Thyrotrophin augmentation after commencing thyroxine replacement in primary hypothyroidism

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Summary: Prospective measurements of serum thyrotrophin and thyroxine concentrations were made in six patients with primary hypothyroidism treated consecutively with an incremental regimen of oral thyroxine. A fall in thyrotrophin occurred over several months, accompanied by a concurrent slow rise in serum thyroxine. Those patients with the highest initial values for thyrotrophin showed the typical curvi-linear decline in thyrotrophin, whereas the remaining patients disclosed a transient rise in thyrotrophin for the first 3 months. This paradoxical rise was not associated with depression of cardiac output or glomerular filtration rate.

The significance of thyrotrophin augmentation is uncertain, but it may be more common than generally appreciated. It did not occur in those patients with the most severe degrees of thyroid deficiency. Thyroxine exerts a dual action, and augmentation of thyrotrophin may reflect a dominant effect of increased protein synthesis, in contrast to negative feedback inhibition which suppresses thyrotrophin. These opposing actions are in competition at different dose levels of thyroxine, and may contribute not only to augmentation or suppression of thyrotrophin, but also to the curvi-linear pattern of fall. Such variations impair the utility of thyrotrophin as an index of euthyroidism.

Introduction

Diminished levels of serum thyroxine (T_4) and 3,5,3¹-tri-iodothyronine (T_3) concentrations in primary hypothyroidism are associated with high levels of thyroid-stimulating hormone (TSH), because pituitary thyrotrope secretion of TSH is governed by negative feedback regulation. The complex processes involved are not fully resolved (Scanlon *et al.*, 1978). Administration of oral thyroxine to untreated patients with primary hypothyroidism promptly initiates a curvi-linear fall in TSH which is roughly proportional to the dose (Cotton *et al.*, 1971). Occasionally, however, the fall in TSH may be interrupted by a paradoxical rise, which has been described in sporadic case reports (Wartofsky *et al.*, 1976; Hood *et al.*, 1976) and in experimental studies (Garcia *et al.*, 1976). It is possible that this rise is more common than generally realized, as revealed by detailed studies of TSH progression (Aizawa *et al.*, 1978). Accordingly, a prospective study of TSH responsiveness to oral thyroxine was undertaken in six patients with primary hypothyroidism.

Patients and methods

Six consecutive patients with characteristic signs, symptoms and laboratory features of primary hypothyroidism were included in the study. Goitre was not present, and thyroid surgery had not previously been performed. All patients showed high titres of thyroid antibodies. There was no clinical evidence of cardiac enlargement or pericardial effusion, and no other endocrine disorder was manifest. There were 5 females and 1 male, with ages ranging from 16 to 65, mean 44 years.

Starting dose of oral thyroxine was 25 µg/day which was continued for 4 weeks, after which there was an increment by 25 µg/day for a further 4 weeks, and this incremental regime was continued until serum TSH eventually returned to the normal range (below 5 IU/ml). The dosage schedule was different in Case 1 when starting dose, and increments, were 50 µg/day.

Serum T_4 and TSH concentrations were measured by radio-immunoassay, using Corning's immophase kit. Cardiac output was estimated by the technique of trans-thoracic cardiac impedance (Kubicek *et al.*, 1966). Glomerular filtration rate (GFR) was measured by single-shot administration of ⁵¹Cr EDTA (Morgan *et al.*, 1977).

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Results

Figures 1, 2, 3, 4, 5 and 6 represent Cases 1, 2, 3, 4, 5 and 6 respectively. The effect of incremental thyroxine dosage on sequential basal serum TSH concentration and serum T₄ concentration is displayed, and concomitant measurements of cardiac output and GFR are included in Cases 4, 5 and 6.

In Cases 1, 2 and 3 the effect on TSH with the lowest dose of thyroxine was notable as the rise in serum T₄ was slight and well below the normal range for serum T₄. A dramatic fall in TSH was observed in these patients initially, but TSH entered the normal range in the third month in Cases 1 and 2, and in the fifth month in Case 3. Serum T₄ entered the normal range at 2.5 months in Cases 1 and 2, and at 2 months in Case 3.

