

RECENT TRENDS IN MANAGEMENT OF THYROID DISORDERS

Thyroid hormones affect every organ system and most biological processes in the body through their actions on the metabolism of energy substrates, nutrients and inorganic ions. The unique actions of thyroid hormones on growth and development are manifest during the first two decades of life and their crucial role in fetal and early postnatal brain development is well established(1). The thyroid gland is the sole source of thyroxine (T₄) about 100 µg/day, while most of the triiodothyronine (T₃) in circulation nearly 75%, is derived from monodeiodination of T₄ in peripheral tissues(2,3). The circulating T₃ and T₄ are associated with carrier plasma proteins and free T₄ (FT₄) and free T₃ (FT₃) concentrations approximate 0.03 and 0.3%, respectively of the total hormone concentrations.

Disorders of the thyroid gland are the most common endocrine problems of childhood. Thyroid gland is also unique among other endocrine glands in being influenced by environmental factors because of its dependence on adequate supply of iodine and its vulnerability to goitrogens. The three common clinical situations in children involving the thyroid gland are hypothyroidism, thyromegaly and hyperthyroidism.

The advent of sophisticated, laboratory and imaging techniques have rendered both the diagnosis and therapy of thyroid disorders more precise. Today we have tests to assess each aspect of thyroid physiology as well as its immunopathology. Neonatal screening for congenital hypothyroidism has led to early therapeutic intervention. The emphasis has now shifted to drug formulation and bioavailability of thyroid preparations(4).

Hypothyroidism

Congenital hypothyroidism is commonly the result of thyroid dysgenesis (aplasia, hypoplasia or ectopia) or dys-hormogenesis. The prevalence approximates 1 : 4000 worldwide(5) with higher incidence of 1 : 2481 in India(6). Acquired hypothyroidism is often due to autoimmune thyroiditis, ectopia, biosynthetic defects, or hypothalamic/pituitary abnormality, endemic iodine deficiency or goitrogens.

The demonstration of delayed skeletal maturation, subnormal serum T₃, T₄ (or FT₃, FT₄) and elevated TSH establish the diagnosis of primary hypothyroidism. Radioactive iodine uptake (RAIU) gives a direct measure of thyroid function and technetium scintiscans or ultrasonography help to locate the size, site and nodularity. The demonstration of high titres of thyroid antibodies, antimitochondrial (ATA) and antithyroglobulin (ATG) are important for the diagnosis of autoimmune thyroiditis. Presence of significant goiter with hypothyroidism should also raise the suspicion of biosynthetic defects which are likely to involve other siblings and hence genetic counselling is essential.

The goal of therapy is to maintain the circulating T4 level in the upper normal range and normalize the elevated TSH. The preferred preparation is sodium-l-thyroxine because of its uniform potency, reliable absorption and increased bioavailability. Administration of T4 closely stimulates physiologic mechanisms and results in required amount of T3 formation(7,8). Most controversies centre around the dose to be administered to newborns detected on neonatal screening so as to further improve the neurological outcome and IQ(9). The dosage used in various programmes vary from 7 to 15 $\mu\text{g}/\text{kg}$ for newborns(9-11).

In our past studies the dosage of T4 increased with age to a maximum of 0.15 to 0.2 mg/day but the dose on a kilogram body weight basis decreased progressively from 10-12 $\mu\text{g}/\text{kg}$ in infancy to 3-4 $\mu\text{g}/\text{kg}$ in older children(12). It is recently concluded that the dose of levothyroxine correlates more closely with surface area (102 $\mu\text{g}/\text{m}^2$) during childhood(13). During infancy and childhood one-third to half the calculated total dose is administered and increased step wise at intervals of 8-10 days to reach the full dose within 3-4 weeks. In older children with suspected prolonged deprivation, the stepping up of T4 should be more gradual at 2-3 weekly intervals. It is recommended to give medication on empty stomach (to avoid interference with absorption) as a single dose and preferably fasting in the morning, to establish a routine. Unlike in the older children full replacement dose can be initiated in the newborn as soon as the diagnosis is confirmed.

