

QUARTERLY MEDICAL REVIEW

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THYROID DISORDERS

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THYROID DISORDERS

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An estimated 108 million people in India suffer from endocrine and metabolic disorders, with the poor mainly bearing the brunt of the disease. Several of these diseases are caused by environmental factors, are preventable and can be also effectively treated at affordable cost. Yet a majority of them remain undiagnosed and untreated due to the lack of technology use. Recent estimates indicate that 800 million to one billion people are exposed to insufficient supply of iodine. At least 200 million have goiter. These conservative figures also include large industrialized countries.

Disorders of Thyroid Gland in India

Disorders of thyroid hormone metabolism are commonly encountered in clinical practice. Thyroid disorders are the most common among all the endocrine diseases in India. Though endemic goiter and related problems of human health and development caused by nutritional iodine deficiency were thought to be confined to Himalayan and sub-Himalayan regions, isolated studies by independent investigators as well as a multi-centric national study by the Indian Council of Medical Research in the eighties showed country-wide prevalence of endemic goiter. Iodine deficiency disorders were widely prevalent in Indian subcontinent before the successful salt iodisation.

Till 1973, it was believed that goitrous enlargement of the thyroid in iodine-deficient populations was adaptive in nature resulting in functional euthyroidism in all but exceptional situations. However, AIIMS scientists showed that majority of the subjects with larger grades of goiter were functionally de-compensated and hypothyroid in severely iodine-deficient regions. These observations, confirmed subsequently by several workers

in other endemic regions of the world, helped focus attention on the serious nature of nutritional iodine deficiency as a health problem. Currently there is national and international recognition that successful salt iodation has virtually eliminated nutritional iodine deficiency in the country. Studies done to assess the impact of salt iodation on incidence of neonatal hypothyroidism in the same districts, where pre-salt iodation studies were done, showed remarkable decline in the incidence from a 100/1000 birth to less than 18/1000 birth. The salt iodation programme is thus saving millions from neonatal hypothyroidism-related mental retardation and other iodine deficiency disorders in the country.

There are several other functional disorders of thyroid found in the country. Thus, thyrotoxicosis is a widely prevalent disorder of the thyroid in north India. Recently a countrywide study was done to assess the prevalence of common thyroid disorders in the post salt-iodation phase among school children, NCC cadets as well as army recruits from all over the country. The results of these studies, show 23% residual goiter prevalence among school children countrywide, with normalized urine iodine excretion, indicating elimination of nutritional iodine deficiency. Functional studies of the goitrous subjects showed overall prevalence of 5.4% hypothyroidism, 1.9% hyperthyroidism. 7.5% prevalence of autoimmune thyroiditis was demonstrable by fine needle aspiration biopsy among female goitrous students. On the basis of this countrywide study and other related studies, it can now be estimated that the total burden of significant thyroid disease in the country in the post salt-iodization phase is approximately 42 million.

The profile of thyroid disorders encountered in pediatric and adolescent age groups in India is similar to that seen in most parts of the world except for the prevalence of iodine deficiency disorders in certain endemic regions of this country. Clinical presentation is most commonly for hypothyroidism and goiters and infrequently for hyperthyroidism.

Thyroid disorders are common endocrine problems encountered in the paediatric and adolescent age group. Amongst the functional thyroid disorders hypothyroidism is far more common than hyperthyroidism. Though simple goitre is common in this age group, nodular goitre and in particular solitary thyroid nodules are uncommon. Functional thyroid disorders lend themselves to effective treatment and monitoring strategies.

The Thyroid Hormones

The principal role of the thyroid gland is to regulate tissue metabolism by producing the thyroid hormones 3,5, 3', 5'-tetra-iodo-L-thyronine (levothyroxine, L-thyroxine, T₄) and, in smaller amounts, 3,5, 3'-tri-iodo-L-thyronine (liothyronine, triiodothyronine; T₃). In infants and children thyroid hormones are also necessary for the development of the CNS and for normal growth and bone maturation.

The production of thyroid hormones depends on an adequate supply of dietary iodine. Iodine is reduced to iodide in the gastrointestinal tract and is then readily absorbed and actively transported into the thyroid gland. Oxidized iodide is incorporated into the glycoprotein thyroglobulin to form L-mono-iodotyrosine (MIT) and L-di-iodotyrosine

(DIT), which are inactive. The hormonally active iodothyronines are formed by a coupling reaction T_3 and T_4 . These are joined by a peptide bond to thyroglobulin and stored in the follicular colloid. The thyroglobulin is degraded to release T_3 and T_4 into the circulation; iodide resulting from this reaction is recycled. Whereas T_4 enters the circulation only by direct glandular secretion, most of the T_3 in the body is produced by the mono-deiodination of T_4 in the peripheral tissues.

Thyroid hormone homeostasis is maintained by autoregulatory mechanisms within the gland, and by the hypothalamic-pituitary-thyroid axis. In response to falling plasma concentrations of T_3 and T_4 , the hypothalamus secretes thyrotropin releasing hormone (protirelin; TRH). TRH stimulates the synthesis and release of thyroid stimulating hormone (thyrotropin; TSH) by the anterior pituitary gland. TSH acts on the thyroid gland to increase production of T_3 and T_4 , and also releases the hormone stored in the gland. The secretion of TSH, and possibly TRH is suppressed as thyroid hormone concentrations in blood increases. The term euthyroidism is used when the thyroid gland is functioning normally and there are normal amounts of thyroid hormone in the blood.

