

Thyrotoxicosis-10 Years Experience

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ABSTRACT:

BACKGROUND:

Thyrotoxicosis is one of the most common presentations in thyroid disease, Graves' disease, multinodular goiter, toxic adenoma and thyroiditis are its main common causes, almost every system is affected and there is great individual variation in the dominant features.

OBJECTIVE:

The study objectives are to explore the pattern of thyrotoxicosis in Sulaimania city during the years 1996-2006.

METHODS:

From January 1996 to January 2006, 452 thyrotoxic cases (165 males and 287 females) were evaluated for the causes, history of iodine prophylaxis program, their manifestations, the eye signs and relation of the smoking with the eye signs.

RESULTS:

Analysis of 452 patients proved to have thyrotoxicosis by thyroid function tests, females were 64% and males 36%, the mean age was around 39 years, Graves' disease was the cause in 59.51% of the cases, followed by Iodine-induced thyrotoxicosis 21.9%, multinodular goiter 9.96%, single nodule goiter 7.97%, then finally subacute thyroiditis 0.66%. Among the thyrotoxic cases 61.06% has weight loss and 50% has hand tremor, in those with eye sign 56% has non-infiltrative and 44% has infiltrative eye signs.

CONCLUSION:

Thyrotoxicosis is twice more common in females than males, Graves' disease is the commonest cause while iodine induced thyrotoxicosis is another important cause in the setting of iodine prophylaxis program, weight loss and hand tremor are commonest manifestation. In between ophthalmopathic smokers infiltrative eye signs were more common than non infiltrative.

KEY WORDS: thyrotoxicosis, graves' disease, iodine induced thyrotoxicosis, thyroid ophthalmopathy.

INTRODUCTION:

The term thyrotoxicosis refers to the hypermetabolic clinical syndrome resulting from serum elevations in thyroid hormone levels, specifically free thyroxine (T₄), triiodothyronine (T₃), or both. Hyperthyroidism includes diseases that are a subset of thyrotoxicosis, that are caused by excess synthesis and secretion of thyroid hormone by the thyroid; they are not associated with exogenous thyroid hormone intake and subacute thyroiditis^(1,2,3,4). Unsuspected & undiagnosed hyperthyroidism arose in roughly 0.5% of women in a large population-based British survey, done in the 1970s⁽⁵⁾. In a more recent survey done in the USA, investigators noted hyperthyroidism in 0.5% of randomly selected individuals⁽⁶⁾.

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An additional 0.8% had subclinical or mild hyperthyroidism, in which serum thyrotropin is low or undetectable, but circulating thyroid hormone is within the normal range⁽⁶⁾, the development of the various forms of hyperthyroidism depends to a great extent on the iodine intake of the population⁽³⁾. For example, an epidemiological survey compared an area of normal iodine intake (Iceland) with an area of low iodine intake (East Jutland, Denmark), Graves' disease accounted for at least 80% of new cases of hyperthyroidism in Iceland, whereas toxic multinodular or uninodular goitre caused over half the new cases in Denmark⁽³⁾. The most common cause of this syndrome is Graves' disease, followed by toxic multinodular goiter & solitary hyperfunctioning nodules, autoimmune postpartum & subacute thyroiditis, tumours that secrete thyrotropin

& drug-induced thyroid dysfunction, are also important causes^(7,8,9). The diagnosis of hyperthyroidism is generally straightforward, with raised serum thyroid hormones & suppressed serum thyrotropin in almost all cases. Appropriate treatment of hyperthyroidism relies on identification of the underlying cause. Antithyroid drugs, radioactive iodine & surgery are the traditional treatments for the three common forms of hyperthyroidism^(3,9,10). Beta-adrenergic blocking agents are used in most patients for symptomatic relief & might be the only treatment needed for thyroiditis, which is transient. The more unusual causes of hyperthyroidism, including struma ovarii, thyrotropin-secreting tumors, choriocarcinoma, & amiodarone-induced thyrotoxicosis is more often than not, a challenge to diagnose & treat^(3,10). Approximately 25-50% of patients with Graves' disease develop thyroid eye disease (TED), and sight-threatening disease occurs in 5% of patient. Conversely, 10% of patients manifesting TED fail to become hyperthyroid⁽¹¹⁾. New studies have shown that smoking may protect against the development of thyroid peroxidase antibodies, which may result in a decreased risk of Hashimoto's hypothyroidism (HH)⁽¹²⁾, whereas it stimulates the development of Graves' hyperthyroidism (GH). According to the above-mentioned hypothesis, to stop smoking would decrease the risk of GH but increase the risk of HH. Also, smoking has been identified as one of the risk factors for the development or worsening of eye changes after I¹³¹ treatment of GH. Additionally, the outcome of medical treatment of Graves' ophthalmopathy (GO) is less favorable in smokers as compared to non-smokers⁽¹³⁾. There is concern also about the effect of passive smoking on autoimmune thyroid disease. In a recent study it has been shown that the latter may have a deleterious effect on childhood GO⁽¹⁴⁾. The study objectives are to explore the pattern of thyrotoxicosis in Sulaimania city in Kurdistan region of Iraq during the years 1996-2006, the effects of iodine prophylaxis program on inducing thyrotoxicosis and the relation of smoking with eye sign in thyrotoxic patients.

