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REVIEW ARTICLE

Not All Low TSH is Graves' Disease!

[1]Pradip P Dalwadi, [2]Parimal Tayde, [3]Bharat R Sharma, [4]Jagdish A Chavan, [5]Pratibha T Pawal, [6]Ameya S Joshi, [7]Manoj D Chadha, [8]Nikhil M Bhagwat, [9]Premlata K Varthakavi

ABSTRACT

Thyroid dysfunction is one of the most common endocrine disorders. Low thyroid stimulating hormone (TSH) is not uncommon finding in routine evaluation of thyroid disease. Thyroid imaging with radioisotope is an important modality of investigation to identify different causes of low TSH. In this review article, we have highlighted different causes of low TSH apart from Graves' disease and how to differentiate among them with the help of thyroid radioisotopes scan.

Keywords: Thyrotoxicosis, Radioisotopes scan, Graves' disease, Thyroiditis.

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INTRODUCTION

Thyroid dysfunction is one of the most common endocrine disorders. Approximately 42 million people in India suffer from thyroid diseases.[1] An autoimmune thyroid disorders are more prevalent in iodine replete areas.[2] We usually ordered thyroid function test (TFT) as the first investigation for evaluation of thyroid dysfunction or thyroid nodules. Low thyroid stimulating hormone (TSH) on routine investigation is not an uncommon finding, suggestive of thyrotoxicosis. Although Graves' disease (GD) is the most common reason for low TSH, we need to consider a number of other differential diagnoses before embarking on treatment. Thyroid imaging with radioisotope likes iodine-123 (^{123}I) or technesium-99 (^{99}Tc) is extremely useful modality of investigation which helps us in the differential diagnosis of thyrotoxicosis.

[1-3,5]Registrar, [4]Resident, [6]Assistant Professor, [7]Associate Professor, [8]Additional Professor, [9]Professor and Head

[1-9]Department of Endocrinology, Topiwala National Medical College and BYL Nair Charitable Hospital, Mumbai, Maharashtra India

Corresponding Author: Nikhil M Bhagwat, Additional Professor Department of Endocrinology, Topiwala National Medical College and BYL Nair Charitable Hospital, College Building, 4th Floor Mumbai-400008, Maharashtra, India, Phone: +91-9820238399 e-mail: bhagwatnik@yahoo.co.in

Thyrotoxicosis

The term thyrotoxicosis and hyperthyroidism are not synonymous. Thyrotoxicosis means the clinical syndrome that result from excess concentration of thyroid hormones which may or may not be associated with hyperfunctioning of the thyroid gland. While the term hyperthyroidism reserved for sustained increases in thyroid hormone biosynthesis and secretion by the thyroid gland. Many patients with thyrotoxicosis may have hyperthyroidism, others do not, like patients with thyroiditis and exogenous thyroid hormone administration.[3]

Although, clinical manifestations of thyrotoxicosis are independent of its cause, an attempt should be made to identify the cause, because it helps us in determining a prognosis and guide therapy. The common clinical manifestations of thyrotoxicosis include fatigue, nervousness, increased perspiration, palpitation, heat intolerance, hyperactivity, tremors, weight loss in spite of increased appetite, menstrual irregularity, warm and moist skin and eyelid retraction. However, certain clinical features provide clues to the cause like, duration of symptom, shape, size and texture of the thyroid gland and systemic manifestation of GD. Most common causes of thyrotoxicosis can be subclassified into disorders causing transient thyrotoxicosis and hyperthyroidism (Table 1).[4]

Graves' Disease

Graves' disease is an autoimmune disease characterized by stimulating autoantibodies to the TSH receptor. The name of disease is credited to Robert James Graves (1835), an Irish physician who had described it.[5] It is also known as Von Basedow's disease in many non-English speaking countries.[5] Graves' disease is the most common cause of thyrotoxicosis, accounts for 60 to 80% cases.[6] The prevalence varies among geographical regions, reflecting genetic factors and iodine intake. The disorder is 10 times more common in female and rarely, begins before adolescence with the usual age of presentation being 20 to 50 years of age. Potential risk factors for development of GD include genetic susceptibility, certain bacterial and viral infections, stress, female sex, pregnancy, iodine and irradiation.[6] In GD, the thyroid gland is diffusely enlarged two to three times its usual size, consistency of the

Table 1: Causes of thyrotoxicosis[4]

Hyperthyroidism	*Transient thyrotoxicosis*
Graves' disease	Thyroiditis
Toxic nodular goiter—solitary or multiple	– Autoimmune
Gestational hyperthyroidism and GTD	– Infectious
Drug induced-iodine, amiodarone, IFN	– Drug induced
TSH secreting pituitary adenoma	Exogenous thyroid hormone administration
Struma ovarii	

gland is usually firm and there may be a thrill or bruit due to increased vascularity of the gland and hyperdynamic circulation. Apart from the clinical features described earlier, 30 to 50% patients have thyroid eye disease[7] (Graves' ophthalmopathy), <5% have thyroid dermopathy[8] and <1% have thyroid acropachy.

