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DIAGNOSTIC STRATEGIES FOR SUBCLINICAL HYPOTHYROIDISM

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ABSTRACT

The aim of this study is to delineate laboratory diagnostic strategies for subclinical hypothyroidism in patients who are clinically symptomatic but may have a normal thyroid profile. Tri – iodothyronine (T_3), thyroxine (T_4), thyroid stimulating hormone (TSH) and anti thyroid peroxidase antibodies (anti-TPO) were estimated on fasting blood samples from 99 patients using electrochemiluminescence methods on ELECSYS 1010 (Roche). 74 % of study subjects had elevated anti-TPO levels.61 % patients had subclinical hypothyroidism. 45 of the 61 subclinical hypothyroid patients had elevated anti-TPO levels (73%). This is an important finding suggesting an autoimmune etiology for subclinical thyroid dysfunction with a higher risk of developing overt hypothyroidism.

KEY WORDS

Hypothyroidism, Thyroid Profile, T_3, T_4, TSH, Anti TPO.

INTRODUCTION

Diseases of the thyroid gland are among the most abundant disorders worldwide second only to diabetes. While signs and symptoms of overt hyper and hypothyroidism are well known, subclinical thyroid conditions have subtle clinical manifestations and may mimic other diseases. Hence it is important to develop rational laboratory strategies to differentiate the various conditions to guide the physician towards correct diagnosis and treatment (1).

In the last decade, the diagnostic strategy for using TSH measurements in delineating thyroid status has changed as a result of the sensitivity improvements in these assays. Currently, immunometric assays are available on a variety of automated immunoanalyser platforms. These are the third generation assays with a functional sensitivity of 0.01mIU/L. Laboratories in several countries including India now employ such assays. WHO recommends the use of sensitive TSH assays as the first line in the assessment of thyroid function as well as free T_4, free T_3 and anti-TPO antibodies for differential diagnosis of thyroid diseases. The algorithms recommended by WHO are presented in Fig 1 and Fig 2 (1).

TSH assays are essential for diagnosing subclinical hypothyroidism which is defined by an isolated elevated serum TSH level in the setting of normal serum T_4 level, in the presence or absence of symptoms. Controversy prevails on the levels of TSH in subclinical hypothyroid patients. The worldwide prevalence of subclinical hypothyroidism ranges from 1% to 10%; the highest age and sex specific rates are in woman over 60 years, approaching to 20% (2,3). Using the TSH of 5 mIU/L as a bottom cutoff, the prevalence of subclinical hypothyroidism has been estimated to be about 8% in women and 4% in men, which might be higher with age above 60 years (8).

Most practitioners believe that such patients should be treated because treatment can prevent further worsening of the hypothyroidism as well as elevation of the TSH and may help eliminate symptoms. Subclinical hypothyroidism is usually due to autoimmune thyroiditis and is typically associated with detectable anti-thyroid peroxidase antibodies (anti-TPO). Subclinical hypothyroidism most commonly results from Hashimoto's thyroiditis but may also be seen following post-partum thyroiditis. Subclinical hypothyroid patients with elevated anti-TPO have higher conversion to overt hypothyroidism than those without and hence it is recommended that anti-TPO measurement should be an integral part of the investigation of subclinical hypothyroidism.

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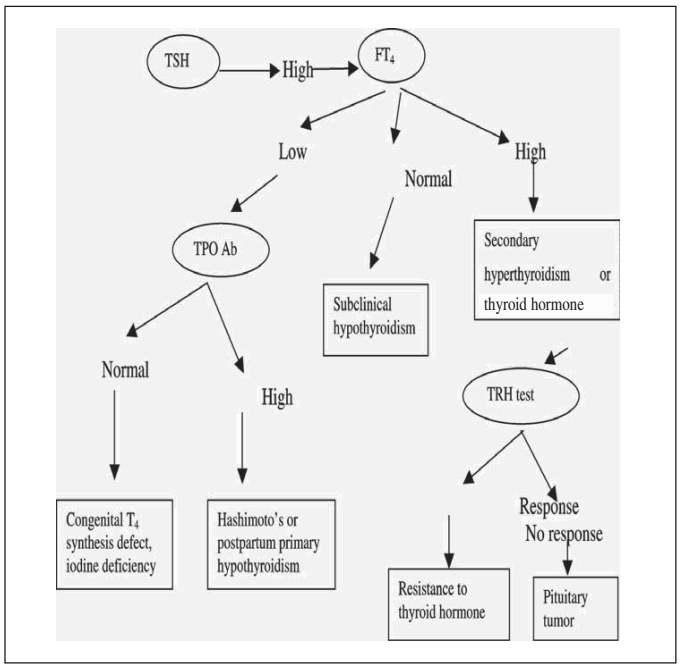

