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Grave's Disease: When to Jump for Operative Management?

Asif Hussain, Jawaria Avais

IMPORTANCE Thyrotoxicosis is mainly due to Grave's disease, toxic adenoma or multinodular goitre. Management depends on underlying etiology, patients age, patient's choices and comorbidities. Diagnosis of Grave's disease can be made clinically but often needs biochemical testing and imaging modalities. Additionally, pros and cons of various available treatment options for Grave's disease often helps for decision making. American Thyroid Association (ATA) has given very clear updated guidelines especially related to Grave's disease. This review is based mainly on the ATA guidelines to provide a summary of management for Grave's thyrotoxicosis.

KEY WORDS: Grave's disease, Grave's thyrotoxicosis, American Thyroid Association, Anti thyroid drugs, preparation for thyroidectomy

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Grave's disease (GD) is an autoimmune disease mediated by TSH receptor antibodies and is among the three most common causes of hyperthyroidism. 80-90% of thyrotoxicosis cases are caused by Grave's disease, toxic adenoma, and toxic multinodular goiter. GD can have ophthalmopathy and dermopathy as well, in addition to thyrotoxicosis. Rarely, GD can present as hypothyroidism. Less common causes of hyperthyroidism include various thyroiditis types (low uptake hyperthyroid), TSH secreting pituitary adenoma, exogenous ingestion of thyroid hormones, etc. The prevalence of thyrotoxicosis in the USA is 1.2% [1], whereas, in Pakistan, the prevalence of hyperthyroidism is 5.1%and is higher in females than males[2].

EVALUATION OF GRAVE'S DISEASE:

CLINICAL EVALUATION:

Complete evaluation of the patient, including hyperthyroidism symptoms, any underlying cardiac disease such as myocardial ischemia / atrial fibrillation/heart failure, neurological complication, or disease such as stroke/dementia, is essential. Cardiac assessment in those who are old (60 and above) or are at higher risk of cardiac disease may include ECG, echocardiogram, Holter monitor, and myocardial perfusion assessment. Still, it shouldn't be the reason to delay the treatment of thyrotoxicosis[3]. Also, thyroid-related review including size and cosmetic effect of any goiter, retrosternal extension, signs of thyroid malignancy such as lymphadenopathy / local compression of the adjacent tissues including trachea is an essential part of the evaluation[4].

BIOCHEMICAL TESTING:

Biochemical assessment includes TSH measurement alone for screening purposes. TSH is the most sensitive hormone to change when there is thyroid dysfunction in the adult population with an intact pituitary-thyroid axis. However, TSH may not be low in thyrotoxicosis cases if the underlying cause is a pituitary adenoma, thyroid hormone resistance syndrome, or the presence of interfering antibodies / heterophilic antibodies [5]. When clinical suspicion is high for thyrotoxicosis or for establishing the diagnosis, measurement of TSH along with free T4 and total T3 are needed. Measurement of free T4 & T3 is more valuable due to the protein binding of these hormones. However, free T3 assay isn't as robust, and hence total T3 is preferred. Total serum T4 (and sometimes T3) may be high without thyrotoxicosis in conditions such as high TBG (Thyroxine Binding Globulins) due to estrogen, pregnancy, hepatitis, porphyria, genetic X-linked trait of TBG, or drugs-related.

Similarly, genetically abnormal albumin (familial dysalbuminic), which has a higher binding affinity for T4, may also cause high T4 [6]. Many drugs such as Amiodarone, propranolol, Amphetamine also inhibit the conversion of T4 into T3 and cause high T4 levels. Free T4 can also be falsely elevated due to antibodies, displacement from albumin caused by protein binding drugs such as heparin, etc. Similarly, high biotin intake can also affect the hormonal measurement by interfering with the assays used [7].

