Asian Journal of Research in Medical and Pharmaceutical Sciences

1(2): 1-7, 2017; Article no.AJRIMPS.35476

Evaluation of Thyroid and Thyroid Stimulating Hormone Status to the Diagnosis of Differential Thyrotoxicosis

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Authors' contributions

This work was carried out in collaboration between all authors. Author MMH designed the study, performed the statistical analysis and wrote the first draft of the manuscript. Author MAM collect the necessary data and managed the literature. Author MRI provided the lab facilities. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJRIMPS/2017/35476
Editor(s):
(1) Davina Hijam, Department of Biochemistry Regional Institute of Medical Sciences, India.
Reviewers:
(1) Liudmila Ivanova, Kuban State Medical University, Russia.
(2) Sembol Yildirmak, Giresun University Medical Faculty, Turkey.
Complete Peer review History: http://www.sciencedomain.org/review-history/20586

Received 14th July 2017
Accepted 7th August 2017
Published 21st August 2017

Original Research Article

ABSTRACT

Aims/ Objectives: To study the thyroid and thyroid stimulating hormone levels of clinical and subclinical thyrotoxicosis patients.
Study Design: Cross-sectional study.
Place and Duration of Study: Institute of Nuclear Medicine and Allied Sciences (INMAS), Rajshahi Medical College Hospital, Rajshahi, between May 2013 and April 2014.
Methodology: In total, 239 assays are performed in 83 thyrotoxicosis patients. Biochemical confirmation of thyrotoxicosis is based on the finding of a suppressed TSH in combination with elevated serum total or free T4 and T3 levels. The serum TSH was measured using standard immunoradiometric assay technique whereas serum T4 and T3 by the method of radioimmunoassay.

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Results: The present study observes that the most common cause of thyrotoxicosis is Graves' disease, followed by thyroiditis, toxic adenoma, and multinodular goiter. The Graves' disease is found to be approximately 2.5 times more common in women than in men. It is also noticeable that majority of the patients with Graves' disease are predominantly in the younger age groups.
Conclusion: The present results produce fairly a good agreement with the reported data and, therefore, will provide a guideline for the diagnosis and management of clinical and subclinical thyrotoxicosis.

Keywords: Thyr oid hormone; Thyroid stimulating hormone; Thyrotoxicosis; Immunoradiometric assay; Radioimmunoassay.

1 INTRODUCTION

Disorders of the thyroid gland are among the most common endocrine maladies. Thyroid diseases manifest mainly by qualitative or quantitative alteration in hormone secretion. Biologically active two principal thyroid hormones are thyroxine (T4) and triiodothyronine (T3) covering, respectively 99.9% and 0.1% of the total secretion. Symptoms of thyroid disorders are due to the overproduction or underproduction of thyroid hormone, which may occur from disease of the thyroid gland itself [1] or from disease of the pituitary and hypothalamus [2]. Autoimmune disease and infection of the thyroid gland, competitive drug reactions, can all culminate in thyroid dysfunction. All the syndromes resulting excess quantities of thyroid hormones are termed as thyrotoxicosis. Thyrotoxicosis and hyperthyroidism are often termed as being the same; however, there are some differences between them. The term thyrotoxicosis refers to all causes of elevate thyroid hormones, whereas the term hyperthyroidism refers secretion of excessive amounts of thyroid hormones by the thyroid gland [3, 4, 5]. This means that hyperthyroidism is one of the thyrotoxicosis but some cases of thyrotoxicosis are not related to the thyroid (e.g. ectopic T4 production).

Thyrotoxicosis is not an uncommon disease, affecting about 2% of women and 0.2% of men [6]. The most common cause of thyrotoxicosis is Graves' disease (GD) [7, 8] followed by toxic multinodular goiter (MNG), solitary toxic adenoma (TA) and thyroiditis (TD). The other less common causes include thyroid stimulating hormone (TSH) secreting pituitary adenoma, struma ovarii, metastatic functional differentiated thyroid cancer and metastatic tumors within the thyroid gland causing destruction induced thyrotoxicosis. It is well known that Graves' disease is rare in children, but the frequency increases to a peak in the fourth decade, thereafter declining. MNG, on the other hand, is commoner in older women [9, 10], with a longstanding previous MNG in which one of the nodules attains functional autonomy.