THYROID DISORDERS

Thyroid disorders are the most prevalent of all autoimmune diseases and identifying them clinically can be challenging.

Autoimmune thyroid diseases (AITD) are the far most common autoimmune disorders.

Disorders of the thyroid gland result primarily from autoimmune processes that either stimulate the overproduction of thyroid hormones (thyrotoxicosis) or cause glandular destruction and hormone deficiency (hypothyroidism). In addition, benign nodules and various forms of thyroid cancer are relatively common and amenable to detection by physical examination.

HYPOTHYROIDISM

Hypothyroidism is the clinical syndrome resulting from deficiency of thyroid hormones. It mainly affects women and is more prevalent in the middle-aged and elderly. Common clinical manifestations include weakness, fatigue, lethargy, physical and mental slowness, and weight gain; puffy, nonpitted swelling of subcutaneous tissue often develops, particularly around the eyes. Menstrual disorders, hyperlipidaemia and constipation can occur and goiter may develop. The term myxoedema is often reserved for severe or advanced hypothyroidism. In the most severely affected patients, progressive somnolence and torpor combine with cold intolerance and bradycardia to induce a state of coma often known as 'hypothyroid' or 'myxoedema coma'.

Untreated hypothyroidism, in children, results in retardation of growth and mental development. Endemic cretinism is a result of maternal, and hence fetal, iodine deficiency and consequent lack of thyroid hormone production.

Hypothyroidism is usually primary, resulting from malfunction of the thyroid gland. In areas where iodine intake is sufficient the commonest cause of hypothyroidism is auto-

immune thyroiditis which is of two types. In **Hashimoto's thyroiditis** there is thyroid enlargement whereas in **idiopathic** or **primary myxoedema (atrophic thyroiditis)** there is no thyroid enlargement. Hypothyroidism can also be caused by either an excess or a deficiency of iodine. An excess may result from intake of iodine or iodine-containing drugs such as amiodarone. Drugs that decrease thyroid hormone synthesis such as lithium can also be a cause of hypothyroidism. Secondary hypothyroidism is due to disorders of the hypothalamus or pituitary gland. The diagnosis of hypothyroidism is essentially clinical, however, biochemical tests are performed for confirmation. A raised thyroid stimulating hormone (TSH) value and a low free T₄ or T₃ concentration indicates primary hypothyroidism.

Subclinical hypothyroidism is a condition in which there are normal concentrations of thyroid hormones, raised concentrations of TSH, but no clinical symptoms. Subclinical thyroid disease is being diagnosed more frequently in clinical practice in young and middle-aged people as well as in the elderly.

Patients with subclinical hypothyroidism are at a greater risk of developing clinical manifestations if they also have thyroid antibodies. Hypothyroidism is a common disorder, which is mainly treated in primary rather than secondary care.

Hypothyroidism is treated by lifelong replacement therapy with levothyroxine. Although the thyroid gland produces both T₃ (lithyronine) and T₄ (thyroxine), T₃ is mainly produced by peripheral monodeiodination of circulating T₄ and it is therefore sufficient to give

levothyroxine alone. In subclinical hypothyroidism, treatment with levothyroxine is controversial. It has been recommended if antibodies to thyroid peroxidase are present, or if TSH levels are above 10 milliunits/litre. Some also recommend treatment if TSH levels are between 5 and 10 milliunits/litre and goiter or antibodies (or both) are evident. Some patients may require progressive increases in levothyroxine dosage during pregnancy.

In congenital hypothyroidism (neonatal hypothyroidism) early treatment with adequate doses of levothyroxine is required to minimize the effects of hypothyroidism on mental and physical development. It should be started as soon as possible after birth. In severe congenital hypothyroidism some small degree of deficit and incoordination remains, although they should be mild enough to permit a normal life.

Hypothyroid (myxoedema) coma is a medical emergency requiring prompt treatment usually with liothyronine given by intravenous injection because of its rapid action, though in some places intravenous levothyroxine is used. Supportive therapy includes intravenous hydrocortisone (because of the likelihood of adrenocortical insufficiency) and intravenous fluids (to maintain plasma-glucose and electrolyte concentrations). Assisted ventilation and oxygen is required. Hypothyroid coma has a poor prognosis, with mortality around 50% even with treatment.

Diagnosis and treatment of hypothyroidism is an extremely rewarding experience both for the patient and clinician because lifelong restoration of a euthyroid state can be safely and economically achieved with the appropriate use of oral L-thyroxine (T₄) replacement

therapy. Autoimmune thyroiditis is the most common cause of primary hypothyroidism. The initial phases of the disease often start in early adolescence. In older patient populations some degree of biochemical hypothyroidism may be present in approximately 8% of males and 20% of females by the age of 70 years. This is due to the underlying destructive autoimmune process.

