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Ophthalmic manifestations of thyroid disease and the association of serum levels of T_3, T_4 and TSH with thyroid eye disease

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Abstract
Introduction: Thyroid-associated orbitopathy (TAO) frequently termed Graves ophthalmopathy is part of an autoimmune process that can affect the orbital and periorbital tissue, the thyroid gland and rarely the pretibial skin or digits (Thyroid acropachy).
Material and Methods: This is a prospective and observational study conducted at Department of Endocrinology. The patients included in the study their demographic data was recorded along with the serum levels of T3, T4, TSH at the time of diagnosis and examination. All the patients detailed ocular examination was carried out with the help of torch light, and slit lamp for anterior segment evaluation, direct ophthalmoscopy for posterior segment evaluation, indirect ophthalmoscopy whenever necessary.
Result: A total of 60 patients were examined. Of the 60 cases, male preponderance was noted. The highest incidence of thyroid orbitopathy, the patients were arbitrarily divided into four groups and least one less than 20 years of age group. Among 60 patients, 11 (18.3%) were hypothyroid, 46 (76.6%) were hyperthyroid, and 3 (5%) patients were euthyroid. The frequency of different symptoms among the study group. Most of the patients came with complaint itching of (31.6%). The second most common symptom was foreign body sensation (23.3%).
Conclusion: We recommend to ophthalmologists to be aware of TED clinical signs and suspect it even if the patients have a normal thyroid function. The assessment for these patients should be based on orbital images, serum T_3, free T_4, TSH, TRAbs, and interdisciplinary management with the endocrinologist.

Keywords: Thyroid disease, hypothyroidism, euthyroidism and hyperthyroidism

Introduction

Thyroid disease (TD) is a quite common condition worldwide. According to hormonal levels, the patients with TD can be classified into three different groups: hypothyroidism, euthyroidism, and hyperthyroidism [1]. Euthyroidism is defined as normal thyroid hormone production and serum levels [2]. Hyperthyroidism is a clinical condition in which thyroid hormones are synthesized excessively. It is seen more frequently in women and adulthood. The clinical manifestations usually involve several systems, for example, weight loss can be evidenced despite no appetite disturbance, limb tremor, tachycardia, and tachypnea [3]. On the contrary, hypothyroidism is the condition in which thyroid hormones are deficient. It occurs more frequently in women over 65 years of age and it is commonly seen in patients with autoimmune diseases, such as type 1 diabetes mellitus and celiac disease, among others. The clinical manifestations are usually weight gain, fatigue, and cold intolerance [4].

Thyroid eye disease (TED) is an autoimmune disorder of the orbital retrobulbar tissue associated with dysthyroidism, mainly hyperthyroidism in Graves' disease (GD), even though it is present in hypothyroid and euthyroid patients [5]. The prevalence of dysthyroidism in patients with TED has been previously evaluated; however, there is no consensus on a global prevalence, and the physiopathological effect of thyroid hormones on the onset and progression of TED has not been fully understood [6].

The thyroid-stimulating hormone receptor (TSHr) and insulin-like growth factor 1 (IGF-1) receptor on orbital fibroblasts are likely to be the most important autoimmune targets in the disease. It has been hypothesized that clinical phenotypes such as euthyroid or hypothyroid TED, or the predominance of muscle or fat enlargement, may be caused by the molecular signature of different anti-thyrotropin-receptor antibodies [7].

Also, previous studies had concluded that dysthyroidism (Hyperthyroidism or hypothyroidism) is associated with more severe presentations of TED, recommending the assessment of thyroid function during antithyroid treatment and the management of TED [8].

Materials and Methods

Study Design: This is a prospective and observational study conducted at Department of Endocrinology.

Inclusion criteria: All the Age groups with either gender subjects who were diagnosed with thyroid disease or those thyroid eye diseases with euthyroid status with thyroid hormone profile at the time of diagnosis and at the time of examination visiting Endocrinology OPD, and who gave consent for this study are included.

Exclusion criteria: Patients without thyroid hormone profile or those who didn't give consent are not included in this study. Patients with thyroid disease and with age less than 10-year-old were excluded from the study.

Sampling Method

The patients included in the study their demographic data was recorded along with the serum levels of T_3, T_4, TSH at the time of diagnosis and examination.

Statistical analysis: Then data was entered on SPSS software and analysed by using chi square test and one way annova test was used to establish the significance of serum levels of T_3, T_4, TSH at the time of study and Pre T_3, Pre T_4 and Pre TSH at the time of diagnosis of thyroid disease with the severity and the frequency of thyroid eye disease signs.

Results

A total of 60 patients were examined. Of the 60 cases, male preponderance was noted as shown in table 1.