Fig 1 : Diagnostic strategy with increased serum TSH. Ovals indicate measurements & boxes suggest diagnosis (Source : WHO document WHO/00.4)

Algorithms for the diagnosis and management of subclinical hypothyroidism have been developed and widely followed.

Since the patients with subclinical hypothyroidism develop overt hypothyroidism at the rate of 5% per year (3, 9), it is important to identify these patients at risk. Although treatment of patients with subclinical hypothyroidism is still a matter of debate, it is generally accepted to treat such patients, because treatment can prevent progression to hypothyroidism and restores normal levels of TSH, may prevent growth of goiter and may help eliminate symptoms and prevent cardiac complications (2, 7).

While prevalence of subclinical hypothyroidism in the western population has been adequately reported in the literature, there are scarce reports published in Indian population(10, 11). A pilot study was undertaken recently to evaluate the incidence of subclinical hypothyroidism among patients attending the outpatient clinic of Medicine, ENT and Neurology at Kamineni Institute of Medical Sciences, Narketpally, A.P, especially with reference to both TSH and anti-TPO levels.

MATERIALS AND METHODS

Ninety-nine patients who were clinically diagnosed with hypothyroidism and subjected to a thyroid profile test were included in the study. The group included both males and females, attending the outpatient department of Medicine, ENT and Neurology at Kamineni Institute of Medical Sciences, Narketpally, A.P. Patients presented with one or more of the following symptoms such as generalized weakness, persistent headache, hoarseness of voice, gain in weight, excessive hair fall and skin complaints. Those already on thyroid replacement therapy were excluded from the study. Clinical examination as well as thyroid function tests was conducted and the thyroid status categorized. Twenty-five age and sex matched controls were taken from clinically and biochemically established euthyroid persons who enrolled for a general health check up in this hospital to ensure that their values were well within the established reference ranges . T_3, T_4, TSH and anti TPO were estimated using electrochemiluminescence method on ELECSYS 1010 (Roche) The reference ranges for our population was primarily established as in the literature mentioned in the kit inserts.. These are 0.3 – 4.0mIU/L, 0.7 – 1.84 ng /ml, 4.2 –12 µgm/dl, and upto 34 IU /L, for T_3, T_4, TSH and anti-TPO, respectively.

