ORIGINAL ARTICLE

Clinical spectrum and various forms of thyrotoxcosis in endocrine clinic of Jinnah Postgraduate Medical Centre

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Abstract

Objective: To evaluate clinical symptoms, signs and various forms of thyrotoxicosis, and to assess the thyroid function status at the first 6-week follow-up.

Methods: The retrospective chart review involved thyrotoxic patients presenting at the Endocrine Clinic of Jinnah Postgraduate Medical Centre, Karachi, between April 2007 and January 2011. All hyperthyroid patients were included with the exception of those with suspected or proven malignancy. The records were maintained on a structured proforma and analysed statistically to work out frequencies and percentages.

Results: A total of 507 patients were included. Most common form of thyrotoxicosis was Graves' disease, with diffuse toxic goiter affecting 269 (53%) patients; followed by toxic multinodular goiter in 102 (20.1%); solitary toxic nodule in 56 (11%); thyrotoxicosis without goiter in 44 (8.7%); subclinical hyperthyroidism in 22 (4.3.%); thyroiditis in 9 (1.8%); and thyrotoxicosis with solitary cold nodule in 4 (0.9%). The common presenting symptoms and signs were goiter (n=415; 85.7%), with eye signs present in 137 (27.7%) patients and heart failure in 20 (4.8%) patients. Of the 321 patients who attended the first six-week follow-up, 309 (94.4%) had their FT4 levels checked. Out of them, 130(42.1%) had euthyroid levels; 113 (36.6%) had lower but still toxic level; 36 (11.7%) had no change; and 30(9.7%) became hypothyroid. TSH levels at first follow-up remained suppressed in 211 (73%) patients; normal in 47(16.3%); and increased in 31 (10.7%).

Conclusions: Graves' disease was found to be the most common cause of hyperthyroidism. At first follow-up 10.4% of patients had become hypothyroid. Therefore the starting dose of antithyroid drugs was reduced in the clinic. Thyroid stimulating hormone assay was of little help in adjusting treatment at the 6-week follow-up, as almost all cases of hypothyroidism could have been picked up on FT4 assay alone.

Keywords: Thyrotoxicosis, Diffuse toxic goiter, Toxic MNG. (JPMA 63: 354; 2013)

Introduction

There are various causes of hyperthyroidism with different clinical presentations. As thyroid disorders are the second most common endocrinopathies after diabetes, evaluation of clinical aspects, and therapeutic and biochemical responses to antithyroid medications help physicians to better understand diagnostic and therapeutic issues in order to formulate appropriate and cost-effective treatment plans. Thyrotoxicosis can occur either as a result of excessive synthesis of thyroid hormone, eg. Graves' disease (GD), or leakage from damaged gland, eg. thyroiditis. In a survey done in the USA, hyperthyroidism was noted in 0.5% of randomly selected individuals, and an additional 0.8% had subclinical hyperthyroidism.[1]

Patients usually have fatigue, nervousness, weight loss, palpitations and heat intolerance. Clinical signs include warm moist skin, tremors and tachycardia. Elderly patients have less symptoms, including lower frequency of goiter and higher prevalence of cardiac features such as atrial fibrillation and congestive heart failure (CHF). About 15% of elderly individuals with new onset atrial fibrillation have thyrotoxicosis.[2,3]

This study was conducted to determine different forms of thyrotoxicosis presenting at our clinic, as determining the etiology is essential to decide the therapy. Thyroid function was also assessed at first follow-up (six weeks) so that management could be suitably modified.

Patients and methods

The retrospective chart analysis was conducted at the Endocrine Clinic, Medical Unit II, Jinnah Postgraduate Medical Centre, Karachi. Data related to 507 patients with thyrotoxicosis was recorded on a pre-designed structured questionnaire. All hyperthyroid patients presenting to the Endocrine Clinic were included in the study. The diagnosis of hyperthyroidism was based on clinical parameters, biochemical levels of FT3, FT4 and thyroid stimulating hormone (TSH) and thyroid imaging by scintigraphy and/or ultrasonography. Patients with clinically suspicious or fine needle aspiration cytology (FNAC) proven thyroid malignancy were excluded. On the basis of thyroid scan,

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they were classified as GD with diffuse toxic goiter, multimodular goiter (MNG), toxic nodule, thyrotoxic phase of thyroiditis, and thyrotoxicosis with cold nodule. In addition, frequency of presenting symptoms and signs were also studied such as palpitation, weight loss, tremors, heat intolerance, goiter, tachycardia and ophthalmopathy.

Patients were routinely reviewed at 6 weeks, regarding their thyroid function status and on the basis of their FT4 levels, classified as hypothyroid, euthyroid and hyperthyroid. TSH levels were also assessed at the first follow-up.

