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Subclinical hypothyroidism among patients with depressive disorders.

Siti Yazmin Zahari Sham,[1] Nor Aini Umar,[2] Zarida Hambali,[1] Rosdinom Razali,[3] Mohd Rizal Abdul Manaf [4]

[1]Department of Pathology, Faculty of Medicine & Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia
[2]Department of Pathology, UKMMC, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia
[3]Department of Psychiatry, UKMMC, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia
[4]Department of Community Health, UKMMC, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia

ABSTRACT

Subclinical hypothyroidism (SHT) is a biochemical diagnosis, defined as an elevated Thyroid Stimulating Hormone (TSH) with normal free thyroxine (FT4). It affects 4-10% of the adult population and is more prevalent in elderly women. Its commonest cause is autoimmune thyroiditis, detected by anti-thyroid peroxidase antibody (TPO-Ab). About 2-5% of SHT patients progress to overt hypothyroidism annually. The SHT prevalence among depressed patients ranges between 3% and 17%. This study aimed to determine the prevalence of SHT and TPO-Ab positivity among patients diagnosed with depressive disorders. It was a cross-sectional study carried out in the Universiti Kebangsaan Malaysia Medical Centre over a 12 months period. Serum TSH, FT4 and TPO-Ab were measured. Results showed that 82% of depressed patients were euthyroid, 4% had SHT, 11% had subclinical hyperthyroidism and 2% had discordant thyroid function. TPO-Ab positivity among the subjects was 7%, one of whom had SHT. In conclusion, the prevalence of SHT and TPO-Ab positivity in the study population, at 4% and 7%, respectively, were comparable to previous findings.

Key words: Subclinical hypothyroid, prevalence, depressed patients, anti-thyroid peroxidase antibody.

INTRODUCTION

SHT is a biochemical diagnosis, characterized by an elevated serum TSH concentration above the statistically defined upper limit of the reference range when serum FT4 concentration is within its reference range.[1] Patients are usually asymptomatic but mild non-specific symptoms may sometimes be present.[1] The magnitude of TSH divides SHT into mild or severe.[2] Biochemically, SHT entity is explained by the exquisitely sensitive inverse log-linear relationship of hypothalamus-pituitary-thyroid (HPA) axis, with each individual having a genetically-determined HPA axis set-point.[3] Diagnosis of SHT is made only after persistent TSH elevation on repeat sample and exclusion of transient increase or laboratory error.[1,4]

Much of the data on the prevalence of SHT comes from two large population-based studies, namely the Whickham Survey and the National Health and Nutritional Examination Survey (NHANES) III.[1] Its prevalence is between 4 and 10% of adult population samples.[5,6] The prevalence increased with age in women (up to 20% over 60 years)[2] and the most common cause of SHT is Hashimoto's (autoimmune) thyroiditis.[1] Not all patients with SHT progress to overt hypothyroidism.[1] The rate of progression is proportional to the baseline serum TSH concentration and is higher in patients with anti-thyroid antibodies.[4]

Depression is the most common mood disorder, estimated to affect 350 million worldwide.[7] The link between thyroid dysfunction and depression has long been recognized.[8] Dysfunctional hypothalamus-pituitary-thyroid (HPT) axis have been documented in patients with depression[9,10] and such abnormalities were often associated with elevated anti-thyroid antibody.[10,11] It has also been suggested that the outcome of treatment and the course of depression, may be related to thyroid status, particularly thyroid autoimmunity.[11,12]

*Corresponding author: Dr. Siti Yazmin Zahari Sham
sitiyazmin@upm.edu.my

The prevalence of depression was higher in patients with SHT than in the general population.[13] Recent studies relating SHT and depression have shown varied findings.[14-16] Nevertheless, the American Association of Clinical Endocrinologists (AACE) guidelines stated that the diagnosis of subclinical or clinical hypothyroidism must be considered in every patient with depression.[17]

As depressive disorders are one of the most common psychiatric illnesses in Malaysia, with a prevalence of approximately 5-6%[18] and the possible link between depression and SHT, this study aimed to determine the prevalence of SHT and TPO-Ab positivity among patients with depressive disorders in Universiti Kebangsaan Malaysia Medical Centre (UKMMC).

MATERIAL AND METHODS

This was a cross-sectional study carried out in the Universiti Kebangsaan Malaysia Medical Centre (UKMMC). Subject recruitment was done by convenient sampling. Potential subjects were identified from the new patient appointment records prior to their appointment dates. Referrals from other wards were traced on a daily basis by checking the referral records and liaising with the staff at the clinic reception and psychiatric medical officer on-call.

