

REVIEW ARTICLE. CURRENT CONCEPTS IN THE MANAGEMENT OF THYROID GLAND DISORDERS.

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ABSTRACT

Thyroid gland disorders are common, being second to Diabetes Mellitus in Endocrine practice. The normal thyroid gland is not visible and is not palpable. More than 90% of thyroid gland disorders present with goitre. Thyroid gland hormone excess has marked effects on most systems of the body, especially the nervous and cardiovascular systems. Similarly, hormone deficiency affects all the systems, although is more insidious in onset.

A detailed history, physical examination, and investigations will determine the diagnosis, and the type and cause of the disorder. There is need to determine if the patient is euthyroid, hyperthyroid or hypothyroid. The management may be medical, surgical, and/or radioiodine therapy. All patients for surgery or radioiodine therapy should be rendered euthyroid as much as possible with medical treatment to reduce the chances of complications intraoperatively or postoperatively.

In the United States of America (USA), most patients with Graves Disease are offered antithyroid drugs, radioiodine therapy, or a mixture of both. Surgery is used to treat large and giant goitre, or patients not likely to achieve relapse on medical treatment – such patients usually require more than 10 mg of Methimazole for maintenance therapy daily, and patients with high titre of Thyroid Receptor Antibodies (TRAbs). Radioiodine therapy could be by dosimetry or ablative dosing. For instance, 20 mCi of radioactive iodine, Iodine 131 (I^{131}) alleviates hyperthyroidism in almost all patients and induce hypothyroidism in 90% of cases. Replacement with Levo-Thyroxine for life is indicated and should be communicated clearly to ensure follow-up. Antithyroid drugs are withdrawn 7 days before radioiodine therapy. Post radioiodine therapy, antithyroid drugs may be needed to ameliorate excess thyroid hormone in the blood. Radioiodine therapy is contraindicated in pregnancy and lactation. Therefore, all women in the child bearing age must undergo pregnancy test before radioiodine therapy.

INTRODUCTION

The thyroid gland weighs 15-25 grams, and is not visible and palpable clinically. The two lobes of the thyroid gland are joined by an isthmus. The oesophagus lies medial to the two lobe of the thyroid gland just behind the trachea. Each recurrent laryngeal nerve on both sides lies between the trachea and the oesophagus. The thyroid hormones: thyroxine (T4) and Triiodothyronine (T3) are formed from Iodine and the amino acid, Tyrosine. Daily adult iodine requirement is about 150 mcg. More iodine is needed in pregnancy and lactation. Thyroid hormones are essential for the normal functions of all tissues, and these include: regulation of growth, mental development and metabolic functions.¹⁻³

Iodine deficiency is the commonest cause of goitre in Nigeria.^{4,7} Other causes of goitre are Graves disease, nodular goitre, thyroiditis, abscess, tuberculosis and metastatic mass.⁸⁻¹³ The use of iodized salt as a national and global policy has markedly reduced the prevalence of iodine deficiency and goitre.

Sea food such as fish is rich in iodine. Intramuscular injection of 480 mg of iodine as iodized oil lasts for 3 to 4 years in the body; or if taken orally is effective for 12 to 18 months. Water can also be iodized. Lugols iodine contains 7 mg of iodine in one drop and this will provide enough use for two weeks.¹⁻²

PROTEIN BINDING AND ANTIBODIES

More than 99% of thyroid hormones are bound to plasma proteins. Only the unbound thyroid hormones are physiologically active in blood and tissues. Protein binding is to: Thyroxine Binding Globulin (TBG), an alpha globulin (70%); Thyroxine Binding Prealbumin (TBPA), now called Transthyretin (TTB) (10%); and Albumin (10-15%). The measure of free T4 and free T3 is clinically more important than measuring the total hormone, either T4 or T3. Most cases of Graves disease and thyroiditis are associated with autoantibodies to some thyroid gland components such as peroxidase enzyme, thyroglobulin and receptors in the thyroid cell membrane. These are anti-thyroperoxidase (anti-TPO), anti-thyroglobulin (anti-Tg) and Thyroid Receptor antibodies (TRAbs).^{8,13-16}

