

REVIEW PAPER**THYROID DISORDERS AND PSYCHIATRIC MORBIDITIES**

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Abstract

The functional behavior of the thyroid is fundamental in most diseases and represents the basis for diagnosis and therapy. The status can be euthyroidism, hypothyroidism or hyperthyroidism. The psychiatric manifestation varies in different thyroid status. Those with hypothyroidism were described to have depression, psychosis and cognitive dysfunction. Meanwhile, those with hyperthyroidism were found to have psychosis, aggression, anxiety as well as cognitive impairment.

***Keywords:* thyroid disease, euthyroid, hypothyroidism, hyperthyroidism, depression, anxiety**

Introduction**Thyroid Disorders**

Thyroid disorders comprise a large proportion of study in endocrine disorders, other than diabetes mellitus¹. The last comprehensive classification of thyroid diseases has been reported by the American Thyroid Association in 1969. It is divided into two; abridged and detailed classifications where the former is provided for simplicity and daily usefulness and the latter for hospital diagnoses and for reports in the literature. It was based largely on thyroid function since classification by etiology was considered premature, by pathology was non-useful to the clinician

and the clinical evolution and follow up have not yet been evaluated². The functional behavior of the thyroid is fundamental in most diseases and represents the basis for diagnosis and therapy.

Euthyroidism means normal production of thyroid hormones by the thyroid and normal levels in the circulation and at the cellular level. Hyperthyroidism means clinical symptomatology due to excessive circulating and intracellular thyroid hormones which normally shown by low TSH and high fT4 or fT3. The causes include Graves' disease which is the most common, toxic multinodular goiter, toxic adenoma and thyroiditis. Among the

important clinical features are weight loss despite good appetite, excessive sweating, irritability, anxiety, tremulousness, palpitations, goiter and proximal muscle weakness³.

As for the Graves' disease, it is usually clinically distinctive; there is a small to moderate, diffuse, firm goiter and around a half of these patients have signs of thyroid-associated ophthalmopathy like lid lag, lid retraction, proptosis, extraocular muscle dysfunction, corneal involvement and loss of sight. Less than 5.0% have pretibial myxedema which is better called thyroid dermopathy. Thyroid dermopathy most commonly occurs as non-pitting plaques with a pink or purple color but no inflammatory signs. Hyperplasia of lymphoid tissue, including splenomegaly and thymic enlargement is sometimes found⁴.

Hypothyroidism is almost always due to the lack of thyroid hormone production and inadequate replacement therapy. It is normally diagnosed when TSH is elevated and fT4 is low. The causes include autoimmune thyroid disease like Hashimoto's thyroiditis, thyroid agenesis and secondary to treatment like post-thyroidectomy or post-radioiodine therapy. Among the important clinical features are apathy, fatigue, cold intolerance, slow speech, weight gain, coarse feature and facial puffiness³.

Subclinical hyperthyroidism is defined as an asymptomatic state in which circulating concentration of free T3 and T4 are normal but serum sensitive TSH is suppressed.

Subclinical hypothyroidism is defined as an asymptomatic state in which circulating concentrations of free T3 and T4 are normal but serum TSH is slightly elevated. Both conditions are not disease entity but a mild stage of thyroid hyper function and hypo function respectively⁵.

Statistic regarding prevalence and incidence of thyroid disorders are difficult to interpret because existing published studies have different significantly in regard to population age range, geographic location and criteria used to define the presence and degree of thyroid failure. Most prevalence studies of thyroid diseases are small and performed in selected groups of the population⁶⁻⁸.

Thyroid disorders are much more common among female^{6,9-12}. Prevalence of thyroid disorders is estimated about 2.0% in female and 0.2% in male¹³. Among the functional disorder of the thyroid, hypothyroidism is the most common with prevalence ranged from 1.0%- 11.7% in female and 0.9%- 5.14% in male whereas prevalence for hyperthyroidism ranged from 0.86%- 2.5% in female and 0.17%- 0.6% in male^{6,10-12}. As for the sub clinical hypothyroidism, the prevalence is found to range from 9.0%- 15.0% and 2.1% for sub clinical hyperthyroidism⁹⁻¹⁰.