A total of 98 patients were recruited over a twelve months period (from 1st May 2007 to 1st May 2008). Inclusion criteria were i) All newly diagnosed patients with a Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) diagnosis of Major Depressive Disorder (MDD), Minor Depressive Disorder, Dysthymia or Adjustment Disorder (with depressed mood), ii) patients who were not on antidepressant or electroconvulsive therapy (ECT). Exclusion criteria included i) patients with psychotic illness other than Depressive Disorders, ii) patients with known thyroid disease, iii) patients who were already on treatment for a depressive illness. The study had been approved by the Medical Research and Ethics Committee, Faculty of Medicine, UKM. Both verbal and written consents were obtained on the enrolment day.

A maximum amount of 5 mls of venous blood was withdrawn from each subject. All serum assays were performed in the UKMMC Chemical Pathology laboratory. The blood samples were centrifuged and analyzed for TSH and FT4 on the same day. Aliquots were stored at -20°C for the measurement of TPO-Ab, which was carried out in batches within one month after sample collection.

Serum TSH concentrations were measured by a third-generation Architect TSH assay, using the Chemiluminescent Microparticle Immunoassay (CMIA) technology. In this study, the TSH reference range was taken as 0.45-4.5 mIU/L. Serum free T4 (FT4) with a reference range of 9.10-23.80 pmol/L was analyzed on Architect Free T4 assay, using the Chemiluminescent Microparticle Immunoassay (CMIA) technology. Serum anti-TPO with a normal range of less than 5.61 IU/ml was analyzed on the AxSYM TPO-Ab assay, based on the Microparticle Enzyme Immunoassay (MEIA) technology. Thyroid status was defined as in Table 1.

Table 1. Biochemical definition of thyroid status*

Thyroid status	TSH (mIU/ml)	FT4 (pmol/L)
Euthyroid	0.4 – 4.50	9.10 – 23.80
Overt hypothyroid	> 4.50	< 9.10
Subclinical hypothyroid	> 4.50	9.10 – 23.80
Overt hyperthyroidism	< 0.10	> 23.80
Subclinical hyperthyroid	< 0.40	9.10 – 23.80
Discordant	High or low TSH levels with inappropriate levels of FT4	

* National Academy of Clinical Biochemistry (NACB) 2003[20]

All clinical and laboratory data were stored and analyzed using the Statistical Package for Social Sciences (SPSS) statistical software version 18. The Kolmogorov-Smirnov test was used to assess normality of the distribution of the data. Results were expressed as mean values and standard deviation for normally distributed variables; whilst non-parametric tests were used for analysis of variables that were not normally distributed and median values with 25 to 75 percentiles were used. In all statistical analyses, $p<0.05$ (95% confidence interval) was considered significant. For categorical variables, measures of significance between groups were evaluated using the chi-square test. Pearson or Spearman correlation coefficients were calculated to estimate the linear correlation between continuous variables as

appropriately indicated. Similarly, either the t-test or Mann-Whitney U test was applied to test for differences between two independent groups on a continuous data.

RESULTS

The general characteristics of recruited patients are shown in Table 2. Thyroid status of the study population is shown in Table 3. Biochemically, majority of patients were euthyroid. Four patients (4%) were found to fit the diagnosis of subclinical hypothyroidism (none of whom had serum TSH levels more than 10.00 mIU/L). Eleven (11%) patients had subclinical hyperthyroidism. The correlation between serum TSH levels and age showed a non-significant weak negative correlation. There was a non-significant difference in the TSH levels of female and male patients.

Table 2. General characteristics and types of depressive disorders in patients with depression

Subtype			Major Depressive Disorder		Minor Depressive Disorder		Adjustment Disorder		Dysthymia	
	(N= 98)	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Gender										
Female	66	67	39	59	3	5	16	24	8	12
Male	32	33	21	65	0	0	7	22	4	13
Age										
<60 years	83	85	49	59	3	4	19	23	12	14
≥60 years	15	15	11	73	0	0	4	27	0	0

Table 3. Thyroid status of patients with depression by gender

Thyroid status	Female		Male		Both gender	
	(N= 66)	(%)	(N= 32)	(%)	(N= 98)	(%)
Euthyroid	57	86	23	72	80	82
Overt hypothyroid	0	0	0	0	0	0
Subclinical hypothyroid	2	3	2	6	4	4
Overt hyperthyroid	1	1	0	0	1	1
Subclinical hyperthyroid	5	7	6	19	11	11
Discordant	1	1	1	3	2	2

Twenty eight patients had comorbidities, three of whom had SHT. Table 4 shows the significant association between SHT and different types of comorbidities, namely hepatitis, liver cirrhosis and beta thalassaemia. In multivariate logistic regression analysis, the significant independent predictor of subclinical hypothyroidism was only hepatitis (Nagelkerke R2 = 0.375 and p = 0.015). However, cirrhosis and thalassaemia were not.