Results

Of the total of 507 patients, 406 (80.1%) were women, while 101 (19.9%) were men. The mean age was 35±12.2 years.

The most common form (n=269; 53%) of thyrotoxicosis was GD with diffuse toxic goiter, followed by toxic MNG (n=102; 20.1%) (Table-1). Some patients with thyrotoxicosis had no goiter (n=44; 8.7%). The common presenting symptom and sign was goiter (n=415; 85.7%) with heart failure in only 20 (4.8%) patients (Table-2). Besides, various grades of ophthalmopathy were seen in 137 (27.7%) patients. Ophthalmopathy was associated with diffuse goiter in 97 (71%) patients; MNG in 19 (14%); no goiter in 15 (11%); and solitary nodule in 6 (4.5%) patients.

Of the 321 patients who returned for follow-up at 6 weeks, on the basis of their FT4 levels, 135 (42%) had become euthyroid, with only 36 (11.2%) having had no change in their status, while 32 (10%) patients had become hypothyroid. TSH levels at first follow-up remained suppressed in majority of the patients (n=234; 73%) (Table-3).

Regarding the treatment offered, most patients were prescribed carbimazole (CBZ) in a dose of 30mg/day in 2 divided doses, whereas propylthiouracil (PTU) was given to a small number of patients in a dose of 300mg/day in 2 divided doses. Those patients who had subclinical hyperthyroidism or thyroiditis (thyrotoxic phase) did not require any anti-thyroid medication and were advised 3-month follow-up with thyroid function test. Radioactive iodine (RAI) ablation therapy was discussed with all patients, but accepted by only 12 (2.3%) as primary treatment; 10 of them had a toxic adenoma, and 2 had relapse of toxicosis. Large MNG with compressive symptoms was found in 2 (0.4%) patients and they were

Table-1: Diagnosis.

Diagnosis	n(%)
Diffuse Toxic	269 (53.1)
MNG	102 (20.1)
Solitary Toxic Nodule	56 (11)
Thyrotoxicosis without Goiter	44 (8.7)
Sub-clinical hyperthyroidism	22 (4.3)
Thyrotoxic Phase	9 (1.8)
Thyrotoxicosis with Solitary Cold Nodule	4 (0.9)
Diffuse Toxic With Thyroglossal Cyst	1 (0.2)

Table-2: Frequency of Symptoms & Signs.

Symptoms	n (%)
Goiter (n=485)*	415 (85.7)
Palpitation (n=503)*	416 (82.7)
Heat Intolerance (n=500)*	357 (71.4)
Tremor (n=498)	316 (63.5)
Muscular Weakness (n=487)*	293 (60.2)
Change In Weight (n=496)	
Wt Loss	339 (68.2)
Wt Gain	57 (11.7)
No Change	100 (20.2)
Change In Bowel (n=490)*	
Diarrhoea	6 (15.5)
Constipation	120 (24.5)
No Change	294 (60)
Signs	**n (%)**
Goiter Type (n=458)	
Diffuse	268 (58.5)
MNG	103 (22.5)
Solitary Nodule	60 (13.1)
No Goiter	27 (5.9)
Tachycardia (n=492)*	173 (35.2)
Eye Signs (n=494)*	137 (27.7)
Brisk Reflexes (n=411)*	66 (16.1)
Bruit (n=350)*	36 (10.3)
Heart Failure (n=417)*	20 (4.8)
Irregular Pulse (n=492)*	13 (2.6)

*Number of patients for each variable are different in accordance with the availability of data.

Table-3: Corelation of TSH and Thyroid Functional Status labelled according to FT4 levels.

TSH at 6 Weeks (n=289)	Euthyroid (n=130)	Improved but still Toxic (n=113)	No Change (n=36)	Hypo-Thyroid (n=30)
Decreased (n=211)	75	102	30	4
Normal (n=47)	38	4	2	3
Increased (n=31)	9	0	0	22
Not done (n=20)	8	7	4	1

TSH: Thyroid stimulating hormone.

referred for surgical intervention. ß blockers were advised in all symptomatic patients after excluding contra-indications.

Discussion

Thyrotoxicosis is characterised by elevated levels of thyroid hormones as a consequence of increased synthesis, secretion, release or over replacement of thyroxine, whereas hyperthyroidism is restricted to diseases in which there is excessive synthesis or secretion. In clinical practice both entities are used interchangeably.[4]

As expected, the study revealed predominance of female patients and GD, which favours autoimmunity as a leading cause for thyroid dysfunction, a finding also evident in other studies.[5-7] The mean age of GD in this study was 32.5 years, which is lower as compared to 40-60 years reported earlier.[5] Typical symptoms of hyperthyroidism are usually present in most patients with GD. They also have features related to immune system that are not seen in other forms. Opththalmopathy is generally defined as soft-tissue swelling around the orbit, protrusion of eyes and extraocular myopathy. Other manifestations include dermopathy, present in 1-2% of patients, affecting pretibial area, feet or areas of injury.[8] Thyroid acropachy noted in < 1 in 1000 patients[9] and other autoimmune events such as vitiligo, premature graying of hair and urticaria may be present.