The correct management of thyroid diseases depends on accurate diagnosis, appropriate treatment and careful monitoring [11]. Thyroid disorders can be difficult to detect clinically, but thyroid function tests can assist in making a diagnosis. There are various modalities currently available for testing thyroid function. Antibody (serum TSH, T4, T3, fT4, fT3) assay is one of the most important tools in testing thyroid condition. Presently, thyroid testing is performed on serum specimens using either manual or automated methods employing specific antibodies. Methodology is still evolving as performance standards are established by the professional organizations and new technology and instruments are developed by manufacturers. Encouraged by our recent measurements [12, 13], we, in the present study, have measured serum TSH with a highly sensitive immunoradiometric assay (IRMA) kits whereas T4 and T3 with commercially available radioimmunoassay (RIA) kits, both are supplied by Beijing Atom Hightech Co. Ltd., Beijing. The present results are compared with other experimental data available in literature.

The rest of the paper is organized as follows. Section 2 outlines the materials and method. Section 3 includes the present results. In section 4, we discuss and compare our results with reported data. Section 5 concludes our findings with a brief summary.

2 MATERIALS AND METHODS

2.1 Sample Patients

The present study was conducted at the Institute of Nuclear Medicine and Allied Sciences (INMAS), Rajshahi affiliated with the Bangladesh Atomic Energy Commission (BAEC). The study protocol was approved by the Ethics Committee of the Nuclear Safety and Radiation Control Division, BAEC. In total, 239 assays were performed in 83 thyrotoxicosis patients referred to the RIA laboratory of the INMAS, Rajshahi for serum T4, T3 and TSH tests. Among the individuals 58 were women and 25 men, with ages ranging from 7 to 65 years. According to age, the total study subjects were classified into four groups: Children ($Y < 20$ years), young ($20 \geq Y \geq 40$ years), adult ($40 > Y \geq 50$ years) and old ($Y > 50$ years).

2.2 Collection of Blood Sample

The blood samples (4-6 ml), from each patient after a 12-hrs fasting, were collected through disposable syringes. The samples were transferred into properly labeled sterilized test tubes and were left for 60 minutes at room temperature for coagulation. The coagulated blood samples were then centrifuged at 3500 rpm for 20 minutes. Serum were separated and transferred into sterile plastic tubes that are approximately labeled for the required test, and the date of sample collection.

2.3 Serum Assay

In the present study, the serum TSH was estimated by a standard IRMA method using BF003/BF028 Immuunoradiomatricassy Kits whereas serum T4 and T3 were analyzed by RIA method, respectively, using BF002 and BF001 Radioimmunoassay kits, supplied by Beijing North Institute of Biotechnology Co. Ltd., Beijing. All the kits were provided with standards, tracer antibody in case of T4 and T3, antibody coated tubes in case of TSH. Assay tubes were labeled as standards, non-specific binding, total count, patient samples and quality control in duplicate. A Gamma counter Model LB 2111 NaI borehole-type scintillation detector manufactured by BERTHOLD TECHNOLOGIES, Germany was used for counting the assay tubes. Finally, hormone concentrations were measured using 4-parameter computer programs with LBIS immunoassay software package.

3 RESULTS

The results of serum T3, T4 and TSH measured in the present study were presented in Table 1. The observed range of T3, T4 and TSH were 2-12 nmol/L, 111-309 nmol/L and 0.05-0.35 mIU/L, respectively. The mean (SD) of serum T3, T4 and TSH found to this study were, respectively, 8 ± 3 nmol/L, 253 ± 49 nmol/L and 0.17 ± 0.07 mIU/L.