MATERIALS AND METHODS:

Cases of suspected thyrotoxicosis were seen in the outpatient clinic & inpatient wards of Sualimani General teaching hospital and the private clinic of the author from 1st January 1996 to 1st January 2006, were evaluated clinically for features of thyrotoxicosis. The patient with normal thyroid function tests namely normal thyroxine (T4) & triiodothyronine (T3) were excluded from the study, also those with subclinical hyperthyroidism were excluded, while patients who were proved to have thyrotoxicosis by thyroid function tests namely elevated thyroxine (T4) & triiodothyronine (T3) were entered in the study for the analysis of their age, sex, family history, cause of thyrotoxicosis, symptoms, signs, eye manifestations & relation of smoking to eye manifestations, the two types of ocular findings were infiltrative and noninfiltrative, the infiltrative findings (lid puffiness, chemosis, proptosis, extraocular muscle dysfunction, optic neuritis, or atrophy), the noninfiltrative findings (lid lag and lid retraction)⁽¹⁵⁾. weight loss was significant if patient loss more than 3kg over 6 months⁽¹⁶⁾, and tachycardia defined if radial pulse rate >100 beats/minute⁽¹⁷⁾. Graves' disease cases were diagnosed on the bases of diffuse goiter and thyrotoxicosis which may be accompanied by an infiltrative ophthalmopathy⁽¹⁸⁾, subacute thyroiditis cases diagnosed when there is palpably enlarged and tender thyroid gland with elevated ESR and transient thyrotoxicosis⁽¹⁶⁾. The thyroid function tests were carried out by the Mini Vidas ELISA and immunoradiometric assay (IRMA) method. Statistical analysis done using SPSS (V15) selecting T-test when needed, a p-value of (p<0.05) was considered to be significant statistically.

RESULTS:

Table 1 shows the number of cases seen in each year from 1996 – 2006 including the number of males & females in each year; it also shows the relation of the thyrotoxicosis cases with history of iodine prophylaxis programs. It shows that most cases were seen during 1999 & least cases in 2005. It also shows that females were approximately twice affected more than males.

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Table 1: Total Number of Cases

Year	Female	Male	Total	History of iodine prophylaxis program
1996	21	13	34	11
1997	58	25	83	24
1998	31	20	51	20
1999	59	35	94	29
2000	42	32	74	12
2001	13	6	19	3
2002	10	7	17	
2003	16	14	30	
2004	24	10	34	
2005	13	3	16	
Total	287(64%)	165(36%)	452	99

P-value was significant ($p > 0.0001$)

The age range was from 9-75 years & the mean age affected was around 39 years. (Mean age of the females 39.602 and males 38.166 years).

Table 2, Shows the etiology of thyrotoxicosis, graves' disease being the most common cause, followed by iodine induced, multinodular goiter, single nodule goiter, then finally subacute thyroiditis.

Table 2: Etiology of Thyrotoxicosis

Cause	No. of Cases	Percentage of Total
Grave's Disease with Diffuse Goitre	269	59.51%
	Bruit +ve 55	(20.5%)
	Bruit -ve 214	(79.5%)
Iodine Induced	99	21.90%
Multinodular Goitre	45	9.96%
Single Nodule	36	7.97%
Subacute thyroiditis	3	0.66%
Total	452	100.00%

Table number 3, shows the symptom manifestations of the cases in this series, indicating that weight loss was the most common feature, followed by other well known features of autonomic hyperactivity. Surprisingly it shows that decreased appetite was more common than increased appetite.