Table 4. Association between subclinical hypothyroidism and comorbidities in patients with depression

Comorbidities	X^2 with Yates correction	P value
Hepatitis	16.67	**0.01***
Liver cirrhosis	5.44	**0.02***
Thalassaemia	5.44	**0.02***
Malignancies	0.00	1.00
End-stage renal failure	1.25	0.26
Type 2 Diabetes Mellitus (T2DM)	2.48	0.12
Hypertension	2.89	0.09
Acute renal failure	0.00	1.00
Adrenal failure	0.00	1.00
Rheumatoid arthritis	0.00	1.00
Opiod-dependency	0.00	1.00
Spondylolysis	0.00	1.00
Tuberculosis	0.00	1.00
Pulmonary embolism	0.00	1.00
Asthma	0.00	1.00
Peptic ulcer disease	0.76	0.38
Paraplegia	0.00	1.00

* Significant at $p< 0.05$

Table 5 shows TPO-Ab status of the study population. There was a weak positive correlation between anti-TPO titre and age, ($r = 0.256$ and $p = 0.01$). However, both the correlations between serum anti-TPO titre with TSH level and FT4 were weak and non-significant. In addition, there was no significant difference between anti-TPO titre of female and male patients and between the levels of anti-TPO titre in depressed patients with SHT and those without.

Table 5. Thyroid autoantibody status of patients with depression.

	TPO-Ab titer			
	Normal		High	
	(N= 91)	(%)	(N= 7)	(%)
Euthyroid	74	82	6	86
Subclinical hypothyroidism	3	3	1	14
Overt hyperthyroidism	1	1	0	0
Subclinical hyperthyroidism	11	12	0	0
Discordant	2	2	0	0

DISCUSSION

The prevalence of SHT in this study population was 4%. Previous studies have indicated that it is probably higher in patients with refractory depression than in other types of depressed patients.[19] In this study, the subjects were all non-refractory cases comprised newly diagnosed, untreated patients.

A diagnosis of SHT relies heavily on the definition of TSH upper reference limit (URL), taken at the 97.5th percentile of a population-based reference range.[20] Recently, there has been much controversy regarding TSH upper reference limit. The arguments for and against has been widely discussed.[1,4] Some authors conclude that the clinically relevant value is between 4 and 5 mIU/L.[1] There has also been much growing interest in having age- and race-based reference range.[1] In this study, the TSH reference range adopted was 0.45-4.5 mIU/L; whilst that of FT4 was 9.1-23.8 pmol/L, as recommended by the experts[4,20,] in keeping with the most widely acceptable clinically relevant ranges.[1]

The time of sampling is also critical as the normal TSH diurnal rhythm, characterized by a peak around midnight and a decrease of up to 50% between 0800 to 0930 hours, may be displaced by sleep deprivation or exercise.[20] It is recommended that TSH reference range be established from fasting morning samples of euthyroid subjects who, in addition to the above criteria, are also free of pathological thyroid ultrasonography findings.[1,20] In this study, although patients were not necessarily fasted, the time of sampling occurred during working hours (between 0800 to 1700 hour), as to minimize the effect of TSH diurnal rhythm.

Inter-assay variability of TSH must also be borne in mind, both within the current third generation and across the different generations. Thus, the differences in the prevalence of SHT observed in various studies not only reflect differences in population studied, but also in TSH reference range used, as well as TSH and TPO-Ab assays.

Transient TSH elevation may also occur during the recovery phase of euthyroid sick syndrome (non-thyroidal illness), chronic kidney disease (CKD) or untreated adrenal failure.[1] In hospitalized patients, transient abnormalities up to 20.0 mIU/L range may be seen during recovery from non-thyroidal illness.[21] Strictly speaking, SHT cannot be easily diagnosed during a hospitalization due to this phenomenon. However, concurrent measurement of TPO-Ab titer would differentiate autoimmune thyroid disease from non-thyroidal illness.[20]

Presence of CKD may explain elevated TSH in 2 out of 4 patients with SHT in this study. Chonchol et al[22] has shown that SHT was a relatively common condition (18%) among persons with CKD, not requiring chronic dialysis. However, in this study, patients with end-stage renal failure (ESRF) were all dialysis-dependent and there was no significant association between ESRF and SHT. Patients with untreated adrenal insufficiency may have high, often reversible, serum TSH.[23] In this study, there was one patient with adrenal failure, whose euthyroid state may be explained by him being on treatment.

Three out of 4 patients with SHT had comorbidities and their TPO-Ab titres were within normal range. Thus, their mildly elevated TSH (<10 mIU/L) may actually be transient, presumably occurring during recovery phase of their acute illnesses. Ideally, evaluation of thyroid function should be deferred until 2-3 months after discharge. Three medical illnesses, namely hepatitis, liver cirrhosis and thalassaemia showed significant association with SHT. On further statistical analysis, however, only hepatitis was shown to independently affect the probability of having SHT. Although statistical analysis showed that hepatitis contributed 37.5% (Nagelkerke R2 = 0.375) of the variation in the occurrence of SHT, it should be interpreted with caution due to the small sample size and convenient sampling method.