Table 2 represents the sex wise diseases characteristics of the studied samples. It is evident that the most common classification reached on the basis of serum measurement are Graves' disease (64%), followed by thyroiditis (20%), toxic adenoma (9%), and multinodular goiter (2%). The pattern is, however, inconclusive in 5% of all patients. Serum T3, T4 and TSH patterns were further analyzed stratifying the patients into two subgroups: clinical and subclinical. The sample distribution for both of these two subgroups was depicted in Fig. 1. The classification indicates that about 88% of the studied samples were in clinical pattern and only 12% were in subclinical.

Table 1. Serum levels of T3, T4 and TSH of the studied samples (n = 83)

Serum	Range	Mean	Standard deviation
T3 (nmol/L)	2 – 12	8	± 3
T4 (nmol/L)	111 - 309	253	± 49
TSH (mIU/L)	0.05 – 0.35	0.17	± 0.07

Table 2. Sex wise disease characteristics of the sample population

Diseases	Female		Male	
	Number	(%)	Number	(%)
GD	37	45	16	19
TD	12	14	5	6
TA	3	4	4	5
MNG	2	2	0	0
Inclusive	4	5	0	0
Total	58	70	25	30

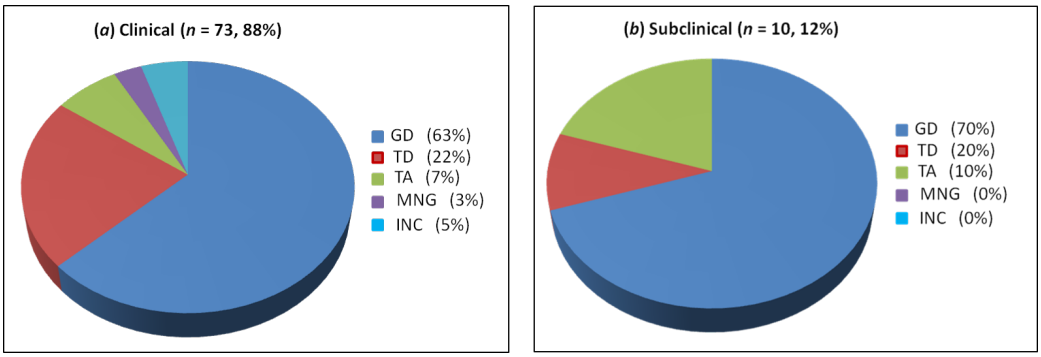

Fig. 1. Disease characteristic of (a) clinical and (b) subclinical thyrotoxicosis patients

The great majority of the samples in clinical group are also Graves' disease (63%) followed by thyroiditis (22%), toxic adenoma (7%) and multinodular goiter (3%). This pattern is inclusive in 5% of all the patients. Subclinical thyrotoxicosis is characterized by partially suppressed serum levels of TSH associated with normal values of T4 and T3 concentrations. It

is evident that there is no inclusive, and the majority patients in this pattern are classified as Graves' disease (70%), thyroiditis (10%) and toxic adenoma (20%).

TSH assay is very much sensitive to detect even subtle thyroid dysfunction [14, 15]. Measurement of serum TSH concentration is, therefore, is the most useful single laboratory test in the initial evaluation of thyroid disorders specially thyrotoxicosis. Fig. 2 stratifies all 73 clinical thyrotoxicosis patients into two subcategories according to their TSH serum levels: (a) $\lesssim$ 0.1 mIU/L (n = 21) and (b) $>$0.1 mIU/L (n = 52). The majority of the patients with TSH $\lesssim$ 0.1 mIU/L are Graves' disease (76%) followed by thyroiditis (19%) and inclusive (5%). In patients with TSH $>$0.1 mIU/L, the Graves' disease is also the most frequent finding (56%), followed by thyroiditis (23%), toxic adenoma (11%), multinodular goiter (4%) and inclusive (6%).

4 DISCUSSION

It has been reported by several authors that the most common cause of both clinical and subclinical thyrotoxicosis is Graves' disease, which accounts for approximately 60% to 80% cases of hyperthyroidism in the United States and in other countries where the population has adequate iodine intake [3, 4, 5, 16]. The great majority of our studied patients are also Graves' disease (64%), which is fairly in good agreement with the reported data.