CLINICAL FEATURES AND SYNDROMES

Swelling in the anterior part of the lower neck which may be generalized or localized is common. Pressure symptoms such as difficulty with breathing or dysphagia are due to compression of the trachea and oesophagus respectively by the enlarged thyroid gland. Cardiac symptoms are common in the elderly with thyrotoxicosis. Symptoms of distant metastasis such as bone pain should be looked for. History of changes in mood, energy, sleep, appetite, bowel habits, menstruation and heat or cold preference are important. A detailed drug history is important. During examination determine thyroid size, nature of enlargement – diffuse or nodular, and check for tenderness. Determine if the thyroid gland is mobile by asking patient to swallow some water. Palpate for the different regional lymph nodes. Percuse over the upper sternum for retrosternal goitre extension. Ascultate for bruit which is common in Graves disease. Check for tachycardia, warm sweaty palms, tremors, elevated Blood pressure and wide pulse pressure. Examine the eyes for proptosis, lid lag and lid retraction. In Graves disease eye signs include soft tissue swelling, conjunctival oedema, proptosis, paralysis of certain eye muscles and corneal eye damage. Clinical syndromes are:

1. Autonomous secretion of thyroid hormones in the setting of goitre may be due to Graves disease, toxic multinodular goitre, adenoma, subacute thyroiditis or metastatic thyroid carcinoma.

2.Excessive ingestion of thyroid hormones or iodide is related to Amiodarone tablets, self-administration of thyroid hormones (Thyrotoxicosis Factita), Jod-Basedow syndrome, and iodine use in the setting of iodine deficiency.¹⁷

3.Rare causes of excess thyroid hormone secretion occur in Thyroid Stimulating Hormone (TSH) secreting tumor, which may be pituitary or trophoblastic in origin; Struma ovarii (thyroid tissue in an ovarian teratomas; excessive human Chorionic Gonadotrophin (hCG) such as in molar pregnancy or Choriocarcinoma; or pituitary resistance to thyroid hormone.

4.Subacute thyroiditis has three types: postpartum thyroiditis which is autoimmune; lymphocytic thyroiditis also autoimmune and is usually silent and painless; and the granulomatous type which usually is painful and viral in origin with Human Lymphocyte Antigen (HLA)-Bw 35 association.^{6,12}

Subacute thyroiditis usually run a short course of 6 to 8 weeks of thyrotoxicosis, followed by 8 to 16 weeks of hypothyroidism, with recovery to normal in 90% of cases. Treatment is mostly symptomatic and follow-up of the clinical course.

5.Amiodarone is used in the treatment of Cardiac Arrhythmias. One molecule of Amiodarone has two atoms of iodine. 200 mg of Amiodarone has 75 mg of iodine. This means that 37.5% of Amiodarone is iodine. Amiodarone has a long half-life of 54 days in plasma and can lead to significant accumulation of iodine in the body. Amiodarone can cause thyrotoxicosis by two mechanisms. Type 1 phenomenon is by the Jod-Basedow mechanism; while the Type 2 phenomenon is by cytotoxic damage to the thyroid cells, with increased interleukin-6 in the blood. Amiodarone inhibits the conversion of T4 to T3 in the peripheral tissues and this could result in hypothyroidism especially when used for a long time.

6. Hypothyroidism is the result of thyroid hormone deficiency over a period of time. Iodine deficiency is the commonest cause of goitre and hypothyroidism. Drugs such as Amiodarone, Lithium and interferon alpha can cause hypothyroidism. Excessive use of thionamide drugs (Carbimazole, Methimazole and Propylthiouracil) in the treatment of thyrotoxicosis can render a patient hypothyroid.^{18,19} Therefore, there is need for close clinical monitoring during use of these drugs.