WORK UP FOR THE ETIOLOGY:

Clinical assessment often helps to establish a diagnosis, mostly diffuse (GD) vs. nodular (TMNG, Solitary nodule), or tender thyroid (De Quervain's), Grave's ophthalmopathy

(GO), or Grave's dermopathy (GD) are helpful but often needs additional workup. Biochemically T3/T4 ratio will be low in thyroiditis or exogenous thyroxine intake. T3/T4 ratio will be high in thyrotoxicosis as hyperactive thyroid makes T3 more than T4. Thyroglobulin will be increased in thyroiditis and low if there is an exogenous Thyroxine intake[8]. Thyroid-stimulating hormone receptor antibodies (TR antibodies) are elevated in GD (rarely may be negative in mild GD) and also have prognostic value [9].

Thyroid uptake scans are often needed in thyrotoxicosis patients when TR antibodies are negative or the thyroid is nodular. Also, GD and nodularity can coexist where uptake scans will help to establish dual pathology. Diffuse uptake is seen in GD, patchy in TMNG, and single focus in TA. Uptake is low or absent in thyroiditis, exogenous thyroid hormone intake, or factitious thyroid disorders. Uptake in the neck will also be low or absent in Struma Ovarii. Pituitary related hyperthyroid will have high uptake in the thyroid. Iodine scans have more radiation risk than Tc pertechnetate scan. An uptake scan can also estimate radioactive iodine dose if chosen for the treatment [10]. However, uptake scans are not safe in pregnancy and lactation. Ultrasound Doppler measuring the blood flow will often help in such cases and shows hypervascularity in hyperfunctioning glands and can also help identify nodules. Suspicious nodules can also be biopsied under ultrasound guidance [11]. Painful thyroid gland with Tenderness on palpation, high ESR, and the low uptake on scans suggest De Quervain's thyroiditis. Post-partum thyroiditis often occurs within one year of the child's birth. The thyroid is painless, family or personal history of autoimmune thyroid disease is usually positive, and anti-TPO is positive [12].

TREATMENT OF GRAVE'S THYROTOXICOSIS:

BETA-BLOCKERS:

Propranolol is needed in almost all patients but especially those at risk of cardiac diseases. In those where non-selective beta-blockers are contraindicated, such as asthma or severe airway disease, selective beta-1 blockers such as Atenolol, metoprolol can be used. Cardiac calcium channel blockers such as Verapamil or Diltiazem can also be used if beta-blockers are not tolerated well [13].

ANTI-THYROID DRUGS (ATD):

ATD is preferred in patients who are not candidates for surgery, such as those with comorbidities, making them high risk for operative options or those who can't have radioactive iodine (RAI). ATD is also useful in GD where remission is likely such as small goiter, a low titer of TR antibodies, or mild GD. Pregnant or lactating females where RAI isn't safe and surgery also have risks are also managed preferably by ATD. Those with limited life expectancy, elderly, those who can't follow radiation precautions, failed previous RAI or surgical treatment, active Grave's Ophthalmopathy (GO), or where rapid disease control is needed are better treated with ATD [14]. Drug intolerance, young age, those with less likely remission of GD such as high titer of TR antibodies, nodular goiter, cosmetic issues with goiter, or large goiter with compression symptoms are not good candidates for drug therapy alone.

Propylthiouracil (PTU) has a higher incidence of side effects, especially hepatocellular injury, cholestatic jaundice, neutropenia, and skin rash when compared to Carbimazole (MMI), [15]. Also, PTU is short-acting with 2-3 doses / 24 hours, whereas MMI is a single daily dose. Hence carbimazole (in some countries like the USA, methimazole) is used preferentially. However, the placental crossing is less with PTU than MMI, and also PTU blocks the peripheral conversion of T4 into T3. These are the reasons why PTU is used preferentially in the first trimester of pregnancy and thyroid storm. PTU is also used if someone has minor adverse effects with MMI. Those with severe side effects with ATD or those who fail to become euthyroid with ATD should be considered for RAI or surgery[16]. Patients with GD are treated with ATD for 12-18 months and can be stopped once they are euthyroid, and TR antibodies are negative. Those who have positive TR antibodies after 12-18 months of treatment with ATD should be considered for alternative options. However, if alternative options are not available, ATD can be continued for the long term with regular monitoring of thyroid functions (TFTs) and TR antibodies, and ATD can be stopped when both parameters are normalized. Those who become hyperthyroid after completion of ATD should be considered for alternate therapy where suitable. Monitoring FBC and LFTs is essential at baseline and then regular intervals while the patient is on ATD, especially when they report any side effects[4].