Among the 165 male cases 2(1.23%) has impotence and in the 287 female cases 62(21.6%) has oligomenorrhea, 47(16.37%) has amenorrhea, 7(2.44%) has menorrhagia and 1(0.35%) has dysmenorrhea.

Table 3: Symptom Manifestations

Symptoms	No. of Cases	Percentage of Total
Weight Loss	276	61.06%
----Decreased Appetite	212	46.90%
----Increased Appetite	64	14.15%
Palpitation	215	47.56%
Increased Sweating	156	34.51%
Heat Intolerance	128	28.31%
Nervousness	107	23.67%
Dyspnea on Exertion	71	15.70%
Hyperdefecation	57	12.61%
Muscle Weakness	48	10.61%
Fatigue	45	9.95%
Diarrhea	28	6.19%
Myalgia	21	4.64%
Family History of thyrotoxicosis	18	3.98%
Insomnia	17	3.76%
Loss of Libido	15	3.31%
Arthralgia	14	3.09%
Pruritus	14	3.09%
Alopecia	13	2.87%
Emotional Liability	12	2.65%
Vomiting	10	2.21%
Constipation	10	2.21%
Exacerbation of Asthma	8	1.76%
Galactorrhea	5	1.10%
Infertility	3	0.66%
Bone Pain	2	0.44%
Angina	2	0.44%
Ankle Edema	2	0.44%

Table number 4, shows the reported signs manifested by thyrotoxic cases. The hand tremor was the most common sign reported while chorea was the least common and among the male cases 3(1.82%) has gynecomastia.

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Table 4: Signs

Signs	No. of Cases	Percentage Per Total
Hand tremor	226	50.00%
Wide Pulse Pressure	128	28.31%
Sinus Tachycardia	102	22.56%
Irritability	65	14.38%
Hyper-reflexia	49	10.84%
Proximal Myopathy	37	8.18%
Heart Failure	28	6.19%
Atrial Fibrillation	23	5.08%
Cardiomyopathy	18	3.98%
Vitiligo	11	2.43%
Apathy	11	2.43%
Palmer Erythema	7	1.54%
Pigmentation	6	1.32%
Splenomegally	5	1.10%
Systolic Pulmonary Murmur	4	0.88%
Digital Clubbing	3	0.66%
Spider Naevi	3	0.66%
Onycholysis	3	0.66%
Lymphadenopathy	3	0.66%
Pretibial myxedema	2	0.44%
Maculopapular Skin Rash	2	0.44%
Bulbar Myopathy	1	0.22%
Chorea	1	0.22%

Table Number 5, shows the eye manifestations of the cases, indicating that non-infiltrative eye signs were more common than infiltrative eye changes.

Table 5: Eye Manifestations

Eye Signs	No. of Cases
Non-infiltrative	89(56%)
Infiltrative	69(44%)
Total	158

P-value 0.1816 not significant

Table number 6 shows the relation of smoking status to eye signs, indicating that smoking was more common among patients with infiltrative than those with non-infiltrative eye signs.

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Table 6: Relation of Smoking with Eye Signs

Eye Sign	Smoking	Not Smoking
Non infiltrative	16(38%)	73(63%)
Infiltrative	26(62%)	43(37%)
Total	42(26%)	116(74%)

P-value <0.0001 and statistically is significant that eye signs are more in non smokers, but infiltrative eye signs were more common among smokers than non-infiltratives.

DISCUSSION:

Table 1 shows that most cases were seen during 1997 & 1999 which can be attributed to a program of giving the population of Sualimani Iodine supplementation in the form of Lipodol (Iodine slow-release oily capsules 200 IU) between the years 1994-1998 to prevent goiter in the community which could have resulted in an increase in the incidence of thyrotoxicosis by the well-known Jod-basedow phenomena⁽¹⁹⁾ & females were approximately twice affected more than males. A study of 203 patients seen at King Abdulaziz University Hospital, Saudi Arabia, The female: male ratio was 3.8:1 & mean age of 35.49±10.86 years. Graves' disease was the underlying cause in 69% of cases, toxic multi nodular goiter in 29%, and toxic adenoma and sub acute thyroiditis in 1% each. Palpitations, tremor, weight loss and nervousness were the commonest presenting manifestations⁽²⁰⁾. The mean age of the affected cases was around 39 years age, in a study from Olmsted County, Minnesota, USA, the peak incidence rates were bimodal, occurring in the age groups 40-44 years & 60-64 years in females & 45-49 years & 65-69 years in males.⁽²¹⁾