Causes of Hypothyroidism

Primary Hypothyroidism

- Chronic autoimmune thyroiditis (Hashimoto's lymphocytic)
- Iatrogenic: ^{131}I therapy, thyroidectomy, external radiation
- Drug induced methimazole, lithium, amiodarone
- Congenital
- Severe dietary iodine deficiency

Central Hypothyroidism

- Pituitary TSH deficiency (secondary hypothyroidism)
- Hypothalamic TRH deficiency (tertiary hypothyroidism)

ETIOLOGY OF HYPOTHYROIDISM

Primary Hypothyroidism

Chronic autoimmune thyroiditis is the most common cause of thyroid gland failure. It results from an immunologic process which leads to cell-mediated destruction of the thyroid gland. Histologically, it can be described as Lymphocytic thyroiditis and Hashimoto's thyroiditis. There is progressive infiltration of the thyroid by lymphocytes, lymphoid follicles, and other inflammatory cells over many years. Ultimately scar remains where the gland was located. The disease starts in early adolescence and primarily in females (5:1 female-to-male ratio). There is a small, irregular, firm, nontender goiter (so-

called adolescent goiter) in an otherwise healthy individual. With advancing age, the cumulative incidence of hypothyroidism gradually rises in both females and males. Exposure to iodine-containing drugs such as intravenous (IV) contrast dyes and to immune modulating agents such as interferon can precipitate this underlying autoimmune process. In postpartum thyroiditis, there is a transient autoimmune exacerbation of thyroid occurring during early postpartum in women with either preexisting or the genetic tendency for autoimmune thyroid disease.

Other causes of Primary Hypothyroidism: Hypothyroidism can also occur due to severe dietary iodine deficiency, surgical thyroidectomy, iodine-131 (¹³¹I) ablation, and excessive antithyroid drug administration. In subacute thyroiditis there may be transient a mild to moderate primary hypothyroidism. However, this form of hypothyroidism is transient and eventually full recovery of thyroid gland function and histology occurs. Neonatal hypothyroidism, or cretinism, represents a rare but important treatable cause of infant mental retardation.

Humans are continuously exposed to many man-made chemicals, which are environmentally persistent and often hormone-like active. Substantial in vitro and in vivo evidence indicate that polyhalogenated aromatic pollutants, such as dioxins, furans, polychlorinated biphenyls and polybrominated diphenylethers, can adversely affect thyroid function mainly resulting in hypothyroidism.

Central Hypothyroidism

Central hypothyroidism is a rare cause representing less than 1% of all cases of hypothyroidism. It results conditions that impair pituitary TSH, secondary hypothyroidism, and/or hypothalamic thyrotropin-releasing hormone (TRH). Other causes of central hypothyroidism include pituitary tumors, empty sella syndrome, trauma, postpartum pituitary necrosis (Sheehan's syndrome).

Clinical features of Hypothyroidism

The classic signs and symptoms of hypothyroidism include weight gain, hypertension, dry skin, hair loss, cold intolerance, chronic fatigue, constipation and fluid retention. The presence of an asymptomatic, small, firm, goiter and delayed deep tendon reflexes are useful to arrive at diagnosis. Common risk factors to develop hypothyroidism include a positive family history of thyroid or other autoimmune diseases and the detection of an elevated serum TSH value with routine blood tests.

Diagnosis of Hypothyroidism

Measurement of serum TSH levels plays an important role in establishing the laboratory diagnosis of primary hypothyroidism, especially in its earliest subclinical stage. As thyroxine secretion declines with progressive destruction of the thyroid gland, even a small decrease in serum FT₄ (Free Thyroxine) concentration within the normal range promptly produces a reciprocal increase in the serum TSH value, for example, a two-fold change in FT₄ produces a 100-fold change in TSH. This isolated elevation in serum TSH serves as an early marker for impending thyroid gland failure. It stimulates the secretion of more biologically active triiodothyronine (T₃) by the thyroid gland, thereby masking the onset of

the signs and symptoms of hypothyroidism. In case of isolated elevation in serum TSH, the serum TSH determination should be repeated along with a serum anti-TPO measurement for diagnostic verification. In such cases complete family history, careful neck examination for the presence of a goiter; and an assessment of deep tendon reflexes is required.

Management of Hypothyroidism

Thyroxine is the standard replacement therapy for patients with clinical hypothyroidism.¹¹ Since thyroxine has a long biological half-life (approximately 7 days), day to day compliance is less of a problem. It produces stable circulating levels of free thyroxine, which can be easily and accurately measured by routine laboratory testing methods. It allows the physiologically adaptive regulation of T₄ to T₃ conversion to occur in response to alterations in nutrition and stresses associated with illness and injury.

It is important to initiate oral thyroxine replacement therapy slowly, starting with a thyroxine dose of 25 µg daily and subsequently increasing the dose by 25 µg every 6 weeks until the serum FT₄ levels reach the midnormal range. A total daily thyroxine dose ranging between 50 and 125 µg usually is sufficient. After this, serial serum TSH levels can be arrived at to achieve TSH levels between 0.5 and 2.0 mU/L. With each thyroxine dosage adjustment, 6 weeks are given before serum TSH is remeasured. Once the final optimal serum TSH level is achieved, the same dose of thyroxine can be maintained. A slight reduction may occur after the age of 60 years due to general slowing of overall metabolism.