A paradoxical rise in TSH is present in Cases 4, 5 and 6. These values reached a peak and then declined spontaneously in spite of a continued incremental dose schedule of thyroxine. Throughout these changes in TSH there was evident rising levels of serum T₄, cardiac output and GFR. Serum TSH returned to the normal range at 7 months in Case 5, and 5 months in Case 6. Continued observations were not possible in Case 4 because she left the area. Serum T₄ reached the normal range in the third month in Cases 4 and 5, and the second month in Case 6.

Figure 1 TSH fell to the normal range by the 3rd month

Figure 2 TSH fell to the normal range by the 3rd month

Figure 3 TSH fell to the normal range by the 5th month

Figure 4 TSH showed a paradoxical rise and was still abnormal by the 3rd month

Figure 6 TSH showed a paradoxical rise but returned to the normal range by the 5th month

Discussion

Sequential measurements of serum TSH are routinely made during thyroxine replacement therapy for primary hypothyroidism in order to define the euthyroid state, which is judged to coincide with the point in time at which serum TSH returns to the normal range. A fall in TSH values is generally anticipated, but it is clear from the present study that an initial rise in TSH is not uncommon, and should not be misinterpreted as a further manifestation of hypothyroidism. Effective gastro-intestinal absorption of thyroxine was present in all patients, as shown by a progressive rise in serum T₄ during incremental dosage. Highly sensitive pituitary thyrotrope responsiveness to low-dose thyroxine occurred at subnormal concentrations of serum T₄. Yet divergent responses were demonstrated, with TSH falling in three patients and rising in three patients. That the pituitary thyrotrope may be directly affected by thyroxine even when serum T₄ remains abnormally low has been previously documented (Erfurth & Hedner, 1982). Fifty per cent of intra-pituitary T₄ is converted to T₃ by binding to specific nuclear receptors in which new protein synthesis takes place (Larsen *et al.*, 1979).

In the three patients who displayed augmentation of TSH after commencing thyroxine there were concurrent rises in cardiac output and GFR, along with a simultaneous rise in serum T₄, indicating appropriate biological responsiveness of peripheral tissues in the face of inappropriate pituitary thyrotrope activity. D'Angela *et al.* (1976) first observed a 'rebound' phenomenon of TSH secretion in chronically hypothyroid rats, noting an increase in TSH biosynthesis with small doses of thyroxine in contrast to large doses which decreased TSH biosynthesis. Further studies by

Figure 5 TSH showed a double peak and returned to the normal range by the 7th month

Spira *et al.* (1981) showed that thyroid hormones actually exert two effects on the TSH synthesizing system within the pituitary thyrotrope: (i) stimulation of protein synthesis which occurs as part of a general effect of thyroid hormone action, and (ii) specific inhibition of the feedback mechanism which determines TSH synthesis and release. These actions are directly opposed, and hence TSH secretion during thyroid hormone replacement depends on the degree of participation of each effect. Thus, if TSH synthesis predominates, the inhibitory effect on the feedback mechanism may be masked. Only by increasing the dose of thyroid hormone will the inhibitory effect become dominant. Sub-physiological doses of triiodothyronine given to patients with primary hypothyroidism stimulated an increase in pituitary TSH reserve following thyrotrophin releasing hormone provocation (Ridgway *et al.*, 1979). This augmented TSH response occurred early in the course of sub-physiological triiodothyronine treatment, when T_3 absorption and peripheral responsiveness was normal.

In this group of patients basal TSH displayed a consistent serial trend over several months of observation, providing a valid reflection of pituitary thyrotrope responsiveness. It is well known that between-batch variability, up to 10%, can occur with

TSH radio-immunoassay tests, but this is unlikely to account for the present observations, with the possible exception of the second peak in Case 4. If thyroxine exerts a dual action of competing stimulatory and inhibitory actions on TSH secretion, then Cases 1 and 2 show mixed effects with a dominant tendency for TSH suppression. Case 3 shows a strong inhibitory effect, whereas Cases 4, 5 and 6 show a dominant stimulatory effect during the first 2 months of treatment, which is subsequently modified by dose increase. The curvi-linear pattern of decline in TSH noted in Cases 1 to 3 may reflect an initial dominant inhibitory effect followed by more equal competing influences of stimulation and inhibition as thyroid dosage is increased. These points are important in euthyroidism is to be judged by titration of the response of pituitary TSH to thyroid hormone administration, as a blurred end-point is common. Perhaps a better index is required for the definition of euthyroidism.

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