Table 2, Shows the etiology of thyrotoxicosis, graves' disease being the most common cause, followed by Iodine-induced, multinodular goiter, single nodule goiter, then finally subacute thyroiditis. In a study from Germany, thyrotoxicosis was one of the most common endocrine disorders; affecting a 2% of the adult population⁽²²⁾ Graves' disease & its variants are the most frequent cause. The prevalence of toxic nodular goitre & toxic adenoma is increased in areas of limited iodine supply. Transient hyperthyroidism may be caused by HCG-induced thyroiditis in pregnancy or de Quervain subacute thyroiditis⁽²²⁾. These data are consistent with the result of this study, in this study 59.51% have Graves' disease and in 20.5% of the Graves' disease cases with diffuse goiter bruit is heard over the thyroid gland which is due to increased blood flow of the gland⁽¹⁸⁾. Thyrotoxicosis in patients with multinodular goitre

can be precipitated by iodinated radiocontrast agents & the anti arrhythmic drug amiodarone^(23,24). As in table 1, ninety-nine cases has history of receiving at least one capsule Lipodol few weeks-few months before the diagnosis of their thyrotoxicosis and in some of them they had received it more than one time, iodine-induced thyrotoxicosis (Jod-Basedow syndrome) occurs in patients with excessive iodine intake⁽²⁾ It occurs in patients with areas of thyroid autonomy, such as a multinodular goiter or autonomous nodule, the thyrotoxicosis appears to be a result of loss of the normal adaptation of the thyroid to iodide excess⁽²⁾. In the majority of the iodine induced thyrotoxic cases in this study there was no obvious thyroid enlargement and their manifestations were not florid as in the cases of the Graves' disease.

Table number 3, shows the symptoms manifestations of the cases in this series, indicating that weight loss was the most common feature, followed by other well known features of autonomic hyperactivity. Interestingly it shows that decreased appetite was more common than increased appetite, Ghrelin is a hormone produced by the stomach that acts on the brain to stimulate appetite, in a study done in 2003 showed serum concentration of ghrelin are lower in women with hyperthyroidism than in normal women making decrease appetite in hyperthyroidism needs further evaluation⁽²⁵⁾. Typical symptoms of hyperthyroidism indicate the action of excess thyroid hormone on the cell, as well as enhanced adrenergic activity. Patients usually have fatigue, nervousness or anxiety, weight loss, palpitations, and heat-sensitivity. Women might have irregular menses & decreased fertility, although frank amenorrhea is rare.⁽²⁶⁾

Men can have reduced libido and sometimes painful gynaecomastia⁽²⁷⁾. Clinical manifestations of thyrotoxicosis range from silent to florid & can mimic

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those of other conditions occurring in pregnancy and old age. The diagnosis may be particularly vexing in elderly patients with apparent dementia. Once clinical suspicion has been aroused, the workup to confirm the diagnosis & establish the cause is easily accomplished.^(28,29)

A study from Nigeria showed that the presence of a goiter, ocular changes, high sleeping pulse rate, fine silky-smooth skin & thin, short & scanty hair have been identified as important clinical clues to look for to aid in the diagnosis of a difficult case in an environment where there are no facilities for thyroid function tests⁽³⁰⁾. Digestive symptoms may represent the only manifestations of hyperthyroidism and up to 25% of patients with hyperthyroidism have mild-to-moderate diarrhea with frequent bowel movements⁽³¹⁾, in this study 12.61% has hyperdefecation and 6.19% has diarrhea. vomiting is present in 2.21% of the cases in this study, and in one case a 67 year lady presented with intractable vomiting with masked face which was the only presenting feature with performing all the available investigations related to vomiting the cause was not evident, on her second admission in hospital, thyroid function test performed and she was a case of apathetic thyrotoxicosis and her vomiting disappeared after 6 days from starting antithyroid therapy. Nausea may be the chief complaint in thyrotoxicosis⁽³²⁾ and vomiting is rarely intractable and may involve neurohormonal mediators along with direct action in older patients⁽³¹⁾, in diagnostic respects only cases of monosymptomatic or masked thyrotoxicosis are of real interest⁽³³⁾, weight loss might be accompanied by anorexia rather than increased caloric intake, prompting an often extensive, expensive, ultimately unsuccessful search for hidden malignant disease.^(34,35) Apathetic thyrotoxicosis are unassociated with the usual signs and symptoms of hyperthyroidism, making the diagnosis difficult⁽³⁶⁾. In this study 3.98% of the cases has family history of thyrotoxicosis in one of the first degree relatives. In a recent study done on familial risks for Graves' disease showed familial Graves' disease cases in offspring constituted 3.6% of all Graves' disease patients and familial risks were particularly high for twins, for individual with two or more affected singleton siblings and for individuals whose parents or siblings were affected at an early age⁽³⁷⁾. Risk factors for thyrotoxicosis include a family history,

high iodine intake, smoking, and certain drugs, for example amiodarone⁽³⁸⁾.