In patients with central hypothyroidism before starting thyroxine therapy, special care must be exercised to ensure adequate glucocorticoid replacement as thyroid hormone may accelerate glucocorticoid disposal and thereby may precipitate an Addisonian crisis. The measurement of serum TSH concentrations cannot serve as a useful therapeutic end-point in patients with central hypothyroidism. Serum FT₄ values have to be measured to ensure the correct dose of thyroxine.

Problems encountered in Management of Hypothyroidism

The clinician should become suspicious that a problem likely exists in the management of thyroxine therapy when marked variability in serum TSH values occurs on a fixed thyroxine maintenance dose. The most likely cause is poor compliance which results in suboptimal thyroxine maintenance therapy. If the patient is taking Drugs that alter thyroxine absorption and metabolism an increase in oral thyroxine dose may be necessary. Administering oral thyroxine separately in the morning before taking drugs that interfere with GI absorption can also be tried.

Adjustment of Thyroxine doses

Increased Administration

- Poor compliance
- Decreased gastrointestinal absorption; oral iron, lipid-binding drugs, calcium carbonate, achlorhydria, proton pump inhibitors
- Altered T₄ metabolism: Phenobarbital, phenytoin, carbamazepine, rifampin, HAART
- Pregnancy

Decreased Administration

- Aging

HYPERTHYROIDISM

Hyperthyroidism is a clinical situation where there is excess thyroid hormones in the circulation due to increased synthesis of hormone from a hyperactive thyroid gland.

Thyrotoxicosis is defined as the state of thyroid hormone excess and is not synonymous with hyperthyroidism. However, the major etiologies of thyrotoxicosis are hyperthyroidism caused by Grave's disease, toxic multinodular goiter and toxic adenomas.

Symptoms of Thyroid Disease	
Hyperthyroidism (too much thyroid hormone)	Hypothyroidism (too little thyroid hormone)
Fast heartbeat	Slow pulse
High blood pressure	Hoarse voice
Moist skin and increased sweat	Puffy face
Shakiness and tremor	Loss of eyebrows
Nervousness	Drooping eyelids
Increased appetite with weight loss	Intolerance to cold
Sleep difficulties	Constipation
Frequent bowel movements and diarrhoea	Weight gain
Weakness	Sparse, coarse, dry hair
Raised, thickened skin over shins	Dry, scaly, thick, coarse skin
	Raised, thickened skin over shins
Swollen, reddened bulging eyes	Carpal tunnel syndrome
Sensitivity of eyes to light	Confusion
Constant stare	Depression
Confusion	Dementia

Hyperthyroidism has several causes, including immunologic reactions (believed to be the cause of Graves' disease). People with thyroiditis, an inflammation of the thyroid gland, typically go through a phase of hyperthyroidism. However, the inflammation may damage the thyroid gland and lead to hypothyroidism.

Toxic thyroid nodules (adenomas), areas of abnormal tissue growth within the thyroid gland, sometimes escape the mechanisms that normally control the thyroid gland and produce thyroid hormone in large quantities. A person may have one nodule or many. Toxic multinodular goiter (Plummer's disease), a disorder in which there are many nodules, is uncommon in adolescents and young adults and tends to increase with age.

In hyperthyroidism, regardless of the cause, the body's functions speed up. The heart beats more quickly, and may develop an abnormal rhythm leading to palpitations. Blood pressure is likely to increase. Many people with hyperthyroidism feel warm even in a cool room and sweat profusely, and their hands may develop a fine tremor. Many people feel nervous, tired, and weak, yet have an increased level of activity; have an increased appetite, yet lose weight; sleep poorly; and have frequent bowel movements, occasionally with diarrhoea. Older people with hyperthyroidism may not develop these characteristic symptoms but have what is sometimes called **apathetic** or **masked hyperthyroidism**. They become weak, sleepy, confused, withdrawn and depressed. However, abnormal heart rhythms are seen more often in older people with hyperthyroidism.

Hyperthyroidism can cause changes in the eyes; puffiness around the eyes, increased tear formation, irritation, and unusual sensitivity to light. The person appears to stare. These eye symptoms disappear soon after the thyroid hormone secretion is controlled, except in people with Graves' disease, which causes special eye problems.

Hyperthyroidism may take the form of Graves' disease, toxic nodular goiter, or secondary hyperthyroidism.

Graves' Disease

Graves' disease (toxic diffuse goiter) is believed to be caused by an antibody that stimulates the thyroid to produce too much thyroid hormone. People with Graves' disease have the typical signs of hyperthyroidism and three distinctive additional symptoms. Since the entire gland is stimulated, it can become greatly enlarged, causing goiter. The other symptoms of Graves' disease are exophthalmos and, less commonly, raised areas of skin over the shins.

Toxic Nodular Goiter

In toxic nodular goiter, one or more nodules in the thyroid produce too much thyroid hormone and aren't under the control of thyroid-stimulating hormone. The nodules are true hyperfunctioning benign thyroid tumors and are not associated with the bulging eyes and skin problems of Graves' disease.