In general, the incidence of thyroid disorder increases with age^{6,9}. For hypothyroidism, the incidence of new cases is in those aged 70 and is rare under the age of 30⁶⁻¹². For hyperthyroidism, the incidence is spread over all ages but the commonest cause (Grave's disease) usually develops between

the second and the fourth decades of life^{6, 9, 14-15}.

There was only handful of study on thyroid in the Asian countries. The studies found that the prevalence also common among females and presence of high percentage of anti microsomal antibodies in the first degree relatives of children with thyroiditis¹⁶⁻¹⁷.

In Malaysia, thyroid disorders are the second most common and prevalent endocrine and metabolic disease after diabetes mellitus³. In University Malaya Medical Center, Kuala Lumpur, the same thing applies. The clinical attendance for thyroid patient in the Endocrine Clinic ranged from 250 to 300 patients per months which comprises the majority of the patients attended the clinic¹⁸.

Thyroid Disorders and Psychiatric Morbidities

Many studies described the psychiatric manifestations of different thyroid status. Those with hypothyroidism were described to have psychosis, cognitive dysfunction and depression. Meanwhile, those with hyperthyroidism were found to have psychosis (mainly paranoia), aggression, anxiety, depression as well as cognitive impairment¹⁹.

In a study by Whybrow et al¹⁹ in 1969, he found that when the hypothyroidism was long standing, the impairment of cognitive function persisted after thyroid replacement therapy. In hyperthyroidism, the impairment was milder, not always recognized by the individual and returned to normal when

euthyroidism was reestablished. In hypothyroidism, the depressive affect differed from hyperthyroidism in terms of severity where it is of a major degree in the former. A high subjective level of anxiety was noticed by the hyperthyroid group which was significantly reduced after treatment.

Depression and anxiety are the most common psychiatric presentation in thyroid disorders. Both subclinical and overt thyroid disorder have been associated with mood disorders and it has been stated that abnormal thyroid functioning can affect mood and influence the course of affective disorders²⁰. The causal relationship for this association remains unclear. Several theories were proposed. The association can be because of specific conditions in the hypothalamic-pituitary-adrenal (HPA) axis regulation or can also be part of coping with a chronic medical condition as discussed earlier.

a) Marangell et al²¹ hypothesized a relation between thyroid hormone status and neurotransmitter activity by postulating that thyrotrophin releasing hormone (TRH) itself is a neurotransmitter that has significant antidepressant properties.

b) Jackson²² concluded that most patients with depression, although generally viewed as chemically euthyroid, have alterations in their thyroid function including slight elevation of serum thyroxine, blunted thyrotrophin response to TRH stimulation, and loss of nocturnal TSH rise. These changes were generally reversed following alleviation of the depression. It

was also postulated that the increase fT4 and blunted TSH response to exogenous TRH was the result of glucocorticoid activation that increased TRH secretion with down-regulation of the TRH receptor as a consequence.

c) A review by Musselman et al²³ stated that patients with primary thyroid disease have high rates of depression caused by alterations of the HPA and that the alteration consists of changes in the TSH response to TRH and elevated TRH concentrations in the cerebrospinal fluid.

d) Cleare et al²⁴ found that depressed patients had higher levels of TSH, and suggested that hypothyroidism reduces central 5-hydroxytyramine (5-HT) activity in the brain.

Most of the studies suggest an association between thyroid disorders and depression but there are studies which opposed these theories. Ordas et al²⁵ stated that thyroid disease per se rarely was an etiological factor of major depression while Fava et al²⁶ found that hypo and hyperthyroidism were extremely uncommon in depressed patients, and that the presence of subtle thyroid abnormalities did not have impact on treatment outcome.

As compared to depression, the association between anxiety and thyroid disorder has been less systematically researched. Several studies indicate an association between panic disorder and thyroid dysfunction²⁷⁻²⁹ Roger et al²⁷ found that patients with panic disorder had more medical problems including thyroid dysfunction than the

population at large and patients with other anxiety disorders. Study by Hoffman³⁰ concludes that agoraphobia unlike depression or panic disorder seems to be less biologically determined in respect to the HPA axis while a study by Patten et al³¹ found social phobia to be the only anxiety disorder associated with thyroid disorder when adjustment to age, sex and other chronic condition was carried out.

