Annotation

Archives of Disease in Childhood, 1975, 50, 497.

Serum TSH measurement in children with thyroid disorders

A number of thyroid function tests have recently been developed in which components of the hypothalamic-pituitary-thyroid axis are directly measured; these include estimation of the total concentrations of the thyroid hormones, thyroxine ($T_4$) and tri-iodothyronine ($T_3$), their free (unbound) fractions, the thyroid hormone-binding proteins, and the serum TSH (thyroid-stimulating hormone, thyrotrophin). Thus, though the peripheral effects of the thyroid hormones are difficult to assess quantitatively, derangement of the thyroid axis can be precisely defined. The theoretical advantages of such direct measurements are reflected in greatly increased diagnostic sensitivity. Of the tests currently available the serum $T_4$ and TSH have become the cornerstones of thyroid investigation, and the papers in this issue by Jackson, Vander-schueren-Lodeweyckx, and Grant (page 522) and Hamilton and Hutchison (page 567) emphasize the value of serum TSH measurement in the assessment of children with thyroid disorders. The laboratory diagnosis of thyroid disease in children was well reviewed by Fisher (1973).

TSH is a glycoprotein hormone synthesized by the thyrotroph cells of the anterior pituitary. TSH secretion is regulated directly by the circulating level of thyroid hormones and indirectly by the tripeptide hypothalamic thyrotrophin-releasing hormone TRH. By stimulation of thyroid epithelial cell adenyl cyclase, TSH enhances iodide uptake, hormone synthesis, and release. Serum TSH concentration shows little diurnal variation and is constant in both sexes throughout life from day 4 onward. Cord blood levels are higher than maternal levels and a marked TSH surge occurs immediately after birth, reaching a peak at 30 minutes and falling to normal by day 3 (Fisher and Odell, 1969).

Early bioassays for serum TSH have been superseded by radioimmunoassays which are now routine procedures in many laboratories and in Britain are widely available through the supraregional assay service. The laboratory and clinical aspects of TSH immunoassay were reviewed by Hall (1972). TSH assays require only small quantities of serum and are reliable and specific. The sensitivity of most current assays is such that basal levels are undetectable in about 10–20% of normal subjects and decreased levels cannot reliably be detected. Normal values should be established for each assay and each laboratory, but basal concentrations in normal subjects usually fall within the range 0–5 μU/ml of the MRC standard 68/38. Evered et al. (1975) found that less than 2·5% of normal adults had serum TSH values greater than 5 μU/ml, and Jackson et al., using a similar assay, now report identical findings in normal children.

Serum TSH may be measured under basal conditions, after stimulation by TRH, and after suppression by administration of thyroid hormones. TRH is active when given orally, but the intravenous stimulation test of Ormston et al. (1971), which can conveniently be combined with insulin and gonadotrophin-releasing hormone stimulation in a comprehensive test of anterior pituitary function (Mortimer et al., 1973), has been most thoroughly evaluated and widely used. After a base-line sample for serum TSH has been obtained, intravenous TRH is given (a dose of 200 μg, given as a bolus, is suitable for all ages; transient nausea occurs frequently but no serious side-effects have been recorded) and the serum TSH is measured 20 and 60 minutes later. Normal subjects show a sharp rise in serum TSH to a peak at 20 minutes and a fall toward the basal value at 60 minutes. The response in children is similar to that in adults (Job et al., 1971; Foley et al., 1972; Malvaux and Beckers, 1973). The value of the test may be enhanced by measurement of the thyroid hormone response, the $T_4$ showing a small, and the $T_3$ a larger, response, both reaching a peak by 4 hours (Uller, Van Herle, and Chopra, 1973). The normal limits of response to TRH stimulation in children have not yet been adequately defined and are clearly subject to the same variability between assays as the basal values. Fortunately, however,
TABLE

Typical test results in disorders of thyroid function

<table>
<thead>
<tr>
<th></th>
<th>Basal TSH</th>
<th>T₄/T₃</th>
<th>After TRH stimulation TSH response</th>
<th>T₄/T₃ response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal thyroid function</td>
<td>Normal</td>
<td>Normal</td>
<td>Early</td>
<td>Present</td>
</tr>
<tr>
<td>Primary hypothyroidism</td>
<td>High</td>
<td>Normal</td>
<td>Exaggerated and prolonged</td>
<td>Nil</td>
</tr>
<tr>
<td>Compensated</td>
<td>High</td>
<td>Low</td>
<td>Exaggerated and prolonged</td>
<td>Nil</td>
</tr>
<tr>
<td>Overt</td>
<td>Low/normal</td>
<td>Low</td>
<td>Delayed/early</td>
<td>Present/nil</td>
</tr>
<tr>
<td>Secondary hypothyroidism</td>
<td>Low/normal</td>
<td>Low</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Hypothalamic lesion (TRH deficiency)</td>
<td>Low/normal</td>
<td>Low</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Pituitary lesion (TSH deficiency)</td>
<td>Low/normal</td>
<td>Low</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Low/normal</td>
<td>High</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

it is possible in most instances to differentiate normal from abnormal patterns of response qualitatively.

