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Chapter

Surgery for Grave's Disease

Kul Ranjan Singh and Anand Kumar Mishra

Abstract

Graves' disease (GD) is the commonest cause of hyperthyroidism followed by toxic nodular goitre. Patients presenting as goitre with clinical features of hyperthyroidism are to be carefully evaluated with biochemically with thyroid stimulating hormone (TSH), free thyroxine (fT4) and radionuclide scan (Technitium-99/Iodine-123). Those with GD also have raised thyroid receptor stimulating antibody levels. Patients are simultaneously evaluated for eye disease and managed accordingly. Initial treatment is rendering patient euthyroid using anti thyroid drugs (ATD) and if remission does not occur either continue medical therapy or proceed for definitive therapy by radioactive iodine ablation (RAI) or surgery. In last decades there is ample literature preferring surgery as preferred definitive therapy. Surgery in thyroid disease has become safer with development of many intra-operative adjuncts but it should be performed by high volume thyroid surgeon. The procedure of choice is near total or total thyroidectomy as it avoids recurrences. Patients who are not eligible or willing for surgery can be managed with RAI.

Keywords: hyperthyroidism, Graves' disease, thyroidectomy, radioactive iodine

1. Introduction

Grave's disease (GD) is the commonest cause of hyperthyroidism world over representing more than 50% of hyperthyroid patients [1]. A woman is 7–10 times more likely to be affected by it [2] . The incidence of autoimmune thyroid diseases like GD and Hashimoto's thyroiditis is on the rise in tropical countries probably due to environmental immunological factors [3]. GD has systemic manifestations. Eyes's are involved to variable extent in more than half the patients. Treatment aims to restore to the thyroid hormones to normal levels along with achieving remission and care of ophthalmological manifestations. Anti-thyroid drugs (ATD), Radioactive Iodine (RAI) and surgery are the current modalities of treatment [1]. They have their unique indications, advantages, disadvantages and complications. ATD are the usual first line of treatment. Relapsing patients or GD with certain co existing conditions may require a definitive treatment. RAI or surgery are indicated in such patients. The choice of definitive therapy depends on the patient and treating physician. Patients involvement in decision making has been associated with increased patients satisfaction [4, 5].

2. Epidemiology and pathogenesis

The peak incidence of GD is observed between 30 to 50 years of age. Annual reported incidence of GD is 50 and of ophthalmopathy is 16 per 100000 population.

Orbital imaging if performed in all patients of GD will reveal changes of ophthalmopathy in upto 70% of patients. Approximately 3% of women and 0.5% of men during their life time can develop GD [6].

GD is an organ specific auto immune disease caused by thyroid stimulating hormone receptor (TSHR) circulating stimulating auto antibodies. The TSHR stimulating antibody binds to leucine rich extracellular domain of TSHR on surface of thyrocytes and orbital fibroblasts and IGF1 receptors. After binding it increases production of intracellular cyclic AMP causing thyrocyte growth and increased thyroid hormone production.

3. Diagnosis

Measurement of Free T4/Free T3 and TSH is the initial diagnostic test. In overt hyperthyroidism FT4 and FT3 are elevated but in milder hyperthyroidism FT4 may be normal with only FT3 elevation. TSH R antibody is sensitive (97%) and specific (98%) tool for accurate diagnosis of GD [7]. High resolution ultrasound reveals diffuse goiter and hypoechogenicity. Diagnosis is confirmed by thyroid scintigraphy by Tc ^{99} pertechnatate or I ^{123} scintigraphy. Scintigraphy is definitely needed for diagnosis.

4. Treatment options

Anti-thyroid drugs (ATD) are used in the initial management of GD with aim to achieve euthyroidism. Once patient is euthyroid it should be maintained to achieve remission. About half of the patients go into remission after 18 to 24 months of treatment with ATD. Patients without remission and recurrent disease (30–40% in the first 12 months and approximately 50–60% in long term) require definitive therapy. Definitive therapy is either surgical or medical ablation of all thyrocytes. The options are radioactive iodine (RIA) or thyroidectomy. After ablative therapy thyroid hormone replacement is provided to control hypothyroidism. There are reports of use of long term ATD to achieve remission. Choice between RIA and thyroidectomy are influenced by physician, patient, institutional and geographical beliefs and practice patterns. The most "effective" therapy for both physician's and patient perspective will be which will provide rapid euthyroidism and prevent recurrences.