An inadequate dose may affect the intellectual and neurological development adversely, whereas excessive replacement dose may lead to craniostenosis, advanced bone age, hyperactivity and brain dysfunction and possibly osteoporosis.

Careful monitoring of individual infants with dosage adjustment is hence imperative. The serum half life of T4 approximates 5 days in the newborn and 6 days thereafter(13). Thus, blood samples of repeat T4, TSH and T3 are obtained 4 weeks after initiating therapy in the newborn or 5 to 6 weeks after reaching the final calculated dose in older infants and children, preferably 12-24 h after the last T4 dose. Occasionally in the young infants even with adequate dose, the serum TSH concentration may remain inappropriately elevated (usually not more than 20 mIU/ml) with T4 in the upper normal range. In such a situation, free FT4 assay or TSH response to thyrotropin releasing hormone (TRH) can be utilized as a guide to therapy.

After the initial stabilization of hormone values, blood samples to judge the adequacy of treatment should be obtained for T3, T4 and TSH at 2-3 monthly intervals during infancy, twice or thrice during the second year and biannually or annually as the child grows. Growth monitoring and bone age still remain equally important and should continue to guide all physicians. These refer to the therapeutic adequacy over a specified period of time under study; thyroid estimations relate more to the present.

The implementation of neonatal screening has also led to the recognition of a variety of thyroid dysfunction syndromes in the premature infant which are transient, such as transient hypothyroxinemia, hyperthyrotropinemia, and low T3 syndrome(2). These abnormalities in preterm babies need careful evaluation before rushing into therapeutic intervention.

Goiter

Goiters may be caused by Graves' dis-

ease, dysmorphogenesis, iodine deficiency, goitrogens, autoimmune and inflammatory thyroid disease or neoplasia. In USA, 2 to 6% of school children have goiters(14,15). In India the prevalence is about 8 to 9% in school surveys with higher prevalence in children of lower socio-economic group (to be published). Female predominance is marked in all surveys. Goiter is classified into 3 or 4 grades; in the WHO staging the terminal phalanx of the subject is compared to the lateral lobe as an index(16).

Management depends on the underlying cause, the functional status of the gland and the presence of nodularity. Generalized firmness favors thyroiditis. Disturbances of thyroid function and multinodularity usually exclude malignancy as opposed to a firm, irregular, painless or a slightly tender single nodule. Assessment of thyroid functions and thyroid antibodies, radionuclide scanning, ultrasonographic evaluation, fine needle aspiration cytology or occasionally a biopsy help in establishing the diagnosis. A trial of thyroid hormone suppression (0.2 to 0.3 mg levothyroxine) is indicated when the aspiration cytology in a nodule before undertaking surgical removal.

The common clinical situation is an asymptomatic goiter with a symmetrically enlarged thyroid of normal consistency with normal TSH and T₃, T₄. This is usually due to simple colloid goiter or chronic lymphocytic thyroiditis (CLT). Presence of thyroid microsomal antibodies will differentiate CLT from the former in about 60% of cases(17), but prolonged follow up and repeat testing by RIA antibody techniques may be needed in a few. It has been our practice to observe euthyroid patients with small diffuse goiters, for 3 to 6 months and institute levothyroxine therapy (100 to 150 µg/day) if the goiter progresses. Routine

thyroid biopsy is not justified as the treatment is limited to thyroid hormone suppression in most.

Hyperthyroidism

Thyrotoxicosis is an uncommon disorder of childhood with an increase in incidence during adolescence. Girls are affected six to eight times more often than boys. The etiology is varied but Graves' disease accounts for 9.5% of cases in this age group(18). Hypothyroidism may be the result of thyroiditis, deliberate thyroid hormone ingestion or iodine induced, neoplasia as in association with McCune-Albright syndrome or rarely due to TSH producing pituitary tumors. Thus, management differs with the underlying cause.