Post thyroidectomy and post radioiodine therapy may require lifelong replacement therapy with Levo-thyroxine tablets. Autoimmune thyroid disease such as Hashimotos disease ends up with scarring of the thyroid gland which results in hypothyroidism. Infiltrative diseases such as sarcoidosis, haemochromatosis and fibrosis can replace thyroid tissue. Congenital absence of the thyroid gland and defects of thyroid hormone synthesis do occur. Pituitary and hypothalamic lesions can cause secondary hypothyroidism.¹⁻³

Most adults require between 100 to 300 mcg of Levo-thyroxine daily after total thyroidectomy and congenital absence of the thyroid gland. Treatment is started with 50 mcg daily and adjusted until TSH is normal and patient is euthyroid and asymptomatic. Cardiac patients may start with 25 mcg daily. Differential diagnosis include depression, psychosis (myxoedema madness), and syndrome of chronic fatigue.



THYROTOXICOSIS IN PREGNANCY

Hyperthyroidism can occur in pregnancy from the known causes; however, Graves disease is the commonest. Maternal T4 crosses the placenta and therefore can affect the fetus. Maternal TRAbs cross the placenta in the last half of pregnancy. The fetal Hypothalamic-Pituitary axis is well developed by 20 weeks of gestation. Propylthiouracil (PTU) and Methimazole cross the placenta. PTU is less teratogenic than Methimazole, and therefore is the drug of choice in treating thyrotoxicosis in early pregnancy. However, Methimazole has fewer side effects than PTU and is therefore used after the first trimester of pregnancy. PTU has side effects of polyarthritis, ANCA positive vasculities, agranulocytosis and hepatitis. Methimazole is more commonly associated with hepatic cholestasis. 100 mg of PTU is equivalent to 5 mg of Methimazole. Beta blockers such as propranolol can be used in pregnancy for short period and in low doses. Generally, drugs are not needed during the third trimester of pregnancy. Maternal pulse rate should be kept at 90 – 100 per minute. Free T4 should be maintained at the upper level of normal or slightly above normal, while TSH is not normalized. This is to prevent fetal hypothyroidism secondary to antithyroid medication. Therefore, a minimal dose of antithyroid medication is indicated. Transient Gestational Thyrotoxicosis (GTT) may occur in pregnancy due to elevated levels of Human Chorionic Gonadotrophin (hCG), a glycoprotein with similar structure with TSH. This usually resolves after the first trimester and may be treated with low doses of PTU. In Familial Gestational Thyrotoxicosis (GFT) the thyroid receptors are very sensitive to hCG due to mutation of the receptor gene.^{1,2}

INVESTIGATIONS

1. Thyroid Function Test (TFT) measures TSH, T4, and T3 ; and as explained already, free T4 and free T3 are more desirable. This gives the metabolic state of the patient: hyperthyroid, hypothyroid or euthyroid. Some drugs may affect thyroid function, such as – heparin, beta blockers, frusemide, corticosteroids and lithium.
2. Neck Ultrasound defines the totality of the thyroid gland – size, volume, nodules, cysts, calcification and possible extension.
3. CXR with thoracic-inlet view to visualize the thoracic inlet for possible goitre extension which could cause airway obstruction.
4. Fine Needle Aspiration Cytology (FNAC) for tissue diagnosis and histology.

5. Biopsy provides more tissue for multiple assessment and clearer definition of cells.
6. Radioiodine Scintigraphy using Tc99m Sodium Pertechnetate. This helps to determine if the thyroid cells are sensitive to radioiodine therapy. It is also used to calculate the dose of radioiodine for each patient if indicated.
7. Other investigations include Barium swallow, Lipid profile, blood sugar, Full Blood Count, Erythrocyte Sedimentation Rate (ESR), Urinalysis and liver function tests.
8. Antibody studies: anti-TPO, anti-Tg and TRAbs helps to define autoimmune relationship of the disease.