Table number 4, shows the reported signs manifested by our cases. Hand tremor was the most common sign reported while chorea was the least common sign. Half of the cases in this study has hand tremor, tremor in thyrotoxicosis and generalized anxiety disorder is an exaggerated physiological tremor and successful treatment of thyrotoxicosis results in a dramatic improvement of tremor⁽³⁹⁾. Clinical findings almost always include tachycardia, warm moist skin, the presence of an enlarged thyroid, and a slight tremor. Less frequent neurological findings include poor concentration and personality changes^(4,7). Hypokalaemic periodic paralysis, typically seen in thyrotoxic Asian men might be due to concomitant mutations in genes coding for potassium channels in muscle⁽⁴⁰⁾ Elderly individuals have less obvious symptoms and signs than have younger patients, including a lower frequency of goitre and a higher prevalence of cardiac manifestations such as atrial fibrillation(AF) and, more rarely, congestive heart failure. About 15% of elderly individuals with new onset AF have thyrotoxicosis^(41,42,43) disorders of cardiac rhythm and repolarization are frequently observed in thyrotoxicosis and less commonly conduction abnormalities with symptomatic complete heart block may occur⁽⁴⁴⁾. Conversely, a high proportion (as many as 25–35%) of elderly people with thyrotoxicosis will develop AF that is resistant to treatment until the underlying thyroid disorder has been corrected⁽⁴⁵⁾, in this study 5.08% of the cases has AF while in other series AF is present in about 10% of all patients with thyrotoxicosis⁽¹⁶⁾. Other indicators of hyperthyroidism include osteoporosis, hypercalcaemia⁽⁴⁶⁾, congestive heart failure, premature atrial contractions, shortness of breath, muscle weakness, anxiety, or amenorrhoea⁽⁴⁷⁾. Deterioration in patients whose diabetes is under glycaemic control also points to possible hyperthyroidism⁽⁴⁸⁾. Various case reports had linked chorea to thyrotoxicosis but it is uncommon, the first case was described in 1888 by Sir William Gowers and the pathophysiology has not been clearly recognized^(49,50,51) our case with chorea was a 23 year female with grave's disease and large goiter with the recovery of her thyrotoxicosis the chorea disappeared.

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Table number 5, shows the eye manifestations of the patients, indicating that non-infiltrative eye signs were more common than infiltrative eye changes 56% versus 44%. Thyroid ophthalmopathy (TO) or Graves ophthalmopathy embraces a broad range of eye abnormalities which up to 90% of patients with hyperthyroidism are affected with. In some 10% of TO patients, this may begin oligosymptomatically, often with double vision and with neither clinical nor biochemical signs of thyroid disease⁽⁵²⁾

Table number 6 shows the relation of smoking status to eye signs, indicating despite that among the 158 cases with eye sign in this study only 42 cases (26%) have history of smoking but smoking was more common among patients with infiltrative than those with non-infiltrative eye signs 26 (62%) versus 16 (38%). According to other study an increased number of smokers is found among patients with Graves' ophthalmopathy, with an overall prevalence of smokers of about 60%, furthermore, the degree of smoking seems to influence the severity of eye disease⁽¹³⁾. An assumed effect of smoking increasing tissue hypoxia was tested and it was shown in hypoxic condition that TNF α , INF γ and IL-1 α stimulated Glycosaminoglycans production by orbital fibroblasts to a greater extent than in basal oxygen conditions, the effect was greater in orbital than dermal fibroblast^(11,53).

CONCLUSION:

Thyrotoxicosis is twice more common in females than males, Graves' disease is the commonest cause while iodine induced thyrotoxicosis is another important cause in the setting of iodine prophylaxis program, weight loss with palpitation and surprisingly decreased appetite are important symptoms while hand tremor, wide pulse pressure and sinus tachycardia are commonest signs. Smoking is not significantly related to thyroid ophthalmopathy while among ophthalmopathic smokers infiltrative eye signs were more common than non infiltrative eye sign.

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