Laboratory findings include low or undetectable TSH with high or high normal serum T3 and T4 levels. The serum T3 concentration is proportionally much more elevated than T4 concentration. Occasionally in patients with iodine deficiency, serum T4 concentration may be normal with an isolated elevation of T3 called T3 toxicosis.[6] Thyroid imaging with radioisotopes is an appropriate test to exclude thyrotoxicosis not caused by hyperthyroidism. Classically GD is described as homogenous high uptake toxicosis while low uptakes with thyrotoxicosis are seen in thyroidits, factitious thyrotoxicosis, ectopic thyroid tissue, recent iodine exposure. Measurement of TSH receptor antibody (TRAb) is very sensitive and specific for GD. Although, it is positive in >90% of the patients with GD its measurement is usually not required for diagnosis.[9] The only indication of TRAb measurement is when the clinical picture or thyroid functions are not clear. These include[9] (1) diagnosis of thyrotoxicosis in pregnancy; (2) to differentiate multinodular goiter from the nodular variant of GD; (3) patient with exophthalmos without thyrotoxicosis (euthyroid Graves' ophthalmopathy).

The aim of treatment in GD is to achieve euthyroid status. It can be achieved by antithyroid drug (ATD) (methimazole, carbimazole and propylthiourasil) which inhibit thyroid hormone synthesis. The remission rate with the use of ATD is only 40 to 50%. Thyroid tissue ablation with radioactive iodine (I^{131}) (RAI) has >90% success rates and now became preferred modes of treatment for patients with GD. Thyroidectomy is only indicated when patients are having huge goiter with compressive symptoms, malignancy and in patients with severe Graves' ophthalmopathy in whom RAI can worsen pre-existing ophthalmopathy.

Transient Thyrotoxicosis due to Hashimoto's Thyroiditis

Hashimoto's disease is the most common cause of hypothyroidism in iodine repleted areas.[10] In early course of the disease, it can manifest as transient thyrotoxicosis due to autoimmune destruction of the thyroid gland and subsequent leakage of a thyroid hormone pool into the circulation. Clinically, two forms of transient thyrotoxicosis are described—painful and painless.[6] Painless form is much more common, in which symptoms of thyrotoxicosis are mild and not associated with local pain or tenderness. Postpartum thyroiditis is a classical example of painless autoimmune thyroiditis, which occurs in 10 to 30% of pregnant women with thyroid peroxidase antibody (TPO-Ab). The painful form represents more acute onset, associated with local pain and/or tenderness which can be unilateral and recur until thyroid gland is completely destroyed. This thyrotoxic phase last for an average of 1 to 2 months, followed by hypothyroidism, which may be transient or in a minority, permanent.[6] Thyroid gland may be normal in size or diffusely enlarged with soft consistency. Histopathologically thyroid gland shows diffuse or local lymphocytic infiltrate, varying degrees of fibrosis, and disruption of the follicular architecture.

Thyrotoxic phase may sometimes be difficult to separate from GD, as both may present with similar hormonal profile (Table 2). Clinically thyrotoxicosis is mild and of short duration in patients with thyroiditis as compared to GD. Thyroid peroxidase antibody is positive in > 90% of patients with autoimmune thyroiditis, but it does not help to differentiate it from GD, as it is also positive in 50 to 80% patients with GD.[11] Whenever there is doubt, definitive diagnosis can be established with thyroid uptake scan which shows low patchy uptake in thyroiditis as compared to diffuse homogenous high uptake seen in patients with GD.