SURGERY

Thyroid gland surgery is fraught with many care and potential complications. Before the discovery of thionamide antithyroid drugs for the treatment of thyrotoxicosis, subtotal thyroidectomy was the common surgery done. Because of the occasional recurrence of hyperthyroidism following subtotal thyroidectomy, most surgeons now perform near total thyroidectomy. Hyperthyroid patients that opt for surgery or radioiodine therapy are rendered euthyroid with antithyroid drugs to reduce or prevent complications. Transient hypoparathyroidism due to the removal of some parathyroid glands or impaired blood flow can occur within seven days postoperative. This should be treated with intravenous Calcium gluconate solution and oral calcium and cholecalciferol (Vitamin D). Permanent hypoparathyroidism will occur if all the parathyroid glands are removed. This should be avoided during surgery by preserving the parathyroid glands – the four of them, or occasionally more than four in number. Damage to the recurrent laryngeal nerve should be avoided during surgery to prevent speech problems. Bleeding into the operation site after surgery is a life threatening complication. Therefore, regular review immediately after surgery and in the next few days is mandatory. Bleeding and haematoma collection can obstruct the airway and lead to death. Tracheostomy may be lifesaving before the haematoma is evacuated. Thyroid gland cancers that are not radioiodine therapy sensitive should be removed by surgery. Papillary carcinomas (PTC) make up 70-90 % of cases in most studies; while, Follicular carcinoma (FTC) make up 5-10 %.²⁰⁻²² Undifferentiated anaplastic cancers are less frequent. Calcitonin producing tumour are derived from the parafollicular cell (C-cells) found in the interstitial space of the thyroid gland. They are called medullary thyroid cancer (MTC). MTC may be sporadic, familial or part of Multiple Endocrine Neoplasia 2 (MEN 2) – A and B. Others tumors include lymphoma, sarcoma, metastasis and others.

RADIOIODINE THERAPY

Radioiodine therapy is preferred to surgery in most advanced countries now because of availability, cost, safety and easy of managing complications after administration. Iodine 131 can be given in calculated doses or ablative dose. Ablative dose completely ablates the thyroid cells and renders the patient hypothyroid. Replacement therapy is with levothyroxine tablets: daily requirement ranges from 100-300 mcg. Start with low dose of 50 mcg and follow up with regular thyroid function test until normal daily requirement is established. Post radiation thyroiditis may occur and should resolve with NSAIDs, steroids and occasional antithyroid drugs. Exacerbation of thyrotoxicosis may occur if patient is not well prepared before radioiodine therapy. Radioiodine therapy may worsen orbitopathy due to increased response and release of TRAbs and cytokines. Radioiodine therapy is contraindicated in pregnancy, lactation and in thyroid nodules suspected of cancer. Only few centres in Nigeria provide radioiodine therapy, such as National Hospital Abuja, University College Hospital (UCH) Ibadan and Eko Specialist Hospital Lagos, a private medical establishment. There is need to create more centres for Radioiodine Therapy, especially in our tertiary health institutions. I expect each state in Nigeria to have at least one of such centres. Established centres should be manned by well qualified staff. Most of our consultants in nuclear medicine are trained in South Africa. It is hoped that very soon that the National Postgraduate Medical College Nigeria and the West African Postgraduate Medical College will provide facilities and educational programme for nuclear medicine in conjunction with the Federal Ministry of Health and the Federal Republic of Nigeria.

CONCLUSION

Thyroid gland disorders are common in Nigeria. Most patients with disease of the thyroid gland present with goitre. The patients are either hyperthyroid, euthyroid or hypothyroid. Hyperthyroid patients should be rendered euthyroid as much as possible before radioiodine therapy or surgery to reduce or prevent complications. Radioiodine therapy is safe and cost effective and is the standard therapy in places where it is commonly available such as the United States of America and Europe. We have only few centres for Radioiodine Therapy in Nigeria. There is need to establish more centres for Radioiodine Therapy in Nigeria.

All patients with thyroid gland disorders should be followed up for life and must be properly educated and informed. Most patients with hypothyroidism require replacement therapy with Levo Thyroxine tablets for life. Hypothyroidism may be primary or secondary to radioiodine treatment or surgery. Both hyperthyroidism and hypothyroidism can be treated in pregnancy. Benign thyroid tumor can be ablated by radioiodine therapy or removed by surgery. Thyroid cancer not sensitive to radioiodine treatment should be removed by surgery in addition to external beam radiotherapy or occasionally chemotherapy. Treatment of thyroid diseases in Nigeria has made significant progress. However, there is need to do more by the Federal Government of Nigeria, Federal Ministry of Health, and Postgraduate Medical Colleges – both National and West Africa.

Key words: Thyroid gland, goitre, thyrotoxicosis, hypothyroidism, pregnancy, radioiodine therapy and surgery.

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