Early and rapid euthyroidism is desirable in all GD patients as it decreases mortality and halts eye disease progression. In a retrospective cohort study of 4189 GD patients regardless of the method of treatment, low TSH at 1 year following GD diagnosis was associated with a 55% increase in cardiovascular mortality (atrial fibrillation, heart failure, pulmonary hypertension, angina pectoris, and stroke) [8]. Lillevang et al. in a cohort study of 235,547 individual investigated association between hyperthyroidism and mortality in both treated and untreated groups and concluded that decreased TSH increases mortality in both groups and with every duration of 6 months of suppressed TSH was associated with 11–13% increase in total mortality [9]. Dale et al. found that even transient hypothyroidism during treatment was associated with greater weight-gain during medical treatment in 162 consecutive hyperthyroid patients [10]. Even consensus statement of the European Group on Graves' orbitopathy (EUGOGO) recommends avoidance of hypothyroidism as it can cause exacerbation of thyroid eye disease [11].

Thyroidectomy is the only modality of treatment which can provide both rapid euthyroidism and prevent recurrence. There are reports of RAI worsening GD ophthalmopathy [12, 13]. In a systematic review of literature between 2001 and 2011which included retrospective and prospective studies (14,245 patients) on the

comparison of RAI and surgery as best definitive treatment for GD, reported surgery to be 3.44 times more likely to be successful than RAI ($P < .001$). And total thyroidectomy (TT) was 95.45 times more successful than RAI ($P < .001$) and concluded thyroidectomy as the most successful modality for the management of GD. [14].

5. Thyroidectomy

Thyroidectomy has been performed for GD since 19th century. However, the earlier years were fraught with significant morbidity and mortality. Introduction of RAI resulted in a rapid decline in popularity of thyroidectomy for GD. Improvements in medical management and refinements in surgical techniques along with knowledge of long term effects of RAI has renewed interests in surgery and it is re gaining the lost grounds [15–17].

6. Indications for surgery

Surgery is the treatment of choice in those with compressive symptoms attributable to goiter, large goiters, presence/suspicion of co-existing malignancy, GD with non-malignant nodule with no/reduced uptake of RAI which is large in size, co-existing parathyroid pathology. Those lactating, pregnant or desirous of pregnancy within next 6 months and presence of significant active ophthalmopathy are advised surgery [5, 18–20]. Pediatric patients failing ATD are more likely to undergo thyroidectomy compared to RAI [21]. Intolerance/non-compliance to ATD, patient preference is an indication in themselves for surgery as treatment of choice.

Indications of thyroidectomy in GD patients include following (6C's):

1. ATD **C**ontraindicated: Difficulty with adequate hormonal control on medications, or Intolerance, or recurrence after ATD treatment

2. RAI **C**ontraindicated: pregnant and nursing women, Large goiter with or without compressive symptoms (dysphagia, dysphonia, dyspnoea), Relatively low uptake of RAI, associated thyroid nodule with confirmed or suspected thyroid malignancy,

3. **C**oexisting moderate-to-severe active Graves' orbitopathy

4. Associated **C**oexiting disease: periodic paralysis

5. Other **C**onditions: Young or pediatric patients, women planning a pregnancy within 6 months, refusal or lack of facilities for RAI, individual preference for surgery

6. **C**igrette Smokers (increased risk of exacerbation of eye disease after definitive treatment with radioactive iodine).

7. Advantages of surgery

Surgery is considered the most effective treatment for GD. It results in prompt control of hyperthyroidism. Co-existing thyroid nodules a subset of which may be harboring malignancy are treated concurrently by surgery [22]. Surgery is said to have

the best ophthalmological outcome in ophthalmopathy compared to ATD and RAI although these observations are based on expert opinion or non-randomized clinical trials [23–27]. Recurrence has been seen both after ATD and RAI with the former having a significantly higher recurrence rate. Though the recurrence rates after RAI and surgery are not significantly different, multiple doses of RAI may be required for cure in a given patient [23]. In a meta-analysis involving 1402 patients across 5 continents, surgery had the lowest recurrence rates even though a sub total thyroidectomy was the procedure performed in those with available surgical records [27]. More over surgery avoids the long-term systemic side effects of ATD and radiation exposure of RAI. Though a matter of debate, patients having chosen surgery as a definitive treatment are likely to be more satisfied compared to RAI [5, 28]. Patients preference should always be taken into consideration. Patients are likely to browse the internet for more information. However, the both reliability and comprehension of available information is occasionally questionable [29]. Hence, the treating physician should make available to the patient pertinent information so that patient can make an un biased decision which will further improve compliance and satisfaction to treatment.

