Comorbidity of Autoimmune Thyroid Disease and Psychiatric Disorders: A Cross-Sectional Study from Southern India.

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ABSTRACT

Background and Aims: Autoimmune thyroid disease (AITD) is associated with a multitude of neuropsychiatric symptoms and cognitive impairment. Though it is one of the most common cause of acquired primary hypothyroidism, there is a dearth of literature regarding the psychiatric presentations of thyroid autoimmunity in southern India. **Objectives**: To study the psychiatric comorbidities in patients with AITD and determine the relationship between thyroid peroxidase antibody level with severity of psychiatric illness and cognitive impairment. **Materialsand Methods** : This cross-sectional study of one year duration was conducted in department of Psychiatry ofa tertiary-care hospital in Kerala. Subjects with AITD andnew onset behavioural symptoms were selected, diagnosis was made based on DSM 5 diagnostic criteria, illness severity was assessed using HAM-A, HAM-D, BPRS rating scales and severity of cognitive impairment was assessed using MoCA scale. Statistical analysis was done using percentage, mean , SD andSpearmann's correlation coefficient. **Results**: Out of 60 subjects, 82%were women and 52%had a family history of thyroid dysfunction. The most common psychiatric diagnosis were Major Depressive Disorder, Panic disorder and Schizophreniform disorderwith moderate to severe illness and mild cognitive impairment. Significant positive correlation between thyroid peroxidase antibody level and severity of depressive and anxiety disorder was found. **Conclusion**: The common psychiatric comorbities, its severity and cognitive impairment in AITD and its relation with thyroid peroxidase antibody level could be described. A holistic teamwork comprising of endocrinologists and psychiatrists can help in early detection and management of these issues.

Keywords: anxiety, autoimmunity, cognition, depression, psychosis, thyroid

INTRODUCTION

Autoimmune thyroid disorders (AITDs) mainly consists of Graves' disease and Hashimoto's thyroiditis (HT), which involves infiltration of the thyroid gland by cytotoxic T cells and B cells that react with thyroid antigens to produce thyroid autoantibodies[1].Antibodiesagainst at least one of the most important thyroid-specific autoantigens, thyroglobulin (Tg) or thyroid peroxidase enzyme (TPO) and thyrotropin receptor (TSH-r) are the main feature of AITD. anti-TPO antibodies are a sensitive and specific diagnostic marker for AITD[2].TPO antibody was positive in 13.3% adults as per studies in India[3].Depressive disorder and panic disorder were the most common psychiatric comorbidity in thyroid autoimmunity and mild to moderate severity depression has been observed in patients diagnosed with autoimmune hypothyroidism in studies conducted in India[4,5].The presence of anti-thyroid antibodies were associated with a more severe presentation, more negative symptoms and poorer functioning in study on early psychotic patients[6] .However, there are studies that have found that there is no link[7,8].Cognitive deficits and psychological comorbidities in patients with HT in euthyroid stateseem to have a relation to anti-TPOlevels[9].In recent years ,more and more studies have found association of autoimmune thyroiditis with cognitive impairment and mood disorders even in the euthyroidstate[10,11]. There is a scarcity of research on the specific psychiatric presentations and morbidity in these patients from India. This knowledge would aid in understanding the psychological burden, early detection and prompt medical and psychotherapeutic treatment of these patients, which

in turn would improve their psychological well-being. The present study is one of its first kind done in southern India, looking into the psychiatric presentations of AITD.This study was conducted with the objectives :to study the psychiatric comorbidities in patients with Autoimmune Thyroid Disease andto determine the relationship between anti-TPO level(marker of thyroid autoimmunity) and the severity of psychiatric illness and severity of cognitive impairment.

MATERIALS AND METHODS

This descriptive, cross-sectional hospital based study was conducted in the department of Psychiatry, SreeGokulam Medical College,Venjaramoodu, a tertiary care medical facility in Kerala, south India. The duration of study was 1 year (January 2022 to December 2022). Institutional ethics committee clearance was obtained prior to study and was done in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Sample size was calculated as 51 ,using proportion of Autoimmune Thyroid Disease patients with psychiatric comorbidity as 65.3% from a previous study,5% margin error, relative precision of 20% and 95% confidence interval [4].

Inclusion criteria**:** Subjects in the age group of 18-60 years ,diagnosed with Autoimmune Thyroid Disease and who were referred to Psychiatry Out Patient Department for evaluation of new onset behavioural symptoms were included in the study.

Exclusion criteria**:** those with other neurodegenerative/ organic brain diseases, neurodevelopmental disorders, traumatic brain injury, delirium, other autoimmune disorders, other endocrine disorders, chronic diseases (malignancies, renal /hepatic failure, connective tissue disorders), pregnancy, previous history of psychiatric disorders and substance use disorders were excluded from the study.