As reported previously, Graves' disease is approximately 5 to 10 times more common in women than in men; the incidence is similar among Caucasian and Asian population, but lower among African Americans [16, 17]. The present study shows that the thyrotoxicosis patients developing Graves' disease are about 70% female, which is about 2.5 times the male (see Table 2). This result is significantly lower than the reported values. This may be argued that our investigated region, Rajshahi is an iodine deficient zone in Bangladesh. Laurberg *et al*. [18] reported that iodine-deficient populations have a much lower incidence of Graves' disease.

It is also well known that patients younger than age 40 years are at the highest risk for the development of Graves' disease [19]. In the present study, about 74% of the patients with Graves' disease are within the age limit from 20 to 40 years, and about 91% are within 20-50 years (see Table 3). It is very clear from this scenario that the patients with Graves' disease are predominantly in the younger age groups, while those with toxic adenoma and multinodular goiters are in the older range. The mean$\pm$SD age of the present study subjects is 35$\pm$12 years, which is significantly lower than that reported by Alsharif *et al*. [20] as 42.4$\pm$15.6 years, Ajoke [21] as 44$\pm$13.6 years and Ikekubo *et al*. [22] as 40$\pm$15 years.

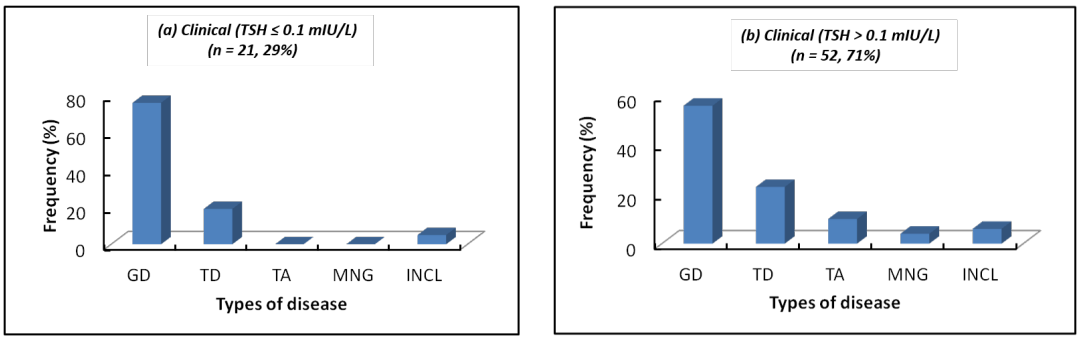

Fig. 2. Clinical thyrotoxicosis into two subcategories with serum TSH (a) $\lesssim$ 0.1 mIU/L and (b) $>$0.1 mIU/L

Table 3. Age wise disease characteristics of the sample population

Diseases	Age (years)			
	Y < 20	20 ≤ Y ≤ 40	40 < Y ≤ 50	Y > 50
GD	4	39	9	1
TD	1	3	2	1
TA	2	8	4	3
MNG	0	0	1	1
Inclusive	0	3	1	0
Total (%)	7	53	17	6

5 CONCLUSIONS

In this paper, we report our experience regarding the contribution of serum TSH, T4 and T3 measurement to the diagnosis of clinical and subclinical thyrotoxicosis. The study consisted of total 83 samples, among them 70% are female and 30% are male. In total, 239 assays are performed applying standard IRMA and RIA methods. Present study shows that the most common cause of thyrotoxicosis is Graves' disease (64%). As most of the patients are younger aged they are at higher risk. Especially, the women, because the Graves' disease is approximately 2.5 times more common in them. Our observations are also compared with the reported data and found to be fairly in good agreement in some cases. We, therefore, expect that the present study will contribute some useful data in literature and provide a guideline for the diagnosis and management of differential thyrotoxicosis.

ACKNOWLEDGEMENT

M. M. Haque thanks Faculty of Science, University of Rajshahi for partial supports through project no-A-31-5/52/UGC/Science-8/2015-16.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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