Secondary Hyperthyroidism

Hyperthyroidism may (rarely) be caused by a pituitary tumor that secretes too much thyroid-stimulating hormone, which in turn stimulates the thyroid to overproduce thyroid hormones. Another rare cause of hyperthyroidism is pituitary resistance to thyroid hormone, which results in the pituitary gland secreting too much thyroid-stimulating hormone. Women with a hydatidiform mole may also have hyperthyroidism because the

thyroid gland is overstimulated by the high levels of human chorionic gonadotropin in the blood. The hyperthyroidism disappears after the molar pregnancy is terminated and human chorionic gonadotropin vanishes from the blood.

Excess thyroid hormones in the circulation are also found in thyroiditis (hormone leakage) and excess exogenous thyroxine intake. Thyrotoxicosis is the term applied when there is excess thyroid hormone in the circulation due to any cause. Thyrotoxicosis can be easily diagnosed by high serum level of thyroxine (T4) and triiodothyronine (T3) and low serum level of thyroid stimulating hormone (TSH). Hyperthyroidism is confirmed by high isotope (I 131 or Tc99) uptake by the thyroid gland, while in thyroiditis it will be low. Treatment of hyperthyroidism depends on the underlying cause.

Treatment of Hyperthyroidism

Hyperthyroidism can usually be managed with drug therapy, but other options include surgically removing the thyroid gland or treating it with radioactive iodine. Each treatment has advantages and disadvantages.

Antithyroid drugs, Radioactive iodine therapy and surgery are the options of treatment of hyperthyroidism. Propylthiouracil or methimazole, the drugs most commonly used to treat hyperthyroidism, slow thyroid function by decreasing the gland's production of thyroid hormone. Both drugs are taken orally, beginning with high doses that are later adjusted according to the results of thyroid hormone blood tests. These drugs can usually control thyroid function in 6 weeks to 3 months. Larger doses may bring the thyroid function

under control faster – however, there is an increased risk of adverse effects including allergic reactions (most commonly, skin rashes), nausea, loss of taste and on rare occasions, depressed synthesis of blood cells in the bone marrow.

Beta-blocking drugs such as propranolol help control some of the symptoms of hyperthyroidism. These drugs are effective in slowing down a fast heart rate, reducing shakiness (tremor) and controlling anxiety.

Hyperthyroidism can also be treated with radioactive iodine, which destroys the thyroid gland. The dose of radioactive iodine is adjusted to destroy only enough of the thyroid gland to bring its hormone production back to normal, without reducing thyroid function too much. However, most of the time, radioactive iodine treatment ultimately creates hypothyroidism.

Surgery is the preferred treatment for toxic adenoma and toxic multinodular goitre, while radioactive iodine therapy may be suitable in some cases. Antithyroid drugs and radioactive iodine therapy are mostly preferred for Graves' disease. Beta-adrenergic blockers are used for symptomatic relief in most patients of thyrotoxicosis due to any cause.

GOITER AND NODULAR THYROID DISEASE

Goiter refers to an enlarged thyroid gland. Biosynthetic defects, iodine deficiency, autoimmune disease, and nodular diseases can each lead to goiter, though by different mechanisms. In a vast country like ours, goiter is endemic and health surgery facilities are stretched to the very maximum. A population of 9 million people is estimated to be affected by goiter.

DIFFUSE NONTOXIC (SIMPLE) GOITER

When diffuse enlargement of the thyroid occurs in the absence of nodules and hyperthyroidism, it is referred to as a diffuse nontoxic goiter. This is sometimes called simple goiter, because of the absence of nodules, colloid goiter, because of the presence of uniform follicles that are filled with colloid. It is most commonly caused by iodine deficiency and is termed endemic goiter when it affects > 5% of the population. Thyroid enlargement in teenagers is sometimes referred to as juvenile goiter. In general, goiter is more common in women than men. TSH levels are usually normal or only slightly increased. Endemic goiter is also caused by exposure to environmental goitrogens such as cassava root, which contains a thiocyanate, vegetables of the Cruciferae family (e.g. Brussels sprouts, cabbage, and cauliflower), and milk from regions where goitrogens are present in grass.

Clinical Features and Diagnosis

Examination of a diffuse goiter reveals a symmetrically enlarged, nontender, generally soft gland without palpable nodules. Most goiters are asymptomatic. Spontaneous hemorrhage into a cyst or nodule may cause the sudden onset of localized pain and swelling. Thyroid function tests should be performed in all patients with goiter to exclude thyrotoxicosis or hypothyroidism. In iodine deficiency, there may be a low total T₄ with normal T₃ and TSH. A low TSH, particularly in older patients, suggests the possibility of thyroid autonomy or undiagnosed Graves' disease, causing subclinical thyrotoxicosis. Low urinary iodine levels (<10µg/dL) support a diagnosis of iodine deficiency.