A total of 60 subjects fulfilling the inclusion criteria comprised of the study population.

Written informed consent was obtained from study subjects after explaining the study procedure and confidentiality maintained. In those patients who were unable to consent, consent has been obtained from nearest kin.A consecutive sampling method was done.Data was obtained from subjects using a semi structured proforma comprising information on the socio demographic details-(age, sex,education,occupation,residence,socio-economic status,marital status),clinical presentation-onset of illness, family history of thyroid disorders, medical comorbidities, presence of psychiatric symptoms-(sleep disturbance, depressive symptoms, anxiety-panic symptoms, psychotic symptoms, obsessive symptoms, death wishes and manic symptoms) and neurological symptoms-(head ache, cognitive symptoms, sensory symptoms, motor symptoms,gait disturbances and seizure). Biochemical investigations- serum TSH level and anti-TPO titer were assessed by the electrochemiluminescence immunoassay method using cobas e411automated immunoassay analyser (Roche). Normal ranges of serum TSH for age >18years= 0.4- 4.2 miu/ml and anti-TPO titre = 0.0-34 iu/ml were considered[12].The following diagnostic tool and standardised rating scales were used for assessment of psychiatric comorbidity:

Psychiatric diagnosis was made by using DSM-5 Diagnostic Criteria[13].All patients were screened for cognitive impairment using Montreal Cognitive Assessment(MoCA) scale.Thisis a 30-item cognitive screening test which is brief and reliable for the detection of cognitive impairment. It assesses visuo spatial and executive functioning, animal naming, attention, language, abstraction, delayed recall, orientation and educational level. Severity grading: score of 26 and above = normal,18-25= mild cognitive impairment, 10-17= moderate cognitive impairment, <10= severe cognitive impairment[14].

Based on the psychiatric diagnosis, the severity of psychiatric illness was assessed using the following standardised rating scales:The Hamilton Depression Rating Scale(HAM-D) has 17 items which assess symptoms of Depressive disorder. A score of 0–7= normal range, score of 10-13 =mild severity, score of 14-17= moderate severity and a score of 17 or higher =severe depressive illness[15].TheHamilton Anxiety Rating Scale(HAM-A) measures both psychic and somatic anxiety. It consists of 14 items and each item is scored on a scale of 0 to 4. A total score of <17 indicates mild severity while a score of 18–24 indicates mild to moderate severity and score of 25–30 indicates moderate to severe anxiety[16].Brief Psychiatric Rating Scale (BPRS) is useful in gauging the severity of psychotic illnesses like schizophrenia ranging from mild to severe. It consists of 18 symptom constructs belonging to positive,negative and affective symptoms that are seen in psychotic disorders. Each symptom has a score ranging from 1(not present) to 7(extremely severe) [17].Score of 31-40 indicates mild severity, 41-52= moderate severity and score above 52 indicates severe illness[18].

Data was analysed using SPSS software version 28. Descriptive analysis was carried out using frequency and percentages for the categorical variables and mean and standard deviation for the continuous variables. Correlations between anti-TPO titer(marker of thyroid autoimmunity) and severity of psychiatric illness(assessed using HAM-D , HAM-A, BPRS rating scale scores) and severity of cognitive impairment(assessed usingMoCA scale scores) were examined using Spearmann's rank order correlation coefficient. A p-value<0.05 was considered as statistically significant.

RESULTS

In the present study, of total 60 subjects, 49 (81.7%) were females, 20(33.3%) subjects were in the age group of 41-50 years and 15(25%) in the age group of 31-40years. 19(31.67%) subjects were educated upto higher secondary and 52(86.6%) were employed in nonprofessional jobs.44(73.3%)subjects were married , 41(68.3%)were from a rural setting and 47(78.3%) subjects belonged to middle class socio economic status.(Table1).

