclinical hypothyroidism upto 23% which is more or less similar to our results. In another study by Kirov et al[9] in UK, the prevalence of hypothyroidism was 10.3% with a higher female preponderance in 274 patients with affective disorders on lithium therapy. Transbol et al[10] found an elevated TSH (thyroid stimulating hormone) level in 23% of patients on lithium (39% of women). But contrary to our results, Srivatsava et al[1] reported a male preponderance of 5:1 in his study population and Kuruvilla et al[11] reported a 3:1 male predominance.

Ozerdem et al[12] Kraszewska et al[13] and Shine et al[14] have evaluated risk factors for development of hypothyroidism like ours. Davis et al[15] found that the risk of developing lithium induced hypothyroidism has been shown to be significantly higher among females, with increasing age (>50 years), presence of family history of thyroid disease and thyroid auto antibodies which is similar to our results. Ann M. Johnston et al[16] found that the prevalence was higher in females (13.8) when compared to males (4.5%) and higher rates were found in women who started on lithium between the ages 40 to 60 years of age and higher incidence in the first two years of lithium treatment which is coincide with our study results. In contrary to our study results Syed Ali et al[17] reported no significant differences between age, family history of affective disorder, but thyroid abnormalities were significantly higher in women than in men. M Kusalic et al.[18] done a case control study in Montreal and found that the all patients having first-degree relatives affected by thyroid illness had accelerated onset of hypothyroidism (3.7 years after onset of lithium therapy) compared with patients without a family history (8.6 years after onset of lithium therapy). Women over 60 years of age were more often affected by hypothyroidism than women under 60 years of age (34.6% versus 31.9%) which is similar to our study results.

Davis et al[15] found that mean duration between onset of treatment and development of hypothyroidism to be 18 months Annick Vincent et al[5] reported that Lithium-associated hypothyroidism develops most often during the first two years which is in concordance with our study results 42.9% of the patients taking lithium for more than 3 years and 39.3% were taking lithium for 1-3 years. Yassa et al[19] reported that rates range from 7.8% with a mean duration of therapy of 3.4 years which was similar to our study results. Srivatsava et al[1] reported that majority of patients were on Iithium therapy for more than 6 to 12 months; Thirty percent were on lithium for 12 to18 months and twenty percent on lithium for 18 to 24 months which was found to be against our study results duration of lithium treatment and onset of subclinical hypothyroidism was found to be 1-3 years-17.9% while 14.3% were taking lithium for more than 3 years and 7.1% patients taking for 6 months - 1 year and no one developed subclinical hypothyroidism in patients taking lithium less than 6 months.

With respect to dosage of lithium, Srivastava et al[1] who reported that the largest group was formed by the patients who received 900 mg of lithium carbonate per day is 50%; 23.3% were on 600 mg, 16.7% on 750mg, 6.7% on 1050 mg and 3.3% received 1200 mg of lithium carbonate per day but we found that in our study 44% were on 900mg of lithium per day which was more or less coincides with the results of the above mentioned study but 48% were on more than 1200mg of lithium per day which was against the findings of Srivastava et al.

The major strength of my study is that the prevalence and risk factors for both overt and subclinical hypothyroidism in bipolar patients treated with lithium were studied separately. Limitation is that the serum lithium levels and antithyrF7oid antibodies were not assessed during the study.

CONCLUSION

Prevalence of overt hypothyroidism is more than subclinical hypothyroidism and the risk of progression of subclinical hypothyroidism to overt hypothyroidism is high. High risk group includes female sex, age group 41-60 years, patients with family history of thyroid disease and weight gain during treatment. Dose and duration of lithium treatment and onset of hypothyroidism is strongly associated, so careful monitoring of thyroid status in bipolar disorder patients on lithium should be done at baseline and at regular intervals.

Early identification and supplementation with thyroxin will improve the patient's mood symptoms, cognition, prevent episodes of rapid cycling and improve the psychotropic efficacy of the adjuvant drugs.

REFERENCES

[1] Srivastava AS, Behere PB, Agrawal JK. Effect of lithium therapy on thyroid function: a retrospective study on Indian patients. IJP 1993;35(2):131-134.

[2] Henry C. Lithium side-effects and predictors of hypothyroidism in patients with bipolar disorder: sex differences. J Psychiatry Neurosci 2002;27(2):104-107.

[3] Lazarus JH. Lithium and thyroid. Best Pract Res Clin Endocrinol Metab 2009;23(6):723-733.

[4] Schou M, Amdisen A, Eskjaer Jensen S, et al. Occurrence of goitre during lithium treatment. Br Med J 1968;3(5620):710-713.

[5] Vincent A, Baruch P, Vincent P. Early onset of lithium-associated hypothyroidism. J Psychiatry Neurosci 1993;18(2):74-77.

[6] Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. Int J Bipolar Disorder 2016;4(1):27.

[7] Kleiner J, Altshuler L, Hendrick V, et al. Lithium-induced subclinical hypothyroidism: review of the literature and guidelines for treatment. J Clin Psychiatry 1999;60(4):249-255.

[8] Bocchetta A, Cocco F, Velluzzi F, et al. Fifteen-year follow-up of thyroid function in lithium patients. J Endocrinol Invest 2007;30(5):363-366.

[9] Kirov G. Thyroid disorders in lithium-treated patients. J Affect Disord 1998;50(1):33-40.

[10] Transbol I, Christiansen C, Baastrup PC. Endocrine effects of lithium, I. hypothyroidism, its prevalence in long term treated patients. Acta Endocrinologica (Copenh) 1978;87:759-767.

[11] Kuruvilla K, Karunanidhi A, Kanagasabapathy AS. Effects of long term lithium carbonate treatment on thyroid function in psychiatric patients. Indian J Psychiatry 1983;25(2):98-101.

[12] Özerdem A, Tunca Z, Çımrın D, et al. Female vulnerability for thyroid function abnormality in bipolar disorder: role of lithium treatment. Bipolar Disorder 2014;16(1):72-82.

[13] Kraszewska A, Chlopocka-Wozniak M, Abramowicz M, et al. A cross-sectional study of thyroid function in 66 patients with bipolar disorder receiving lithium for 10-44 years. Bipolar Disorder 2015;17(4):375-380.

[14] Shine B, McKnight RF, Leaver L, et al. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. Lancet 2015;386(9992):461-468.

[15] Kibirige D, Luzinda K, Ssekitoleko R. Spectrum of lithium induced thyroid abnormalities: a current perspective. Thyroid Research 2013;6:3.

[16] Johnston AM, Eagles JM. Lithium-associated clinical hypothyroidism. Prevalence and risk factors. Br J Psychiatry 1999;175:336-339.

[17] Ahmadi-Abhari SA, Ghaeli P, Fahimi F, et al. Risk factors of thyroid abnormalities in bipolar patients receiving lithium: a case control study. BMC Psychiatry 2003;3:4.

[18] Kusalic M, Engelsmann F. Effect of lithium maintenance therapy on thyroid and parathyroid function. J Psychiatry Neurosci 1999;24(3):227-233.

[19] Yassa R, Saunders A, Nastase C, et al. Lithium-induced thyroid disorders: a prevalence study. J Clin Psychiatry 1988;49(1):14-16.