Treatment

Iodine or thyroid hormone replacement induces variable regression of goiter in iodine deficiency. In younger patients, the dose of thyroxine can be started at 100µg/d and adjusted till TSH is maintained into the low-normal but detectable range. Treatment of elderly patients should be initiated at 50µg/d. Significant regression is seen in younger patients within 3 to 6 months of treatment; after this time it is unlikely to occur. In older patients less than one-third demonstrate significant shrinkage of the goiter. Surgery is not routinely carried out for diffuse goiter unless there is evidence of tracheal compression or obstruction of the thoracic inlet. Surgery should be followed by mild suppressive treatment with levothyroxine to prevent regrowth of the goiter. Radioactive iodine reduces goiter size by about 50% in the majority of patients.

NONTOXIC MULTINODULAR GOITER

Depending on the population studied, multinodular goiter (MNG) occurs in up to 12% of adults. MNG is more common in females and increases in prevalence with age. There is a

wide variation in nodule size. On histology, there may be seen hypercellular regions or cystic areas filled with colloid. Fibrosis is often extensive, and areas of hemorrhage or lymphocytic infiltration may be seen.

Clinical Features and Diagnosis

MNG typically develops over many years and is generally detected on routine physical examination or when an individual notices an enlargement in the neck. Most patients with nontoxic MNG are asymptomatic and, by definition, euthyroid. If the goiter is large enough, it can ultimately lead to compressive symptoms including difficulty in swallowing, respiratory distress (tracheal compression), or venous congestion. Sudden pain in a MNG is usually caused by hemorrhage into a nodule but could be due to invasive malignancy. Hoarseness, reflecting laryngeal nerve involvement, also suggests malignancy. TSH level is measured to exclude subclinical hyper- or hypothyroidism, but thyroid function is usually normal. Tracheal deviation is common.

Treatment

Most nontoxic MNGs are managed surgically. But surgery is not without risk, particularly in older patients with underlying cardiopulmonary disease.

TOXIC-MULTINODULAR GOITER

In addition to features of goiter, the clinical presentation of toxic MNG includes subclinical hyperthyroidism or mild thyrotoxicosis. It is more common in the elderly and may present

with atrial fibrillation or palpitations, tachycardia, nervousness, tremor, or weight loss. Recent exposure to iodine, from contrast dyes or other sources, may precipitate or exacerbate thyrotoxicosis. The TSH level is low or minimally increased with normal T₄ levels. Thyroid scan shows heterogeneous uptake with multiple regions of increased and decreased uptake.

Treatment

Antithyroid drugs, often in combination with beta blockers, can normalize thyroid function and reduce clinical features of thyrotoxicosis. This treatment, however, stimulates the growth of the goiter. Radioiodine can be used to treat areas of autonomy, as well as to decrease the mass of the goiter.

HYPERFUNCTIONING SOLITARY NODULE

A solitary, autonomously functioning thyroid nodule is referred to as toxic adenoma. There is mild Thyrotoxicosis and the nodule is generally large enough to be palpable. There is absence of clinical features suggestive of Graves' disease or other causes of thyrotoxicosis. On thyroid scan, focal uptake in the hyperfunctioning nodule and diminished uptake in the remainder of the gland is demonstrated as activity of the normal thyroid is suppressed.

Treatment

Radioiodine ablation with large radioiodine doses (e.g. 370 to 1110 MBq (10 to 29.9 mCi) ¹³¹I] have been shown to correct thyrotoxicosis in about 75% of patients within 3 months. Hypothyroidism occurs in <10% of patients over the next 5 years. Surgical resection is also effective and is usually limited to lobectomy, minimizing risk of hypoparathyroidism

or damage to the recurrent laryngeal nerves. Medical therapy is not an optimal long-term treatment.

Thyroid Function in Pregnancy

Pregnancy induces normal physiologic changes that affect thyroid function and thyroid function testing. Increased renal blood flow and glomerular filtration rate lead to an increase in the excretion of plasma iodide, and as a result, dietary iodide requirements are increased from 150 micrograms/day for a normal adult to 200 micrograms/day for a pregnant or lactating woman. Second, because of broad structural homology between the beta-subunits of both TSH and human chorionic gonadotropin (hCG), hCG has an intrinsic—albeit weak—thyroid-stimulating effect. At the end of the first trimester, up to one fifth of euthyroid pregnant women will exhibit a small and transient increase in free T4 levels and a partial TSH suppression. During the remainder of the pregnancy, serum TSH levels return to the generally accepted normal range of 0.4 to 4.0 mIU/L.

Women with hypothyroidism who become pregnant usually require substantial increases in their oral thyroxine maintenance dose very early in pregnancy. Normal fetal brain development in the first 12 weeks depends on maternal thyroxine as a source of thyroid hormone. Deficiency in maternal thyroxine at this stage of pregnancy can reduce the intelligence quotient in the offspring. One possible cause for this increased thyroxine may be due to oral iron supplements, which interfere with thyroxine absorption.

Thyrotoxicosis during pregnancy is almost always caused by Graves' disease and tends to improve as the pregnancy proceeds. PTU is the drug of choice. TSH receptor antibodies are measured in the second or third trimester to look for neonatal hyperthyroidism. Maternal thyroid function tests should be monitored frequently. Mothers may experience an exacerbation of thyrotoxicosis after delivery. All infants of mothers with Graves' disease should have thyroid function tests within the first few days of life and should be seen by a neonatologist.