Table 1: Sex distribution of patients

Sex	No. of patients	Percentage
Male	23	38.3
Female	37	61.6
Total	60	100

Table 2: Age distribution of patients

Age group	No. of patients	Percentage
<20	2	3.3
21-40	19	31.6
41-60	31	51.6
>61	8	13.3
Total	60	100

According to table 2, 41-60 years age group had the highest incidence of thyroid orbitopathy, the patients were arbitrarily divided into four groups and least one less than 20 years of age group.

Table 3: Ocular manifestations

Thyroid status	No. of patients	Percentage
Hypothyroid	11	18.3
Hyperthyroid	46	76.6
Euthyroid	3	5.0
Total	70	100

In table 3, among 60 patients, 11 (18.3%) were hypothyroid, 46 (76.6%) were hyperthyroid, and 3 (5%) patients were euthyroid.

Table 4: Severity of Thyroid-associated ophthalmopathy

Severity of TAO	No. of patients	Percentage
Mild	44	73.3
Moderate	13	21.6
Severe	3	5.0
Total	60	100

Table 5: Symptoms of thyroid eye disease patients

Sign	No. of patients	Percentage
Itching	19	31.6
Foreign body sensation	14	23.3
Dry eye	8	13.3
Lid swelling	6	10
Redness	5	8.3
Difficulty in reading	4	6.6
Protrusion of eye	2	3.3
Diminution of vision	1	1.6
Watering	1	1.6

In table 5 shows the frequency of different symptoms among the study group. Most of the patients came with complaint itching of (31.6%). The second most common symptom was foreign body sensation (23.3%).

Discussions

Thyroid function measurement is made from the level of hormones produced by the thyroid gland and the hormone that stimulates its production. The normal thyroid function is called euthyroidism, described by the American Thyroid Association as a normal range between 0.4 and 4.0 mU/L for thyroid-stimulating hormone (TSH) [9]. On the other hand, hyperthyroidism presents elevated free thyroxine (T_4) and triiodothyronine (T_3) and decreased TSH serum levels (0.0–0.4 mU/L) [10]. Besides, hypothyroidism is diagnosed with elevated serum concentration of TSH (Above 4.0 mU/L) and decreased free T_4 levels [11].

TED is the most common autoimmune disease of the orbit. The disease appears two to six times more frequent in young women, but severe cases occur more frequently in men older than 50 years [12]. In TED´s physiopathology, the orbit becomes infiltrated by B and T cells, activating genes involved in inflammation and tissue remodeling [13]. Orbital fat and extraocular muscles expand from accumulating hyaluronidase-digestible material and adipogenesis. These events are mediated by interleukins 1β, 6, 8, and 16; tumor necrosis factor α (TNF-α); RANTES (regulated on activation, normal T cell expressed and secreted); and CD40 ligand. The action of these cytokines turns bone marrow-derived fibrocytes into CD34+ fibroblasts that further differentiate into myofibroblasts or adipocytes [14].

The CD34+ fibroblasts express low levels of TSHr and other thyroid antigen receptors and overexpress IGF-1 receptors [15]. Thyroid-stimulating immune globulins activate the IGF-1 receptor complex, leading to the expression of inflammatory molecules and glycosaminoglycan synthesis; This signaling can also be activated in adipocytes [16]. Clinical manifestations of TED mainly include eyelid retraction (90%), exophthalmos (62%), restricted extraocular motility (43%), eye pain (30%), tearing (21%), diplopia (17%), photophobia (16%),

blurred vision (8%), and optic nerve dysfunction (6%) [17]. Patients with euthyroid/hypothyroid TED developed significantly less severe ocular symptoms, less active, and more asymmetrical disease than hyperthyroid patients [18].

TED management starts with the control of environmental factors to decrease the risk of disease progression, such as smoking cessation. Local management of TED includes ocular lubrication, conjunctival autograft, or even orbital decompression in severe cases. The oral glucocorticoids are recommended to be administered as prophylaxis for mild active TED when treated with radioactive iodine in patients with GD. Intravenous glucocorticoids are the first line of treatment for moderate-to-severe and active TED. Options for disease maintenance are many and include orbital radiotherapy, selenium, cyclosporine, azathioprine, mycophenolate mofetil, tocilizumab, or rituximab [19]. Recently, a new pharmaceutic molecule was approved for TED, teprotumumab. This is a fully human monoclonal antibody that attenuates signaling initiated at the IGF-1 receptor complex blocking pathologic immune responses [20].

Conclusion

We recommend to ophthalmologists to be aware of TED clinical signs and suspect it even if the patients have a normal thyroid function. The assessment for these patients should be based on orbital images, serum T3, free T4, TSH, TRAbs, and interdisciplinary management with the endocrinologist.

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