8. Geographic variability in preferred treatment options

There are wide variations in the preferred first line treatment for GD. The choice is culmination of patient and physician preference along with disease status. In the US, RAI is likely to be the primary therapy though its popularity is decreasing. ATD are preferred in Latin America, Europe and Japan [30, 31]. Popularity of ATD has also surpassed RAI in New Zealand [32]. Once again ATD are the favored first line treatment in middle east and north African regions. Also, the physician practices were found to be that between European and American preferences, probably attributed to their training and affiliations [33].

9. Peri operative management

Imaging of thyroid is essential, and ultrasonography is useful. It aids in surgical planning and presence of nodule(s) mandates a fine needle aspiration cytology before surgery. Contrast enhanced CT scan (CECT) may be required for large goiters. Euthyroid state should be achieved in all patients before surgery [30]. This is achieved by ATD which is continued till the morning of surgery. Tachycardia if present is controlled by institution on beta blockers. The role of pre-operative Iodine solution remains controversial but the authors favor same [34]. Lugols Iodine/collosal Iodine/SSKI is given thrice a day for 7–12 days prior to surgery. Iodine has been shown to decrease the vascularity the thyroid and makes the gland firmer. These changes aid the surgeon [35]. Guidelines suggested by various professional bodies aid in management and peri operative preparation of hyperthyroid patients of which American Thyroid Association (ATA) seems to be most commonly followed. However, a study by Siddique Akram et al. found that adherence to ATA guidelines did not impact the outcome significantly but for increased intra operative tachycardia in patient not following ATA guidelines [36]. In fact, almost 28% of the cohort remained hyperthyroid at the time of surgery but no adverse impact was noted. Pre-operative vit D deficiency may result in higher incidence of post thyroidectomy hypocalcemia [37]. Vit D and calcium may be supplemented in pre-operative period to reduce the incidence of post-surgery hypocalcemia [38, 39]. However unpublished data from authors have not shown any advantage of supplementation in reducing post TT hypocalcemia.

Surgery is best performed by a high-volume surgeon in a specialized unit for best outcome [40]. Surgical adjuncts may be utilized as per need, availability, cost constraints and surgeon preference. Meticulous surgery parathyroid vascularity is of prime importance in bettering outcomes. Parathyroid auto transplantation after inadvertent injury or excision results in increased occurrence of temporary hypocalcemia but not permanent hypocalcemia [41].

Post thyroidectomy, patients are kept under observation for development of hypocalcemia or risk of bleed. These were traditionally said to occur at a higher incidence after surgery performed for GD [41]. Hungry bone syndrome, Vitamin D deficiency, female sex are factors that have been associated with apparent higher incidence of post TT hypocalcemia in GD. However, recent studies have concluded that hypocalcemia and post thyroidectomy bleed do not occur at a significantly higher rate in GD [42]. Post TT PTH may be evaluated as per institutional protocols to predict hypocalcemia and plan early discharge. PTH gradient is said to better predict hypocalcemia than any single value. Same day safe discharge of patients is feasible for GD after surgery with no adverse outcomes [43]. ATD are discontinued and Beta blockers if prescribed are tapered gradually in the post-operative period. Thyroxine supplement is started between POD1–7 at a dose if 1.6–2.1 microgram/Kg.

10. Rapid preparation for graves surgery

Patients are usually rendered euthyroid by ATD to reduce peri operative complications with thyroid storm being the most dreaded one. However, a subset of patients may require urgent/emergent surgery in view of significant compression, intolerance of drugs or failure of drugs. Such patients may be subjected to a rapid preparation protocol where in two or more of dexamethasone, beta blocker, sodium iopodate, iopanoic acid, collosal/lugols Iodine, cholestyramine, iodinated radiographic contrast agent, lithium and ATD if tolerated are used for 10–12 days prior to anticipated surgery. No significantly increased morbidity has been reported after surgery in the rapidly prepared patients and this strategy is required and is feasible in a subset of patients [44–46]. The occurrence of thyroid storm is rare and biochemically hyperthyroid patients may undergo thyroidectomy safely if the surgeon and anesthetist are comfortable [47]. However, the consensus remains that the outcome is best when surgery is performed on a euthyroid patient.