The treatment of thyrotoxic phase requires symptomatic treatment to alleviate peripheral manifestations through use of B-blockers. Glucocorticoids may alleviate the symptoms and shorten the duration of thyrotoxic phase, but it is not needed except when thyroiditis is associated with disturbing pain. The steroid may also dramatically decreases antibody titers, but it returns to pretherapy levels when treatment is stopped.[12]

Subacute Thyroiditis

Subacute thyroiditis (Granulomatous, Giant cell or De-Quervain thyroiditis) is caused by viral infection, usually follows upper respiratory tract infection and is more

Table 2: Differentiating points between thyroiditis and GD

	Graves' disease	*Autoimmune thyroiditis*
Duration of symptoms	Long (several months)	Short (usually 1-2 months)
Thyrotoxicosis	Usually marked symptoms	Mild
Goiter	Diffuse and firm	Diffuse and soft
Extrathyroidal manifestation	May be present like Graves' ophthalmopathy and dermopathy	Absent
Total T3/T4 ratio[13]	>20	<16
TPOAb	50 to 80%	90 to 100%
TRAb	>90%	Absent
RAIU	Diffuse and high	Patchy and low
Thyroid Doppler[14]	Increase STV and TBF	Normal

STV: Peak systolic blood-flow velocity in the superior thyroid artery; TBF: Thyroid tissue blood flow; RAIU: Radioactive iodine uptake

Table 3: Differentiating points between Hashimoto's thyroiditis and subacute thyroiditis

	Hashimoto's thyroiditis	*Subacute thyroiditis*
ESR	Normal	Marked increase
TPOAb	Higher titer	May be positive
Histopathology	Diffuse lymphocytic infiltration with germinal center formation and obliteration of thyroid follicle	Patchy lesion with various stage of development
	Ashkenazy cells	Giant cell

common in middle-aged women as compared to men. Viruses implicated in causation of subacute thyroiditis are mumps, coxsackie virus, epstein-barr virus, cytomegalovirus, influenza, echo and adenovirus.[15] Clinically, patients have gradual or sudden onset of unilateral or bilateral pain in the region of thyroid with or without fever and may have associated thyrotoxic symptoms in early phase. Thyroid gland is firm, tender and moderately enlarged. Symptoms usually last for a few months and full recovery is seen in more than 90% patients. Clinically, this condition is sometimes difficult to differentiate from the painful variant of Hashimoto's thyroiditis. Some point which help us in differentiating these conditions are as follows (Table 3).

Patient with mild disease usually required symptomatic treatment like NSAIDs for pain, B-blocker for thyrotoxic manifestation. In patients with more severe throat pain steroids (Prednisolone-40 mg/day with rapid tapering) are useful for relief of symptoms.

Drug Induced Thyroiditis

Thyroiditis has been found to be associated with numbers of drugs like amiodarone, lithium, interferon-α, sunitinib, iodinated contrast and radioactive iodine.[16] Manifestations are usually similar to other forms of thyroiditis. Patients usually require removal of the offending drug and symptomatic treatment (Table 4).

Table 4: Amiodarone induce thyroiditis (AIT)[16]

Type 1 AIT	*Type 2 AIT*
Iodine induced form of thyroiditis	Destructive form of thyroiditis
Patient usually has underlying thyroid disease (Jod Basedow effect)	Due to direct toxic effect on thyrocyte
RAIU-Measurable	RAIU-low
Doppler shows increase vascularity	No increase in vascularity
Treatment symptomatic care Antithyroid drug Potassium perchlorate	Symptomatic care Steroid

RAIU: Radioactive iodine uptake

Toxic Nodular Goiter

Toxic nodular goiter is the second most common cause of hyperthyroidism. It may be solitary or multinodular. It is also more common in females as compared to males and is usually seen in older patients after the age of 50. During the natural course of nontoxic nodular goiter, cells in the nodules can acquire functional autonomy leading to the formation of toxic nodular goiter. Sixty percent of patients have a TSH receptor mutation. Clinically the course is characterized by long standing goiter with mild thyrotoxicosis (marginally elevated T3 and T4 as compared to GD). Thyroid uptake scan shows heterogeneous, marginally elevated uptake. Patients usually require radioactive iodine ablation or surgery for definitive management. A choice between surgery and radiotherapy depends on the size of nodules and obstructive symptoms of patients. Surgery is preferred in patients with large goiter causing obstructive symptoms otherwise RAI is preferred options.