THYROIDITIS

Thyroiditis is an inflammation of thyroid. Causes of thyroiditis are autoimmune, chronic lymphocytic thyroiditis (CLT), post-partum (painless) thyroiditis, sporadic thyroiditis, subacute thyroiditis, Reidel's thyroiditis and infective thyroiditis.

Chronic Lymphocytic Thyroiditis (Hashimoto's Thyroiditis)

Chronic lymphocytic thyroiditis can present with only goiter or goiter with hypothyroidism. The benefit of treating euthyroid goiter with thyroxine is not clear. Thyroxine therapy may be tried for 3 – 6 months and if goiter reduces, drug can be discontinued. If the goiter reappears on stopping therapy then the treatment should be as in hypothyroidism.

Postpartum Thyroiditis (PPT)

Autoimmune thyroiditis in postpartum women it is known as postpartum thyroiditis or painless postpartum thyroiditis. The histopathology shows extensive lymphocytic

infiltration, but no fibrosis as in Hashimoto's disease and no joint cells as in subacute thyroiditis. The hormonal features present in three stages: Transient toxicosis: during the active phase, there are symptoms of mild toxicosis which may be missed. This period lasts about 8 – 12 weeks. This is followed by a period of hypothyroidism lasting from 2 to 6 months. Then the patient becomes euthyroid again. Treatment consists of beta-blocker during toxic phase and levothyroxine in replacement dose during the hypothyroid phase.

Subacute Thyroiditis (De Quervain's Thyroiditis or Giant Cell Thyroiditis or Granulomatous Thyroiditis)

It is possibly a viral infection of the thyroid. Clinically, there is painful enlargement of the thyroid gland with symptoms of fever, malaise etc. The ESR is very high and the diagnosis is confirmed on histopathology. There is transient toxicosis followed by hypothyroidism and then return to euthyroid state (as in post partum thyroiditis). Aspirin may be given for symptomatic relief. If there is not response to aspirin, steroids (prednisolone 40 mg/day) may be tried. Beta blockers are given during the toxic phase and levothyroxine is administered during the hypothyroid phase.

Reidel's Thyroiditis

There is a very rare disease wherein the thyroid and nearby structures are invaded by dense fibrous tissue causing firm goiter. On palpation, a "woody" hard feel of the thyroid gland is a classic feature. Rarely, hypothyroidism may occur. Riedel's thyroiditis can be associated with retroperitoneal and mediastinal fibrosis. Steroid therapy can be tried to halt fibrous tissue invasion.

Infection of The Thyroid

This is an extremely rare condition and presents with painful thyromegaly and transient toxicosis. Usually this follows upper respiratory infection. Treatment of infection and symptomatic treatment for toxicosis with beta-blocker is required. If an abscess is formed, it should be treated with antibiotics and drainage, if required should be performed. If not, there is danger of mediastinitis.

SOLITARY THYROID NODULE

Thyroid nodule is a discrete swelling that forms a lump in the thyroid gland. It is termed as isolated or solitary. It can occur in any part of the gland. About 70 percent of discrete thyroid swellings are clinically isolated. Some nodules can be felt quite easily, while others can be hidden deep in the thyroid tissue or located very low in the gland where they are difficult to feel. Although most of these swellings (thyroid nodules) are benign, some 15% may prove to be malignant and an additional 30-40% are follicular adenomas. The remainder are non – neoplastic, largely consisting of areas of colloid degeneration, thyroiditis or cysts. These may be asymptomatic or produce symptoms of hyperthyroidism.

Diagnosis and management

If hyperthyroidism associated with a discrete swelling is confirmed biochemically, it indicates either a toxic adenoma or manifestations of a toxic multinodular goitre. On scanning, swellings may be hot (overactive), warm (active) or cold (underactive). A hot nodule takes up the isotope (on isotope scanning) while surrounding tissue is inactive. A warm nodule takes up isotope and so does normal thyroid tissue. A cold nodule does not take up isotope. FNAC (Fine needle aspiration cytology) is the established investigation of choice.

If the nodule is hot, TSH is suppressed and suggestive of autonomously functioning thyroid nodule, it should be treated with surgery or radioactive ablation. The main indication for operation is the risk of neoplasia which includes follicular adenoma as well as malignant swellings. It is seldom possible to distinguish between a follicular adenoma and a carcinoma cytologically, hence removal of a follicular neoplasm is advocated. The value of suppressive therapy is controversial.

The cold solitary thyroid nodule has been a clinical enigma, to both surgeons and pathologists, due to its tendency of harbouring a malignancy, in as high as 20% of the cases. The majority of swellings which are benign, can be treated conservatively and the patient observed at regular intervals.

If FNAC is benign and the nodule is cold and TSH is normal, a trial with thyroxine may be given for 3 to 6 months. If the size reduces, therapy is continued. If there is no response to thyroxine, it must be discontinued and the patient should be observed.

THYROID CANCER

Thyroid carcinoma is the most common malignancy of the endocrine system. It is subdivided into follicular and papillary. Secondary growths are rare. Blood borne metastases occur from primary carcinomas of breast, colon and kidney. Differentiated tumors, such as papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC) are often curable, and the prognosis is good for patients identified with early-stage disease. However, anaplastic thyroid cancer (ATC) is aggressive, responds poorly to treatment, and is associated with a poor prognosis.