Another study however, found higher rates of panic disorder, simple phobia and obsessive-compulsive disorder in thyroid patients than in the general population which suggest that the occurrence of psychiatric and thyroid diseases may be the result of common biochemical abnormalities³². The same study found that the most frequently encountered anxiety disorder was panic disorder, followed by generalized anxiety disorder, social phobia and obsessive-compulsive disorder.

The lifetime prevalence of depression and anxiety is 11.8% to 36.8% and 5.0% to 41.2% respectively in the group with previously known thyroid disorder^{20, 31-32}. In hypothyroid patients (overt and sub clinical), the prevalence is 20.0% to 33.0% and 33.0% to 43.0% for anxiety disorder and depressive disorder respectively. The prevalence is also as high as 53.0% to 69.0% for anxiety and 30.0% to 70.0% for depressive symptoms in hyperthyroidism³³. When looking at the subtypes of anxiety, it was found that the prevalence of panic disorder ranged from 5.0%-45.6%, social phobia from 7.4-8.7%, OCD 7.4% and GAD 41.2%³¹⁻³².

Autoimmune Thyroid Disorder and Depression and Anxiety

Autoimmune Thyroid Disease or Disorder (AITD) is a term that includes the various clinical forms of autoimmune thyroiditis, such as the classical Hashimoto's thyroiditis, Grave's disease and primary myxedema. An almost invariable feature of AITD is the production of antibodies to at least one of the main thyroid specific autoantigen i.e. thyroglobulin (Tg), the main protein of the colloid; thyroperoxidase (TPO), the enzyme that catalyzes iodine organification, and the receptor for the thyrotropin (TSH-R)³⁴.

AITD is an autoimmune process characterized by the lymphocytic infiltration of the thyroid gland and by the presence of autoantibodies against the thyroid antigens³⁵. Results of FNAC as well as results of autopsy show that up to 40% of women have AITD evident by lymphocytic infiltration of the thyroid gland³⁵. Assessment of thyroid antibodies in peripheral circulation shows that the prevalence of AITD is 13.9% to 17.0% in the female population^{6, 35-37}.

In clinical practice, a diagnosis of AITD is usually based on the presence of thyroid antibodies in serum. However, this approach could miss some patients with AITD because not all AITD patients are positive for thyroid antibodies in peripheral circulation, including those with thyroid dysfunction³⁶.

An association between mood disorder and thyroid immunity had been demonstrated in community samples, psychiatric patients as well as primary care patients³⁶⁻⁴⁰.

Fountoulakis et al⁴⁰ found a link between autoimmune thyroid disease and unipolar depression where in the study, compared to control patients, all depressive subtypes had significantly higher thyroid binding inhibitory immunoglobulin and higher thyroid microsomal antibodies. A community study by Pop et al⁴¹ concluded that women with elevated TPO-Ab levels are especially vulnerable to depression.

As for the anxiety disorder, the association also been shown by several studies^{37, 42}. A recent study found that a general population of women with AITD, diagnosed by hypoechoic thyroid pattern and by presence of thyroid antibodies in serum, showed higher scores of anxiety independently from their thyroid function³⁶. Furthermore, several studies provide evidence that autoimmune thyroid process per se may be related to mood and anxiety disorders^{36-37, 42} and the presence of autoantibodies itself may produce abnormal behavior even in euthyroid states⁴³⁻⁴⁵.

The possible explanations are described as follow:

1. The effects of psychological stress on the dysregulation of the immune system. Since several neuroendocrine secretory systems are involved in the control of immune reaction, a common neuroendocrine dysregulation involving cytokines might concur towards the pathogenesis of both affective disorders and autoimmune disease. Recent evidence suggests that thyroid autoimmunity may be affected by HPA axis through the balance of proinflammatory and anti-inflammatory cytokines⁴⁶.

2. The effects of the autoimmune disease to the central nervous system. Involvement of thyroid immunity in brain functioning was reported by several neuroimaging studies, demonstrating a higher prevalence of brain perfusion abnormalities in euthyroid patients with autoimmune thyroiditis and higher levels of anxiety and depression in these patients³⁶⁻⁴⁷. The brain perfusion abnormalities are similar to those observed in Hashimoto's encephalopathy and may suggest a higher than expected involvement of the brain in AITD⁴⁸.

Conclusion

Depression and anxiety are the most common psychiatric presentation in thyroid disorders. However the causal relationship for this association remains unclear.

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