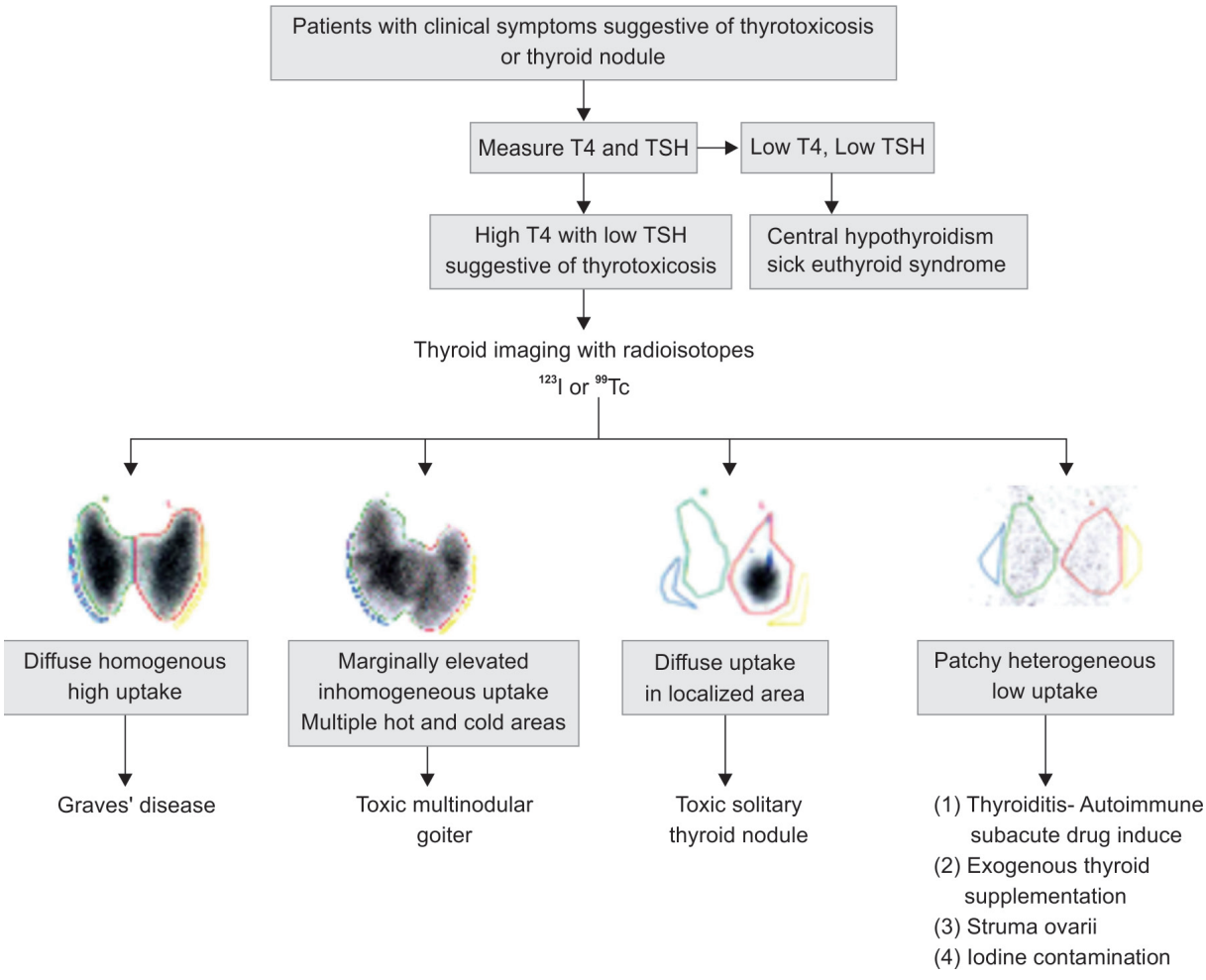

Fig. 1: Algorithm showing investigation of patients with thyrotoxicosis

Thyrotoxicosis due to Struma Ovarii

Struma ovarii comprises 1% of all ovarian tumors, 2.7% of all dermoid tumors and vary rarely present as malignant form.[17] It is extremely difficult to diagnose on the basis of clinical features. Patients usually present with abdominal pain with or without palpable mass, abnormal vaginal bleeding, ascites and features suggestive of thyrotoxicosis. Tumor marker CA-125 may be elevated in patients with benign or malignant struma ovarii.[17] Surgical resection is the treatment of choice for benign conditions while adjunctive radiotherapy is required in patients with malignant disease (Fig. 1).

CONCLUSION

- Although the GD is the most common cause of thyrotoxicosis, investigation to rule out other causes of thyrotoxicosis should be attempted before starting treatment.
- Thyroid uptake scan using radioisotope is the first line investigation to differentiate various causes of thyrotoxicosis and it should be ordered in all patients with low TSH.

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