Table 1.Socio-demographic characteristics of subjects with AITD and psychiatric illness

AGE in years	No: of subjects(60)	%
<20	2	3.3
20-30	13	21.7
31-40	15	25
41-50	20	33.3
51-60	10	16.7
SEX		
Male	11	18.3
Female	49	81.7
EDUCATION		
Primary	2	3.3
Secondary	16	26.7
Higher Secondary	19	31.7
Graduate	18	30
Postgraduate	5	8.3
OCCUPATION		
Non-professional	52	86.7
Professional	7	11.7
Unemployed	1	1.6
MARITAL STATUS		
Married	44	73.3
Single/widowed	16	26.7
RESIDENCE		
Rural	41	68.3
Semi urban	13	21.7
Urban	6	10
SOCIOECONOMIC STATUS		
Lower	9	15
Upper lower/Lower middle/Upper middle	47	78.3
Upper	4	6.7

46(76.7%) subjects had no other medical comorbidities. The most common symptoms were cognitive seen in 56(93.3%) subjects, sleep disturbances in 55(91.7%) subjects, and 30 subjects (50%) had

suicidal ideas. Major depressive disorder was diagnosed in 21(35%) subjects, followed by Anxiety disorder in 20(33.3%) and Psychotic disorder in 19(31.7%) subjects. Panic disorder and Schizophreniform disorder was the most common anxiety and psychotic disorder respectively, found in 11(18.3%) subjects each.(Table.2)

Table.2- Clinical profile of subjects with AITD and psychiatric illness

Onset of Illness	No: of subjects(N=60)	**%**
<2 weeks	11	18.3
2weeks-1month	24	40
1month-3month	25	41.7
Family history of thyroid disorders	N=60	**%**
yes	31	51.7
no	29	48.3
Diagnosis	N=60	**%**
Major Depressive Disorder	21	35
Panic disorder	11	18.3
Generalized Anxiety disorder	5	8.3
Unspecified Anxiety disorder	4	6.7
Schizophreniform disorder	11	18.3
Brief Psychotic disorder	5	8.3
Delusional disorder	3	5

The mean anti-TPO titer =262.49,SD=152.815.In view of wide variation in anti-TPO levels, the median was estimated as 216, Interquartile range as 297,lower range=62 and upper range=600. The mean TSH level=14.12,SD=19.17. The mean HAM-D score of 21 subjects with Depressive disorder was 28.33 and SD= 7.137.The mean HAM-A score of 20 subjects with Anxiety disorder was 30.1 with SD=5.656. The mean BPRS score of 19 subjects with Psychotic disorder was 58.95 with SD=10.617.The mean MoCA score of 60 subjects was 23.63 with SD= 3.173.

Table3.Severity of psychiatric illness and cognitive impairment in subjects with AITD

Severity score	No: of subjects	Severity of illness
HAM-D	21	
10-13	nil	mild
14-17	6(29%)	moderate
>17	15(71%)	severe
HAM-A	20	

<17	1(5%)	mild
18-24	7(35%)	moderate
25-30	12(60%)	severe
BPRS	19	
31-40	nil	mild
41-52	6(32%)	moderate
>52	13(68%)	severe
MoCA	60	
>=26	13(12%)	Normal score
18-25	44(73%)	mild
10-17	3(5%)	moderate

All subjects with Major Depressive Disorder and Psychotic Disorder had moderate to severe illness.19(95%) subjects with Anxiety disorder had moderate to severe illness and cognitive impairment of mild/ moderate severity was found in 47(78%)subjects.

Table 4.Correlation between anti-TPO level and severity of psychiatric illness &cognitive impairment

	Correlation	HAM D	HAM A	BPRS	MoCA
Anti-TPO titre	rho(r)	0.614	0.599	-0.326	-0.014
	P value	0.003*	0.005*	0.173	0.9157
	N	21	20	19	60

* significant p value<0.05

Statistically significant positive correlation was found between anti-TPO level and HAM-D scores (severity of depressive disorder) as well as HAM-Ascores (severity of anxiety disorder) indicating that subjects with high anti-TPO titer(marker of thyroid autoimmunity) had severe illness. Negativecorrelation was found between anti-TPO titer and MoCA scores (severity of cognitive impairment) though not significant. No statistically significant correlation was found between serum TSH level(marker of thyroid function) and severity of illness(HAM D: r= -0.442,p=0.05; HAM A: r=0.172,p=0.47;BPRS:r=0.225,p=0.35 and severity of cognitive impairment (MoCA: r= 0.20,p=0.13).

DISCUSSION

Thyroid autoimmunity is connected with psychiatric comorbidities, cognitive impairment and the nature of correlation between marker of thyroid autoimmunity (anti-TPO level) and severity of psychiatric illness and cognitive impairment could be ascertained from this study.The findings in this study is in tune with the findings of a study from north India on patients with AITD, in which majority of the subjects were women in the age group of 25-40years with most common psychiatric illness being Major Depressive Disorder, Panic disorder and Psychotic disorder[4] .However,in a study by Radhakrishnan et al from south India,it was found thatthe rate of anti-TPO positivity in the schizophrenia spectrum disorder group was 13.58 per cent and 5.6 per cent in the mood disorder group [19].The severity of Depressive and anxiety disorder in subjects with AITD were high as has been shown by findings of systematic review by Seigmann et al. and study bySteiner et al[20,21].Moderate to markedly ill subjects were high among subjects with AITD and Psychotic disorder. This finding is consistent with that of study by Barbero et al. in which those with positive thyroid antibodies had more negative symptoms and poorer function[22].Moderate to severe illness in majority of subjects