A recent study showed that a spectrum of thyroid dysfunction existed in untreated chronic hepatitis C patients, and that SHT was the most prevalent type.[24] The underlying pathogenesis of thyroid dysfunction in these untreated patients was likely to be associated with autoimmunity.[24] Another recent study has also shown that thyroid dysfunction developed in 10% of patients treated with interferon-α, with hypothyroidism being the most common presentation.[25] It is currently suggested that interferon induces thyroid dysfunction by both autoimmune and non-autoimmune mechanisms.[26] In this study, two of SHT patients had chronic hepatitis, (the subtype of which was not ascertained), and none was on interferon treatment.

SHT is a common finding in type 1 diabetes mellitus (T1DM)[27] and probably other autoimmune diseases. A recent study has found significant prevalence of either SHT (6.3%) or overall thyroid dysfunction (32.4%) in T2DM.[28] In this study, 2 patients with SHT had T2DM. However, statistical analysis showed no significant association between T2DM or autoimmune diseases, such as rheumatoid arthritis, with SHT.

Incidentally, there was a relatively high prevalence of subclinical hyperthyroidism among the subjects, found in 11 patients (11%), 4 of whom had other medical illnesses. In the latter group of patients, as their TSH levels varied between 0.03-0.33 mIU/L, their TSH levels may be explained by transient mild TSH suppression commonly seen in non-thyroidal illness.[20] Nevertheless, although subclinical hyperthyroidism is less prevalent than subclinical hypothyroidism, and is less commonly associated with depression[2], this finding may reflect that subclinical thyroid disorders, in combination, are prevalent among patients with depressive disorders.

TPO-Ab is involved in the thyroid hormone synthesis. Pathologically, it is implicated in the tissue destructive process in Hashimoto's thyroiditis. Thus, TPO-Ab is the most sensitive test for detecting autoimmune thyroid disease

(AITD) and its detectable titre typically precedes TSH elevation, making it the first biochemical abnormality detected in the disease course.[20] Varying degrees of clinical and subclinical hypothyroidism as well as positive TPO-Ab titres, suggestive of asymptomatic autoimmune thyroiditis, have been observed in depressed patients.[9,10,19,29]

Several studies have shown 8% to 20% prevalence of anti-thyroid antibody positivity among depressed patients, supporting the hypothesis of subtle thyroid dysfunction in these patients. However, these findings must be interpreted with caution.[8]

In this study, the prevalence of anti-thyroid antibody positivity was 7%, which was comparable to figures found by the previous studies and not significantly different from the rate in the general population. One patient with positive TPO-Ab titre had SHT, which in this case may be due to symptomless autoimmune thyroiditis. Upon confirmation of the diagnosis of SHT, one may proceed with an ultrasonic examination of the thyroid gland. The risk of her developing an overt hypothyroidism was favoured by her female gender and positive TPO-Ab. However, young age and mild degree of TSH elevation may favour normalization. Six patients with positive TPO-Ab titer were biochemically euthyroid and were all female, including 3 elderly (≥60 years). These patients might have symptomless Hashimoto's thyroiditis and therefore were at risk of developing thyroid failure. They should be followed up, as suggested above.

The prevalence of thyroid autoantibodies increases in patients with non-thyroid autoimmune diseases, such as rheumatoid arthritis and T1DM.[30,31] Among patients with positive TPO-Ab titre, two had concurrent spondylolysis, which is a degenerative non-immune condition. Their positive TPO-Ab titre, therefore, could not be explained by presence of non-thyroidal autoimmune disease. However, being an elderly (≥60 years) female is a known risk factor for positive TPO-Ab.

With limitation such as short duration and small sample size, the findings were strong enough to propose a more extensive study with a bigger sample size. A repeat testing of serum TSH and FT4 at 2-12 weeks is strongly recommended to confirm the diagnosis of SHT, as well as to see the progress of the illness. It would also be interesting to assess the association between severity of depression and thyroid dysfunction.

CONCLUSION

The prevalence of SHT among patients with newly-diagnosed depressive disorders was 4%. Incidentally, the prevalence of subclinical hyperthyroidism was 11%. Hepatitis showed a significant association with SHT; whilst other comorbidities did not. TPO-Ab titer was positive in 7% of the study population, one of whom had SHT. However, TPO-Ab positivity was more prevalent in young female subjects, in contrast to that found in the general population. Although the prevalence of SHT alone was low, in combination, the prevalence of subclinical thyroid disorders in this study was 15%. This may support routine thyroid function test all newly diagnosed depressed patients. TPO-Ab testing would be complementary in identifying possible cases of asymptomatic thyroiditis.

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