11. Choice of surgical procedure

Bilateral subtotal thyroidectomy (STT), Dunhill procedure (DP), near total thyroidectomy (NTT) and total thyroidectomy (TT) are the four procedures that have been or are being performed for GD. STT, DP, NTT were the procedure of choice till 21st century due to said higher incidence of hypoparathyroidism, nerve damage or hematoma [15]. However, these have not been verified in recent large studies or meta-analysis [48]. A retrospective cohort study 8032 patients of benign thyroid disease having undergone STT or TT found no difference in temporary of permanent nerve damage and permanent hypoparathyroidism though temporary hypocalcemia was significantly higher in TT compared to TT (13.12% Vs. 2.7%) [49]. A similar trend has been seen in most other studies. TT for GD has been found to have lower rates of recurrent hyperthyroidism compared to other procedures (STT more than DP) [17, 50]. The nerve damage rates have been higher however hypocalcemia rates have been slightly higher though they do not reach statistical

significance [50]. The choice of surgical procedure did not have a difference in their effect on Graves' ophthalmopathy [17, 50]. RAI with steroid cover was found to be not inferior to surgery. The TT performed by trained surgeons at high volume center have no higher rates of these morbid complications. More and more TT are now being performed for benign diseases throughout world. Thomas WT et al. in an analysis of nationwide in patient analysis in US noted an increase in TT for benign diseases from 17.6% in 1993–1997 to 39.6 in 2003–2007 [51]. This trend is seen across the globe even in less developed regions [40, 52]. However TT may be avoided in in situations where lifelong thyroxine supplements may be un reliable, more common in the lesser developed countries [3]. Never the less, 2016 ATA guidelines for Hyperthyroidism suggest that a NTT of TT should be performed for GD if surgery is being contemplated [30].

12. Disadvantages of surgery

Patients would require lifelong thyroxine replacement after thyroidectomy and compliance may be an issue in some. Also, potential risk of permanent hypoparathyroidism and recurrent laryngeal nerve damage or neck hematoma are present. However, in trained hands, their incidence is no higher than after surgery for euthyroid goiters. Vis a vis ATD and RAI, surgery is the least cost effective first line treatment of Grave's disease [53, 54]. In recurrent GD after ATT, surgery was more cost effective than RAI or lifelong ATD to a large extent [55]. The cost implications are likely to vary across the globe depending on various factors.

13. Surgical approach to thyroid

Though conventionally, open thyroidectomy through a transverse collar incision is the standard of care, heightened cosmetic demands of patients along with refinements in surgical instruments and surgical training has resulted in significant shift favoring minimally invasive procedures. Meta-analysis of 846 cases between 1999–2011 by Zhang et al. concluded that endoscopic thyroidectomy provides better cosmetic satisfaction along with lesser blood loss at the expense of higher costs and operative time with acceptable rates of hypocalcemia and nerve compromise [56].

Robotic surgery is now a feasible option for grave's disease with comparable complication rates [57]. Also, larger glands can be excised via robotic technique. Retrospective analysis of 44 robotic TT via bilateral axillo- breast approach was no inferior when compared to 144 cases of open thyroidectomy in terms of recurrence, hypocalcemia and nerve damage on prolonged follow up of 35 months [58]. This is now a valid option for those concerned about cosmesis.

14. Conclusion

Etiology of hyperthyroidism has to be determined thoroughly to determine the line of management. Radioactive iodine ablation (RAI) or surgery is the main modality of treatment in GD. Anti-thyroid drug is essential to make the patient euthyroid prior to definitive therapy. Prompt discussion with patients regarding delayed outcome and retreatment in those who opt for RAI is mandatory. Surgical treatment of choice in the form of NTT or TT ought to be performed in a high-volume centre to reduce complication and recurrence. Toxic adenoma and TMNG are managed similarly to GD i.e., rendering euthyroid with ATDs, followed by

definitive therapy. Extent of surgery in toxic solitary adenoma depends on radiology, nuclear imaging after malignancy is ruled out. Newer ablative therapies like RFA, EA, LTA are considered as a substitute for definitive therapy in selective patients. Nonetheless malignancy should always be treated by surgery.

Conflict of interest

"The authors declare no conflict of interest."

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