would point to impairment in the socio occupational functioning, low quality of life and need for early detection, prompt pharmacological and psychotherapeutic management. This psychological burden in turn adds to the burden of somatic symptoms of thyroid dysfunction and the cost of treatment in addition to the cost of hormonal treatment. Presence of suicidal ideas in 50% of the subjects would call for caution and need for screening for psychiatric illness in these patients. Early detection, detailed evaluation and treatment by Psychiatric team is essential to prevent chronicity, complications of untreated illness like suicide and improve the psychological wellbeing of these patients.

Statistically significant positive correlation between anti-TPO titer and severity of Depressive and Anxiety disorder is consistent with findings of a previous study by Krysiak et al. in which TPO antibody levels were directly proportional to BDI scale total scores[23].These findings implicate that higher the anti-TPO level, severe the autoimmune thyroid pathology as well as severe psychiatric morbidity when it is present. Fewer no: of subjects with Psychotic disorder in the study sample could have contributed to lack of correlation between anti-TPO level and severity of psychotic illness. However, no correlation could be found between anti-TPO level and severity of cognitive impairment as in the study by Napthali et al[24], though a negative trend could be found between the two variables. The mild cognitive impairment seen in significant no: of the subjects could be part of symptomatology of the underlying psychiatric illness than due to raised anti-TPO titer and also due to the fact that those with symptoms of encephalopathy/delirium were excluded from study. The finding that TSH level (marker of thyroid function) did not have any correlation with severity of illness is pointing towards the connection to anti-TPO levels. Thus, a patient with normal thyroid function which is indicated by normal TSH levels would have severe psychiatric illness when it is present if the anti-TPO level is high. It is essential to initiate the proper pharmacological and psychotherapeutic treatment of the specific psychiatric disorder in addition to hormonal treatment.

The findings of this study shed light into the psychiatric burden in AITD and the lacunae of knowledge regarding this subject in the background of southern India. Though it is not possible to ascertain the exact mechanism of association between mood/psychotic/anxiety disorders and AITD based on this study, a plausible explanation for the association could be the bidirectional interaction between the central nervoussystem, endocrine and immune systems.The reason for such heterogeneous results in studies may bedue to the methodological variations including study sample, sample size estimation, interview or assessment instruments, diagnostic criteria used and presence of TPO antibodies in general population. Patients with AITD seek treatment for somatic symptoms from other specialties and psychological issues may go unnoticed. Psychological symptoms might get dismissed off easily especially when in euthyroid state during routine screening by TSH level estimation. Knowledge on the psychological burden and its severity in AITD patients especially depressive and anxiety disorder and its correlation with anti-TPO levels and not with serum TSH level is useful to create awareness in other specialist, resulting in screening of these patients for psychiatric illness and prompt referral. The presence of higher psychiatric comorbidity of severe nature in these patients would require early detection, prompt pharmacological and psychotherapeutic treatment by a psychiatric team. Delay in recognizing this would result in illness becoming chronic and add to the somatic burden of AITD. Euthyroid AITD patients with raised anti-TPO level are likely to have severe depressive and anxiety disorder , even though TSH level is within normal range. In patients with severe neuropsychiatric symptomatology and family history of thyroid disorders, evaluation for AITD would be beneficial in identifying euthyroid patients who would otherwise be missed in routine screening with serum TSH levels. AITD being one of the most common cause of acquired primary hypothyroidism, having higher psychiatric comorbidity and severe illness, it is suggested to screen these patients for psychiatric illness for early detection and treatment of the condition.

LIMITATIONS

The major limitation of the study is that the study participants were selected from patients who sought help at a tertiary care teaching hospital. Hence, the findings may not be generalized to patients with similar problems in the community. The premorbid personality was not considered which might have had an influence on the severity of the behavioral symptoms.

CONCLUSION

The most common psychiatric presentations seen in patients with AITD were Major Depressive disorder, Panic disorder and Schizophreniform disorder with moderate to severe illness and mild cognitive impairment. The serological marker of AITD, the anti-TPO level, had significant correlation with the severity of Depressive and Anxiety disorder. A good team approach and liaison among endocrinologists, neurologists & psychiatrists is suggested for early detection and proper treatment of these patients. Longitudinal, prospective studies would be required to infer about the direction of relationship between autoimmune thyroid disease and psychiatric comorbidities.

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