FAILURE OF THE TRH TEST TO PREDICT THE CLINICAL COURSE OF PATIENTS IN REMISSION AFTER ANTITHYROID DRUG THERAPY FOR GRAVES' DISEASE

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ABSTRACT

In an attempt to assess the predictive value of the TRH test in patients in remission after stopping antithyroid drugs for thyrotoxicosis, 11 euthyroid patients with a subnormal (group I) and 23 euthyroid patients with a normal serum TSH response to TRH (group II) were followed-up for one year. The mean ± se intervals since the withdrawal of drug therapy were 23.2 ± 1.6 and 20.4 ± 0.7 months, respectively, at the outset of the study. Five patients (45 %) from group I and 7 patients (30 %) from group II relapsed during the period of observation. In addition, a change from a subnormal to a normal serum TSH response to TRH and vice versa occurred in some patients. It is not possible to predict by means of the TRH test the subsequent clinical course of patients in remission following antithyroid drug therapy.

The majority of patients treated with a 12–18 month course of antithyroid drugs for thyrotoxicosis will relapse, usually within the first post-therapy year (Hershman et al. 1966). Both late relapse of thyrotoxicosis and the development of thyroid failure are not uncommon however (Irvine et al. 1977b), and long-term follow-up of patients treated with antithyroid drugs is advisable, as in the case for patients treated with radioiodine or surgery. The review of patients who have been treated previously with antithyroid drugs would be more efficient if it was related to the likelihood of relapse or thyroid failure,
and was not performed indiscriminately. It is conceivable that an absent or subnormal serum thyrotrophin (TSH) response to TSH-releasing hormone (TRH) in euthyroid patients previously treated with antithyroid drugs alone for Graves' disease might indicate the continued presence of stimulating TSH receptor antibodies in the serum and therefore the possibility of future relapse. The present study was designed to assess the value of the TRH test as a predictor of the clinical course of patients in remission after stopping carbimazole therapy for Graves' disease.

PATIENTS AND METHODS

Eleven euthyroid patients (10 females, 1 male) who were in remission after a course of carbimazole for Graves' disease and who had a subnormal serum TSH response to TRH (group I) and 23 similarly treated euthyroid patients (19 females, 4 males) with a normal serum TSH response to TRH (group II) were followed-up for one year. The mean ± se ages of the patients in groups I and II were 39.4 ± 1.4 and 31.8 ± 0.4 years, respectively. The patients in group I had been treated with carbimazole for 31.6 ± 2.3 months and had been in apparent remission for 23.2 ± 1.6 months before the initial TRH test. The corresponding times for the patients in group II were 20.9 ± 0.6 months and 20.4 ± 0.7 months. No patient had been in remission for less than 3 months, or for more than 5 years.

At follow-up all patients not known to have relapsed during the preceding year were examined clinically and blood was withdrawn for the estimation of serum total thyroxine (T₄) and triiodothyronine (T₃). Serum TSH was estimated before and 20 min after the intravenous administration of 200 μg TRH in all patients in group I and in 17 out of 23 patients in group II. The diagnosis of recurrent thyrotoxicosis was made in each case on clinical grounds and on the basis of raised levels of circulating thyroid hormones and a lack of response of serum TSH to TRH.

Serum total T₃ and T₄ were measured by specific radioimmunoassays (Seth et al. 1976), the inter-assay precision using anonymous control sera averaging 7.9% for T₃ and 11.7% for T₄, expressed as coefficient of variation. The normal ranges for serum total T₃ were 1.1-2.2 nmol/l for males and 1.1-2.6 nmol/l for females, and those for serum total T₄ 60-150 nmol/l for both sexes. Serum TSH was also measured by radioimmunoassay in which the between-assay coefficient of variation was 11.2% (Irvine et al. 1973). The normal range for serum TSH was <0.7-5.7 mU/l and the normal range of response 20 min after the intravenous administration of 200 μg TRH was 3.9-25.3 mU/l (Toft et al. 1978).