Toxic MNG is characterised by at least two autonomously functioning nodules leading to features of hyperthyroidism.[10] Its cause is unknown, but mutations in individual cells leading to clonal expansion and autonomous thyroid treatment may contribute to it.[11] Toxic MNG tends to be more common in areas where iodine intake is relatively low.[12] This form of hyperthyroidism is treated with RAI in USA with similar cure rates as that of GD,[13] but higher doses of RAI may be required. Compressive symptoms are common when size is large, in which case near-total thyroidectomy is a preferred option after patients are rendered euthyroid. Pakistan is an area of iodine insufficiency and MNGs are common particularly in the northern areas.

Solitary toxic nodules usually grow to at least 3cm in size before producing overt hyperthyroidism.[14] In one study, it accounted for only 5% of hyperthyroidism.[4] However, in our cohort a slightly higher percentage (11%) was recorded. RAI ablation therapy is the preferred treatment and, unlike GD, post-ablative hypothyroidism is less likely as the contralateral suppressed gland does not take up RAI.[1]

Thyroiditis is characterised by inflammation secondary to autoimmune phenomenon, infection or toxic agent, which leads to the death of follicular cells by affecting apoptotic pathways and eventually release of hormonal stores. During thyrotoxic phase, β-blockers may be required and when hypothyroid state ensues, thyroxine may be needed.

In the current study, subclinical hyperthyroidism was seen in 4.3% using TSH cut-off of 0.4mIU/L, which is slightly higher compared to a study which showed a prevalence of 3.2% using a cut-off of 0.4mIU/L and 0.7% using TSH cut-off of 0.1mIU/L.

In our patients, majority presented with goiter and palpitation followed by heat intolerance, weight loss, tremors, muscular weakness and diarrhoea in decreasing frequency. The commonest finding was goiter, followed by tachycardia, eye signs, brisk reflexes, bruit and irregular pulse. The proportion of ophthalmopathy in this study was 27.7%, comparable with 25-50% reported in literature.[15] However, some studies showed lower rates of 3-11.1%.[16-18]

Only 4.8% of patients had heart failure.Thyrotoxicosis not only aggravates pre-existing heart problems, but may be the principle factor leading to atrial fibrillation (AF), cardiomegaly or heart failure.[19] It has serious consequences with increased mortality in patients of all age groups.[20,21] This study revealed that 13 (2.6%) patients had irregular pulse, which was much lower compared to a study that showed 13% of all patients with hyperthyroidism had developed AF.[22] A younger patient cohort may explain this difference.

The three main treatment options are medical therapy, RAI therapy and surgical intervention. The choice is multi-factorial depending upon the preferences of patients and clinicians, cost, restrictions on the therapeutic use of radioisotope and the availability of skilled surgeon. RAI ablation is the most common treatment for hyperthyroidism in adults in the United States[23,24] whereas in Japan and Europe anti-thyroid therapy is the first line of treatment.[25] Even though RAI ablation therapy was suggested as the preferred option and is available in our set-up at a very reasonable cost, our patients were very reluctant, and preferred medical or surgical options over RAI because of fear of harmful effects of radiation.

Antithyroid drugs methimazole, CBZ and PTU have played a central role in the management of hyperthyroidism since their introduction in the 1940s. CBZ is a pro-drug as after absorption it is converted to the active form, MMI, which then prevents the thyroid peroxidase enzyme from

coupling and iodinating the tyrosine residues on thyroglobulin, hence reducing the production of the thyroid hormones. PTU acts by inhibiting the same enzyme and also interferes with the conversion of FT4 into FT3. Observations over several decades have shown that MMI/CBZ are better than PTU in controlling severe hyperthyroidism, having high adherence rates, and cause less toxicity, especially in lower doses.[26] This has led to a review of recommendations that MMI/CBZ be the first-line drug when anti-thyroid drug therapy is initiated, either for primary treatment or to prepare for RAI or surgery.

In accordance with endocrine society guidelines,[27] CBZ was prescribed in the majority of patients (76%) and preferred over PTU in our endocrine clinic. PTU was reserved for patients who were allergic to or intolerant of CBZ, women in their first trimester of pregnancy and lactating.

Conclusion

GD with diffuse toxic goiter was the most common form of thyrotoxicosis. A substantial proportion of patients with thyrotoxicosis had no goiter, which may cause delay in diagnosis. As a result of data analysis, the starting dose of CBZ and PTU was reduced to 20mg/day and 200mg/day respectively, so that hypothyroidism could be avoided.

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