RADIOACTIVE IODINE (RAI):

It's contraindicated in patients who can't follow precautions related to RAI, pregnancy or those who have a plan to be pregnant within the next six months of treatment, lactating mothers, those with thyroid cancer or suspected cancer of the thyroid or concomitant hyperparathyroidism. It's not a preferred treatment if there are suspicious nodules. Active Grave's Ophthalmopathy is also a contraindication for RAI. RAI is the right choice for those who want to avoid surgery, have previous neck surgery, have adverse events with ATD, have comorbidities such as cardiac issues, liver disease, periodic paralysis, or elderly. A pregnancy test should be done 2-3 days before using RAI, and contraception should be reassured for the next six months. It should be assured that other people are not at risk of radiations hazard by following precautions to avoid this risk.[17]

Patients should be started on beta-blockers and ATD (MMI) before starting RAI. MMI should be stopped 2-3 days before and then recommenced 5-7 days after the RAI, especially

for those who are at high risk of complications related to hyperthyroidism, such as cardiac patients. TFTs should be regularly monitored initially fortnightly and then 4-6 weekly till the first six months. Once patients are in the hypothyroid phase, Levothyroxine is started to maintain euthyroid status. Those with inadequate response to RAI can be considered for a repeat dose of RAI at three months [4.18].

SURGERY FOR GRAVE'S DISEASE:

Patients who are in the first or third trimester of pregnancy should be treated with ATD as surgery has high complications risks. It's relatively safe in the second trimester. Surgery is also avoided in cases where there are comorbidities such as cardiopulmonary, liver or renal disease, old frail patients, or where life expectancy is limited. Surgery is best for cases where there are nodules, suspicious nodules, risk of cancer, confirmed cancer, or associated primary hyperparathyroidism requiring surgery as well. Patients who have active GO or periodic paralysis are better managed with surgery [4].

The patient should be rendered as close to euthyroid as possible using ATD & beta-blockers before surgery to minimize the risk of perioperative complications, especially thyroid storm (TS)[19]. If emergency surgery is needed or ATD fails to achieve euthyroid status before surgery or the patient can't tolerate ATD, we need to use beta-blockers, corticosteroids, and inorganic iodine in the immediate preoperative period. Cholestyramine can also be added to promote fecal loss of thyroid hormones. Inorganic iodine such as Potassium Iodide (KI) is used 2-3 days before surgery as it helps normalizing thyroid functions and also reduces vascularity of the gland. Lugol's iodine is an alternative to KI. Vitamin D (calcitriol) and calcium replacement are needed as hypocalcemia is a common postoperative complication. Postoperatively ATD is stopped, and beta-blockers are slowly tailored. Levothyroxine is started after the operation, roughly at 1.6 microgram/kg. However, patients with cardiac history or at risk of cardiac disease are started at a lower dose. TFTs are monitored at regular intervals postoperatively to adjust the dose of the Thyroxine[4].

Total or subtotal thyroidectomy is performed, but the risk of recurrence is 8-10% with subtotal thyroidectomy, whereas recurrence is almost zero 0% with total thyroidectomy. The outcome is much better when the surgeon is experienced for these procedures[20]. Surgeons who perform more than 25 thyroidectomies in a year have a superior clinical and financial outcome, whereas the complication rate is almost 50% higher when the surgeon is less experienced. Experienced surgeons have less than 2% risk of permanent hyperparathyroidism and less than 1% risk of recurrent laryngeal nerve injury (RLN injury) [21].