Well-Differentiated Thyroid Cancer may be papillary, follicular or medullary

Papillary PTC is the most common type of thyroid cancer, accounting for 7 to 90% of well-differentiated thyroid malignancies. PTC tends to be multifocal and to invade locally within the thyroid gland as well as through the thyroid capsule and into adjacent structures in the neck. Papillary tumours contain a mixture of papillary and colloid filled follicles. Histologically, the tumour shows papillary projections and characteristic pale, empty nuclei. It spreads via the lymphatic system but can metastasize haematogenously to bone and lung. Lymph node involvement by thyroid cancer can be remarkably well tolerated but probably increases the risk of recurrence and mortality, particularly in older patients. Most papillary cancers are identified in the early stages and have an excellent prognosis. Mortality is markedly increased in stage IV disease (distant metastases), but this group comprises only about 1% of patients.

Follicular: Follicular thyroid carcinoma (FTC) is more common in iodine-deficient regions. Microscopically, there is invasion of the capsule. FTC tends to spread by haematogenous routes and blood borne metastases occur in bone, lung and central nervous system. Mortality rates are twice as high as for PTC and blood borne metastases are twice as common. This is because larger proportion of patients present with stage IV disease. Poor prognostic features include distant metastases, age >50 years, primary tumor size >4 cm and the presence of marked vascular invasion.

Treatment

Surgery - All well-differentiated thyroid cancers are basically treated with Total Thyroidectomy. In addition to removing the primary lesion, surgery allows accurate histologic diagnosis and staging and multicentric disease is commonly found in the contralateral thyroid lobe as also with follow up. With Radioactive iodine scan it is possible to rule out remnant carcinoma or metastasis. Lymph node spread can also be assessed at the time of surgery, and involved nodes can be removed.

TSH Suppression Therapy - As most tumors are still TSH-responsive, thyroxine suppression is mainstay of thyroid cancer treatment for differentiated thyroid carcinoma. Though TSH suppression provides therapeutic benefit it should be confirmed by TSH measurement. Suppressive thyroxine is probably not of value in Follicular carcinoma. For patients at low risk of recurrence, TSH should be suppressed into the low but detectable range (0.1 to 0.5IU/L). For patients at high risk of recurrence, or with known metastatic disease, complete TSH suppression is indicated. Thyroid hormone replacement is necessary after near total thyroidectomy.

Radioiodine Treatment - The use of therapeutic doses of radioiodine remains an area of controversy in thyroid cancer management. Well-differentiated thyroid cancer incorporates radioiodine, less efficiently than normal thyroid follicular cells. After near-total thyroidectomy, substantial thyroid tissue remains, particularly in the thyroid bed and surrounding the parathyroid glands. Postoperative thyroid ablation and radioiodine treatment of known residual PTC or FTC reduce recurrence rates. For tumors that take up iodine, ^{131}I treatment can reduce or eliminate residual disease with relatively little associated toxicity. If metastases take up radioiodine, they may be detected by scanning and may be treated with large doses of radioiodine. Most patients with stage 1 PTC with primary tumors <1.5 cm in size can be managed safely with thyroxine suppression, without radiation treatment, as the risk of recurrence and mortality is very low. For patients with larger papillary tumors, spread to the adjacent lymph nodes, FTC or evidence of metastases, thyroid ablation and radioiodine treatment are generally indicated. Cases in which suppression has failed and radioiodine has given permanent control appear to be uncommon.

Anaplastic Thyroid Cancer

This occurs mainly in elderly women and local infiltration is an early feature of the tumours. ATC is a poorly differentiated and aggressive cancer. The prognosis is poor, and most patients die within 6 months of diagnosis. An attempt at curative resection is only justified if there is no infiltration through the thyroid capsule and no evidence of metastases. The uptake of radioiodine is usually negligible, but it can be used

therapeutically if there is residual uptake. Chemotherapy may be tried with multiple agents, including anthracyclines and paclitaxel, but is usually ineffective. Radiotherapy should be given in all cases. If these lesions present in advanced stage with tracheal obstruction, trachea may be decompressed.

Malignant Thyroid Lymphoma - Lymphoma in the thyroid gland often arises in the background of Hashimoto's thyroiditis. A rapidly expanding thyroid mass suggests the possibility of this diagnosis. Response to radiation is good. Surgical resection should be avoided as initial therapy because it may spread disease that is otherwise localized to the thyroid. The prognosis is good if there is no involvement of cervical lymph nodes.

Medullary Thyroid Carcinoma - These are tumours of the parafollicular C cells and not from the cells of the thyroid follicle. High levels of serum calcitonin may be produced by these tumours. MTC can be sporadic or familial and may account for about 10 to 20% of thyroid cancers. The management of MTC is primarily surgical. Involvement of lymph node occurs in about 50-60% cases. These tumors do not take up radioiodine and they are not hormone dependent. Treatment is by total thyroidectomy and resection of involved lymph nodes.

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