RESULTS

Recurrent thyrotoxicosis developed in 5 of the patients in group I 3 to 7 months after the initial assessment. The remaining 6 patients were clinically euthyroid with normal serum total T₃ and T₄ levels at the end of the study. The serum TSH response to TRH was still subnormal in 4 of these patients, but reverted to normal in the other two. In group II, 7 of the patients relapsed 9-12 months
after the initial assessment. The remaining 16 patients were clinically euthyroid with normal circulating thyroid hormone levels.

The serum TSH response to TRH, estimated in only 10 of these 16 patients, was again normal in 9 patients but became subnormal in the other patient.

**DISCUSSION**

In the past attempts to predict the likelihood of relapse or remission of thyrotoxicosis have been unsuccessful (Alexander et al. 1970), and the best clinical indicator of prolonged remission is a reduction of goitre size during treatment (Solomon et al. 1953). More recently it has been shown that patients with histocompatibility antigen HLA-B8 (Irvine et al. 1977a) or DW3 (Bech et al. 1977) are at increased risk of recurrent thyrotoxicosis, but such a measurement is of limited practical value in the management of the individual patient. Davies et al. (1977) measured TSH receptor antibodies in patients with Graves' disease at the end of a course of antithyroid drugs and found that those with high titres of antibody relapsed whereas those with low titres of antibody remained in remission. However, the majority of patients in the study had intermediate titres of antibody and their disease followed an unpredictable course, probably reflecting the fact that the present membrane-receptor binding assay detects not only stimulating but also blocking TSH receptor antibodies.

The serum TSH response to TRH is very sensitive to minor changes in the levels of circulating thyroid hormones within the normal range and will become subnormal before the levels of serum total T₃ and T₄ are in the thyrotoxic range (Snyder & Utiger 1972). A subnormal serum TSH response to TRH is therefore an indicator of thyroid autonomy. If Graves' disease is due to stimulating TSH receptor antibodies, a subnormal serum TSH response to TRH should provide an indirect in vivo marker for the presence of these antibodies. However, in the present study of patients in remission for between 3 months and 5 years after prolonged treatment with carbimazole for Graves' disease, there was no apparent relationship between the serum TSH response to TRH and the subsequent clinical course of the disease. In a similar study, however, Lamberg et al. (1978) found a significantly higher rate of relapse in patients with subnormal serum TSH response to TRH than in those with a normal response and concluded that the TRH stimulation test was of some predictive value.

Like us Martino et al. (1976) found the TRH test to be of little value in predicting the future thyroid status of patients treated with antithyroid drugs. Their conclusion, however, was fortuitous and was based on the observation that patients with a normal or even an exaggerated serum TSH response to TRH within 3 months of stopping antithyroid drugs subsequently developed
recurrent thyrotoxicosis. The thyroid gland is relatively iodine-deficient in the early weeks after prolonged antithyroid drug therapy and its ability to secrete excess thyroid hormones with an associated subnormal serum TSH response to TRH will be impaired despite the presence of stimulating TSH receptor antibodies in the serum. On the basis of the results of T₃ suppression tests and the serum TSH response to TRH, Buerklin et al. (1976) concluded that in most patients with Graves’ disease who remained clinically and biochemically euthyroid after a course of antithyroid drug therapy, the disease persisted in a mild or subclinical form. It is likely that periodic fluctuations occur in the titre of stimulating TSH receptor antibodies in such patients. A normal serum TSH response to TRH in patients in apparent remission need not necessarily imply a disappearance of the stimulating antibody, but merely a critical reduction in its titre. Furthermore, in Graves’ disease there would appear to be a balance between thyroid stimulating and thyroid destructive autoimmune mechanisms which may change from being predominantly the former to predominantly the latter (Irvine 1979).

Presumably there is likely to be a stage in between when TSH receptor stimulating antibodies may be present and associated with a subnormal TSH response to TRH, and yet destructive mechanisms prevent the development of recurrent thyrotoxicosis and indeed may eventually gain predominance with the late onset of hypothyroidism (Irvine et al. 1977b).

It is not surprising, therefore, that the serum TSH response to TRH proved to be of no value in predicting the clinical course of patients treated with antithyroid drugs or that the response changed from normal to subnormal and vice versa in euthyroid patients during a relatively short period of observation.

REFERENCES


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