DIAGNOSIS OF HYPOTHYROIDISM

Pages with reference to book, From 49 To 50

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Hypothyroidism can be either primary, secondary or tertiary depending whether the defect lies in the thyroid gland, pituitary gland, or the hypothalamus.

Primary thyroid dysfunction is' by far the commonest cause of hypothyroidism. As the clinical features of early hypothyroidism are usually very subtle, chemical determination of thyroid hormones is needed to confirm the diagnosis. Estimation of T4, T3 and Free T4 Index is usually done to confirm the diagnosis. However, it is important to rule out secondary or tertiary causes before institution of thyroid hormone replacement therapy.

In cases of Pituitary or hypothalamus hypothyroidism, other trophic hormones especially ACTH may be deficient and institution of thyroid hormone replacement therapy without first replacing cortisol can cause acute adrenal crisis.

Thyrotropin (TSH) is synthesized and secreted by the pituitary thyrotroph. TSH binds to a specific receptor site on the thyroid cell membrane, activating cyclic adenosine monophosphate (cAMP) and stimulates every step in the biosynthesis of the thyroid hormones, thyroxine (T4) and tri-iodothyronine (T3). Increased secretion of T4 and/or T3 decreases TSH synthesis and secretion. Because of the sensitive negative feedback relationship between the levels of thyroid hormones and pituitary TSH, measurement of serum TSH has been found to be important clinically in the diagnosis of both thyroid and pituitary disorders.

Before the advent of Radioimmuno assay of TSH, it was usually believed that a significant increase in radioactive iodine uptake (RAI' 31) by the thyroid gland after administration of TSH eliminates the possibility of primary thyroidal failure.[1]

However our group showed in 1973[2] that this was not always so and some patients even with primary thyroid failure (Primary Hypothyroidism) can occasionally respond to TSH administration and elevated TSH level is the single most important test in distinguishing primary from secondary hypothyroidism.

Serum TSH concentrations are relatively consistent throughout the day. Therefore, useful clinical information can be obtained from a single blood sample drawn at any time. There is only a small diurnal variation in TSH levels, with a brief increase in the early morning hours. TSH levels are not affected by glucose, aminoacids, Stress, exercise and most drugs. Certain drugs such as lithium Carbonate[3] and iodides[4] can cause elevation of serum TSH, presumably due to small depressions in the Serum thyroid hormone concentrations. Furthermore Dopamine agonists such as L-Dopa and Bromocriptine have been shown to reduce elevated TSH levels found in hypothyroid patients. [5] Cold exposure significantly increases serum TSH levels only in the human neonate, not in the adult.[6]

Another important role of estimation of serum TSH is in ascertaining adequacy of thyroxine replacement therapy. Levels of circulating T4 and T3 may not reflect the actual metabolic control in hypothyroidism and the end point should be normalization of TSH levels. This, however, is not true in patients with congenital hypothyroidism, as these patients appear to have an alteration in the pituitary threshold for TSH secretion such that with normal levels of Serum T4, their seruni TSH concentration may remain elevated, and one should not attempt to normalise Serum TSH levels in children under treatment for congenital hypothyroidism.

Thyrotropin Releasing hormone (TRH), a tripeptide amide was the first of the hypothalamus releasing hormones to be isolated and characterised[7,8] It was termed TRH by virtue of its ability to stimulate the release of TSH from the mammalian anterior pituitary and much evidence has occurred over the past decade to attest its function as the most important hypothalamic hypophysiotropic factor involved in

regulation of TSH Secretion.
While immunoreactive TRH has been reported in the peripheral blood of humans, and other mammals, the findings are controversial and the authenticity as well as the source of material measured has not been fully established.

Clinical Application of TRH Administration:

Pituitary thyrotroph cells will respond to an intravenous dose of TRH as low as 6.25 ug (mcg) with a detectable increase in the Serum TSH within one to two minutes. The peak TSH level occurs at 15 30 minutes, a dose response curve is obtained upto approximately 500 Mg.
Taken orally TRH is also effective but doses 20 40 times greater are needed to produce an equivalent effect, presumably a reflection of impaired absorption or of breakdown in the gastrointestinal tract or liver. Among normal euthyroid subjects, women tend to have a greater response to TRH than men in whom it is inversely related to age.[9]
In primary hypothyroidism a TSH hyperresponse characteristically occurs, primarily due to a deficiency of the counter-regulatory thyroid hormones. However, since the basal TSH level is usually elevated TRH testing is required infrequently for clinical management. In some cases of latent primary hypothyroidism in which TSH and other thyroid function tests are within normal range, an enhanced TSH increase after TRH administration may be useful diagnostically.
When TRH was first introduced as a test of Pituitary TSH reserve, it was believed that it would permit the differentiation of hypothalamic from pituitary dysfunction in patients with TSH deficiency on the basis of Classic formation of hypothalamic-pituitary thyroid axis. It was anticipated that pituitary (Secondary) hypothyroidism would be associated with an impaired TSH response to TRH, whereas hypothalamic (tertiary) hypothyroidism would be associated with a normal or increased TSH level. Although in primary hypothalamic disorders associated with hypothyroidism there is frequently a peak TSH response that is characteristically delayed to 60 minutes, and although primary pituitary disease typically causes an impaired response, anomalies occur frequently enough to impair the usefulness of this test as a means of separating hypothalamic from pituitary disorders.
For practical purposes in most patients, estimation of TSH level remains the single most important estimation for distinguishing between primary and secondary (or tertiary) thyroid failure.
The paper published in this issue of the journal and another study on hormone level in hypothyroidism[10] are not only worth-while efforts in re-emphasizing the practical values of TSH estimation, but also first study of its kind in Pakistan which has also established the normal values of thyroid hormones in apparently healthy Pakistani population. It is hoped that more such studies will be undertaken in future.

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