Elevate thyroid hormone levels in particular T₃, and subnormal TSH by the more sensitive immunometric assay or more recently FT₄ and FT₃ are diagnostic. These patients also have an absent or depressed response to TRH. Radioiodine uptake studies are not usually necessary. The estimation of some of the thyroid autoantibodies have important implications for treatment, as these are related to the underlying mechanisms causing hyperthyroidism.

None of the currently available modalities of therapy, effectively cure the primary immunological abnormality stimulating thyroid activity. The therapy is, therefore, directed to reducing the production of thyroid hormones and blunting their effects. The three conventional forms of treatment are use of antithyroid drugs, subtotal thyroidectomy and radioactive iodine.

Antithyroid drug treatment is most commonly employed and the thioureyline drugs are most effective(2). The major disadvantage is the long duration of therapy and toxic side effects. There is a lag time of

4 to 8 weeks before the euthyroid state is established as the block in iodothyronine synthesis is not complete and the stores of preformed hormones must be depleted. Propylthiouracil (PTU), methimazole (MTZ) and carbimazole (CBI) are used for long term therapy. Initial remission may be achieved in 95%(18). Single daily dose therapy with MTZ though controversial may be effective(18). There is significant incidence of toxic reactions to this group of drugs, especially agranulocytosis which develop during the first few months.

Three therapeutic approaches to achieve a euthyroid state have been utilized while employing antithyroid drugs. An attempt to induce sufficient blockade so as to maintain a euthyroid is one way—the blocking/replacement regimen. Alternatively, the dose of antithyroid drugs can be titrated to normalize thyroid hormone levels. The former has a higher incidence of toxic side reactions whereas the latter have a lower incidence of disease remission(19). Some physicians discontinue drugs as soon as normal thyroid levels are achieved but the remission rate is lower(20). There is general agreement on two or more years of therapy with antithyroid drugs with gradual tapering. The best clinical prognostic guide is the reduction in the size of the thyroid gland and the disappearance of thyroid stimulating antibodies(2,18,21). T3 suppression test is occasionally utilized to judge remission.

β -adrenergic blockade with propranolol is an effective modality for control of adrenergic symptoms during the early phase. The use of iodide is restricted to short term therapy in severely thyrotoxic patients in conjunction with antithyroid drugs and in preparation of patients for thyroidectomy(2,18,21). Sodium ipodate or iopanoate are iodinated organic radio-

graphic contrast agents with effective anti-thyroid action(22). These prevent iodination of T4 to T3 and rapidly decrease the serum T3 level, and inhibit secretion from thyroid gland. Data on its use of children is limited.

Surgery, total or subtotal thyroidectomy, offers the most rapid resolution of thyrotoxicosis. Surgery in hands of an experienced surgeon has little risk.

In terms of ease, cost, efficacy and short term safety, treatment with radioiodine ¹³¹I is superior. It is gradually becoming more acceptable as long term experience accumulates. The use of radioiodine is usually reserved for old adolescents failing to follow a medical regimen, those with toxic side reactions to antithyroid drugs and those who are poor candidates for surgery. Recent reports suggest that this approach may be safe for consideration as initial treatment in some patients(23). Thus, the choice of therapy in thyrotoxicosis needs to be individualized.

Neonatal Graves' disease though rare, deserves a special mention as mortality approaches 25% in severe disease(2). A transient form is due to the transplacental passage of TSI from a mother with active or inactive Graves' disease or Hashimoto's thyroiditis(24). Usually, it resolves in 3 to 12 weeks. Lugol's solution in doses of one drop thrice (about 8 mg), antithyroid drugs, corticosteroids, sedatives and digitalis may be required.

Management of thyroid disorders in children is simplified in the past few years with the development of various laboratory techniques which are now more readily available. Interpretation of thyroid function tests in children is more difficult than in adults. Though normal ranges from birth to maturity are now compiled, all laboratories continue to refer to adult values as

laboratory norms. This has occasionally led to erroneous diagnosis of hypo- or hyperthyroidism in normal newborns, preterms and infants where levels of thyroid hormones differ physiologically and can result in unnecessary treatment.

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