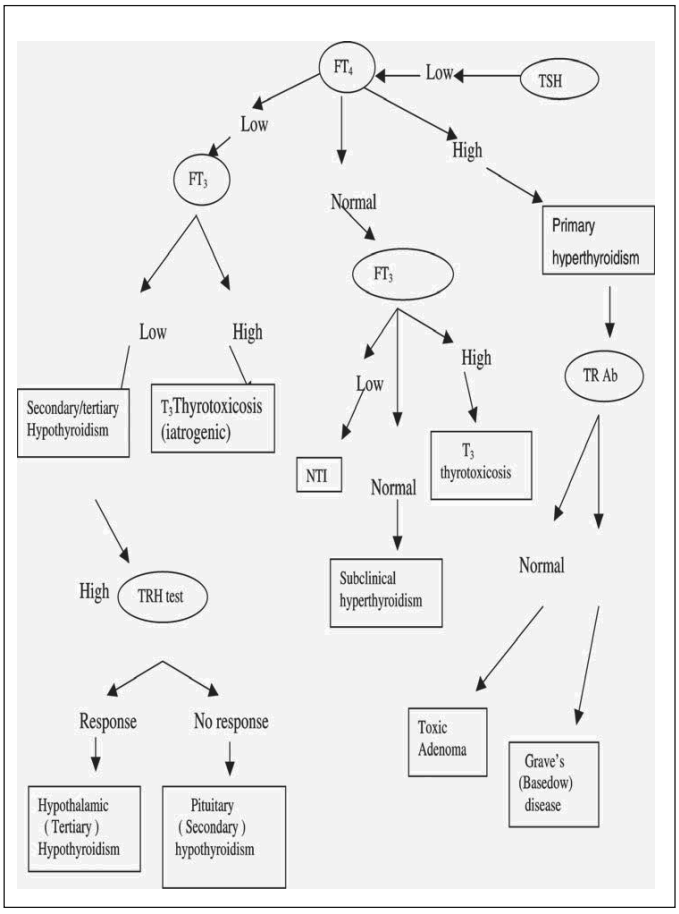

Fig 2 : Diagnostic strategy with decreased serum TSH. Ovals indicate measurements & boxes suggest diagnosis (Source : WHO document WHO/00.4)

RESULTS AND DISCUSSION

The serum levels of TSH, T_3, T_4 and ATPO in the control euthyroid group are shown in Table I. Table II shows the ATPO and TSH values in patients with hypothyroidism. In the majority of the clinical sub groups of patients presented in Table II , either ATPO or TSH were several fold elevated when compared to the mean value of controls. The present study demonstrates that 74 % of study subjects had elevated anti-TPO levels. The prevalence of subclinical hypothyroidism was 61% in the same group. Among the 38 frank hypothyroid patients, 76 % had raised anti-TPO, indicating an autoimmune etiology. Importantly, 45 of the 61 subclinical hypothyroid patients also had elevated anti-TPO (73%). This is a crucial finding suggesting to the clinician to initiate treatment in these patients as raised anti-TPO identifies an autoimmune etiology for thyroid dysfunction and would predict a higher risk of developing overt hypothyroidism (7). In the present scenario of the post –iodination status in India, the high prevalence of subclinical hypothyroidism is significant as similar findings were reported from other countries stating hypothyroidism is more prevalent and marked in subjects consuming excessive amounts of iodine. Excessive iodine intake should be considered an etiology of hypothyroidism in addition to chronic thyroiditis in these areas (12-15).

Table I : Serum levels of TSH, T_3, T_4 and antithyroid peroxidase (Anti-TPO) antibodies in controls (n = 25)

Parameter	Mean ± SD
TSH (mIU/L)	2.32 ± 1.20
T3 (ng/ml)	1.62 ± 0 .58
T4 (μgm/dl)	9.35± 4.2
Anti thyroid peroxidase antibodies (IU/L)	19.83± 3.58

The data suggest that the incidence of elevated anti-TPO cannot be directly correlated with different levels of TSH. While 26 subclinical hypothyroid patients had TSH in the 5-10 mIU/L range (mild elevation), they all had elevated anti-TPO. Whereas 16 subclinical hypothyroid patients with TSH in the 5-10 mIU/L range had normal anti-TPO; likewise, 19 subclinical hypothyroid patients with normal TSH had very high anti-TPO (62 – 600 IU/L). In the 16 subclinical hypothyroid patients with TSH level 5 – 10 mIU/L range, other causes for such elevation in TSH such as pituitary tumor, non-thyroid illnesses and untreated Addison's disease have been ruled out (4,6). Even in patients with normal TSH, subclinical hypothyroidism can exist as indicated by raised anti-TPO. Hence one would overlook the detection of subclinical hypothyroidism in such patients if anti-TPO analysis were not to be carried out.

The significant conclusion from this study is that both serum TSH and anti-TPO analyses are essential in determining thyroid status particularly for the diagnosis of patients suspected with subclinical hypothyroidism. Estimation of only TSH would overlook the diagnosis of quite a significant percentage of subclinical hypothyroid patients.

Table II : Serum levels of TSH and ATPO in patients of hypothyroidism (n = 99)

Clinical status	n	ATPO (IU/L) Mean ± SD	TSH (mIU/L) Mean ± S.D
Frank hypothyroidism with elevated ATPO and TSH	29	411.8 ± 194.7	52.41 ± 48.29
Frank hypothyroidism with elevated TSH	09	18.6 ± 2.4	35.34 ± 23.2
Subclinical hypothyroidism (Elevated ATPO and TSH)	26	359± 234	8.6± 3.6
Subclinical hypothyroidism (Elevated TSH)	16	18.8 ± 2.40	6.4± 2.2
Subclinical hypothyroidism (Elevated ATPO)	19	269.19 ± 245.68	2.61± 1.43

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