A thyroid storm is a feared and dreadful complication that can happen, especially intraoperatively or postoperatively. It presents systemic decompensation, especially hyperthermia, cardiac, respiratory, hepatic, neurological, and renal complications. It can be precipitated by inadequate biochemical control, the stress of the surgery, or anesthesia. Thyroid storm should be avoided by aggressive monitoring, achieving euthyroid status before surgery (when possible), and the procedure carried out by an experienced thyroid surgeon[22]. It's assessed using Burch-Wartofsky Point Scale (BWPS) with a score equal to or > 45. BWPS score b/w 25-44 needs clinical judgment to manage. Other scoring systems, such as the Japanese Thyroid Association (JTA) or Thyroid Storm 2 (TS2), are less reliable. Caution should be practiced to diagnose thyroid storm in patients who don't have severe thyrotoxicosis as most of the manifestations of thyroid storm can also be seen in any significant illness such as sepsis etc., which are also triggers for the storm[23]. Thyroid storm is treated with combination therapy of ATD (preferably PTU), hydrocortisone, beta-blockers, intravenous fluid, cooling by paracetamol and cool blankets, cardio-respiratory support as needed, nutritional help, and monitoring in intensive care. Almost every step of hormone synthesis and action is blocked by combining these pharmacological options. Doses of the drugs used are much higher than regular doses; hence its significant to establish the diagnosis with certainty to avoid drug toxicity [4,23,24].

DISCUSSION:

Grave's disease can present in a wide range of clinical presentations from subclinical thyroid disease, thyrotoxicosis to thyroid storm. Rarely GD can coexist with Hashimoto's thyroiditis or can present as Grave's hypothyroidism. Diagnosis is often straightforward when it presents diffuse goiter and hyperthyroidism associated with Grave's ophthalmopathy and/or dermopathy and positive TSH receptor antibodies. However, an additional workup is often needed when the clinical, biochemical, and serological evidence is not conclusive. Uptake scans are not safe in pregnancy and lactating mothers, where ultrasound doppler often helps.

Decisions regarding further testing and management are guided by many factors, including age, sex, pregnancy/lactation, associated comorbidities, and patient preferences. Old frail patients with a lot of comorbidities are better managed with no-operative options. RAI is avoided in pregnancy, lactation, anyone with cancer or suspected cancer, and active GO. Surgery is the best choice when there is a possible or confirmed malignancy. If the patient is fit for a surgical option, total or subtotal thyroidectomy after achieving biochemical euthyroid status is the right choice when an experienced thyroid surgeon is available. Thyroid storm is a deadly complication that can be prevented and treated promptly in an ICU setup. Postoperative calcium management is an important aspect. Levothyroxine

replacement is needed after the use of RAI or surgical option. Post-op complications of permanent hypoparathyroidism and RLN injury is 1-2% in a high volume surgical set up for thyroidectomies.

	Onset Of Effect	Long Term Remission	Hypothyroid After Operation	Advantages	Disadvantages	Patients Factors Favoring The Treatment Option
ATD	2-4 weeks onset Most achieve euthyroid in 8-12 weeks	30-50%	15-20% over many years	Non invasive Cheaper Outpatient No preparation needed. No worsening of GO Low hypothyroid risk.	Side effects Low remission rate Compliance & monitoring issues	Poor surgical and RAI candidates. GO Pregnancy and lactation High remission chances
RAI	4-8 weeks. Most achieve euthyroid in six months	75% in 6-12 months	Almost 50% in one year and increases with time.	Cost effective Outpatient Few sides effect Reduced goitre size Can be used in those with comorbidities	Radiation risk and precautions. Needs to delay pregnancy. Worsens GO in 15-20%. Permanent hypothyroidism risk. Transient worsening of hyperthyroidism	Low chance of remission Poor surgical candidates and/or contraindications to ATD.
Surgery	Immediate	Almost 100%	Almost 100%.	100% effective and immediate effect. No worsening of GO Removes any suspicious nodule / cancer, associated hyperparathyroidism treatment also. Recurrence is very low.	Surgical complications (RLN injury, hypoparathyroidism) and surgical scar. Costly and inpatient Permanent hypothyroidism Not safe with other comorbidities.	Thyroid cancer or suspicious nodules. Associated hyperparathyroidism Pregnancy and lactation when ATD don't work. Active GO. Large goitre, cosmetic reasons or compression symptoms.

Table 1: Comparison of various treatment options for Grave's Thyrotoxicosis.

Abbreviations: ATD (Anti thyroid drugs), GO (Grave's Ophthalmopathy), GD (Grave's Disease), RAI (Radioactive Iodine). Comparison of various therapeutic modalities for Grave's Thyrotoxicosis [25].

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