The use of serum TSH measurements in the diagnosis and management of disorders of thyroid function in childhood is discussed briefly below and, typical results are summarized in the Table. The discussion is of necessity simplified and two introductory truisms may perhaps be justified; firstly, all thyroid function tests must be interpreted in the light of the clinical findings and, secondly, exceptions have been recorded to all the general rules outlined.

The diagnosis of primary hypothyroidism is established by showing low levels of thyroid hormones in conjunction with high serum TSH levels. Serum TSH is an extremely sensitive indicator of thyroid failure and is greatly raised in established hypothyroidism (Hall, 1972), especially in children (Hayek, Maloof, and Crawford, 1973; Barnes, Hayles, and Ryan, 1973). In the neonatal period results must be interpreted with due regard for the postnatal TSH surge and the normally high levels of thyroid hormones (Fisher, 1973). In a preliminary study the serum TSH in cord blood and on day 5 of life has been used as a screening test for cretinism (Winkler, Camus, and Delange, 1974). In early hypothyroidism from any cause, but especially that associated with lymphocytic thyroiditis, a rise in serum TSH may maintain the thyroid hormones within normal limits, and such a state of 'compensated' hypothyroidism may persist for a prolonged period (Fisher, 1973; Hayek et al., 1973). Eventual progression to overt hypothyroidism, however, can often be anticipated and either careful observation or thyroid hormone replacement is indicated. Although it has been a matter of controversy, there is increasing evidence that raised serum TSH reliably indicates a fall in circulating thyroid hormones below the optimal level (Evered et al., 1975) and my strong personal inclination, especially in children, is towards adequate replacement without undue delay. In primary hypothyroidism serum TSH shows an exaggerated and prolonged response to TRH stimulation (Ormston et al., 1971). Such a response may be seen before the basal serum TSH exceeds the normal range and is probably the earliest indication of decreased thyroid reserve.

Serum TSH is also of value in assessing the treatment of primary hypothyroidism. Accurate adjustment of thyroid hormone dosage has hitherto been difficult especially in the growing child. Thyroxine is preferred for replacement and clinical euthyroidism is generally achieved when the serum T₄ is in the high normal range. Suppression of serum TSH, however, provides a far more precise measure of chemical euthyroidism, and the smallest dose of thyroxine which maintains serum TSH within the normal range is probably optimal. In adults 0·2 mg daily consistently suppresses serum TSH (Cotton, Gorman, and Mayberry, 1971) and children generally require from 0·1 mg to 0·2 mg.

Secondary hypothyroidism is indicated by a normal or low serum TSH in the presence of low levels of thyroid hormones (and normal levels of binding proteins). The distinction between hypothalamic disease with TRH deficiency, and pituitary disease with TSH deficiency, can often be made by assessing the serum TSH response to TRH stimulation. If the defect is hypothalamic and the pituitary is intact, the serum TSH will show a response to TRH stimulation which typically, but not invariably, is delayed, the 60-minute
value exceeding that at 20 minutes (Hall et al., 1972; Faglia et al., 1973). A thyroid hormone response is usually but not always present (Shenkman et al., 1972). In true hypopituitarism, however, an absent or impaired response of serum TSH, and hence also of thyroid hormones, is found. Such a response in the absence of overt hypothyroidism suggests decreased pituitary TSH reserve (Hall et al., 1972).

In hyperthyroidism, due either to Graves’s disease (diffuse thyrotoxicosis) or an autonomous nodule, the serum levels of the thyroid hormones (occasionally the T₃ only) are raised and the serum TSH is low. The serum TSH shows no response to TRH stimulation (Ormston et al., 1971). In difficult cases a normal response is most valuable in excluding, and an absent response in confirming, the diagnosis. The treatment of hyperthyroidism frequently results in a state of iatrogenic primary hypothyroidism of which, by analogy with the naturally occurring disease, the first indication is a rise in serum TSH. This is of special value in detecting oversuppression during treatment of children with antithyroid drugs and it is useful therefore to monitor serum TSH regularly.

In conclusion, measurement of the serum TSH has rapidly become established as an invaluable aid in the diagnosis and management of all the major disorders of thyroid function. It amply justifies a place in every paediatricians’ diagnostic armamentarium.

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Arch Dis Child 1975 50: 497-499
doi: 10.1136/adc.50.7.497

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