MEDICAL PRACTICE

*Occasional Review***Ophthalmic Graves's disease: natural history and detailed thyroid function studies**

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British Medical Journal, 1977, 1, 273-275**Summary**

Of 27 patients with ophthalmic Graves's disease (OGD) who had been clinically euthyroid three years previously, one became clinically hyperthyroid and seven overtly hypothyroid. Improvement in eye signs was associated with a return to normal of thyroidal suppression by triiodothyronine (T3) and of the response of thyroid-stimulating hormone (TSH) to thyrotrophin-releasing hormone (TRH). Of a further 30 patients with OGD who had not been studied previously, three were overtly hypothyroid.

Of the combined series, 46 patients were euthyroid, 18 (40%) of whom had an impaired or absent TSH response to TRH, and 3 (6.7%) an exaggerated response. Eleven out of 37 patients (29.7%) had abnormal results in the T3 suppression test.

There was a significant correlation between thyroidal suppression by T3 and the TSH response to TRH. Total serum concentrations of both T3 and thyroxine (T4) were closely correlated with T3 suppressibility and TRH responsiveness. Free T4 and T3 (fT3) concentrations were normal in all but three patients, in whom raised fT3 was accompanied by abnormal TSH responses and thyroidal suppression.

The presence of normal free thyroid hormone concentrations in patients with impaired or absent TSH responses to TRH is interesting and challenges the concept that free thyroid hormones are the major controlling factors in the feedback control of TSH.

Introduction

Rundle and Wilson¹ used the term "ophthalmic type of Graves's disease" to describe the ocular changes of Graves's disease occurring in the absence of goitre or hyperthyroidism. Hall *et al*² expanded the definition to include thyroid enlargement provided that the patient was euthyroid and had no history of hyperthyroidism. Now, however, owing to the description of ophthalmopathy characteristic of Graves's disease in Hashimoto's thyroiditis,³ patients with clinical or biochemical evidence of hypothyroidism are included.⁴

The natural history of ophthalmic Graves's disease (OGD) remains to be established. In 1975 we reviewed clinically and biochemically a group of patients with OGD who had been clinically euthyroid in 1972.⁴ Our objective was to define the disturbance of thyroid hormone metabolism by measuring the total and free thyroid hormone concentrations and the thyrotrophin (TSH) response to thyrotrophin-releasing hormone (TRH) and carrying out a triiodothyronine suppression (T3S) test.

Patients and methods

We reviewed 27 out of 34 patients with OGD who had been studied in 1972.⁴ Of the remaining seven patients, four had died of unrelated illnesses and three could not be traced. A further 30 patients attending the endocrine unit were added to the series, making a total of 57 patients.

Ocular changes were assessed clinically and scored by the scheme

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adopted by the American Thyroid Association,⁵ and an ophthalmopathy index was derived for each patient.⁶ The progression of eye changes was assessed from the outpatient records and from the patients' own observations. Thyroid function was assessed clinically and by the following methods: measurement of serum protein-bound iodine (PBI; AutoAnalyzer method 56); residual thyroid-hormone binding test (Thyopac-3); calculation of free thyroxine index (FTI) from the previous two results⁷; radioimmunoassays of triiodothyronine (T₃),⁸ thyroxine (T₄),⁹ free T₃ (fT₃),¹⁰ and free T₄ (fT₄)¹⁰; and the TRH test.¹¹ The TSH response to TRH was recorded as normal, exaggerated, impaired, or absent according to criteria previously described.¹² The T₃S test was performed by measuring the six-hour thyroidal uptake of ¹³¹I before and seven days after the daily administration of 120 µg of T₃. Reasons for not performing TRH and T₃S tests in some patients were treatment with thyroxine (10 patients), coexisting heart disease, and social inconvenience. Antibodies to thyroglobulin were detected by the tanned-red-cell technique, and thyroid cytoplasmic antibodies by complement fixation as described in the World Health Organisation manual for autoimmune serology.

Results

CLINICAL FEATURES

Of the 27 patients first studied in 1972, seven had become overtly hypothyroid and were receiving thyroxine replacement, and one had developed hyperthyroidism after 12 years of eye trouble and was therefore excluded. Three of the 30 additional patients were clinically hypothyroid. Thus 46 patients were clinically euthyroid. Of the 56 patients included in the study, 41 were women aged 29-73 years (mean age 52) and 15 men aged 41-75 years (mean age 62). Ten patients had a family history of thyroid disease. Goitre was found in 16 patients, while in another 12 the thyroid was just palpable. The following eye signs were noted: exophthalmos (23 cases; 14 unilateral, 9 bilateral); lid retraction (14; 12 unilateral, 2 bilateral); periorbital swelling (45; all bilateral); ophthalmoplegia (15; 3 unilateral, 12 bilateral); and chemosis (3; 2 unilateral, 1 bilateral).

Seven patients showed progressive deterioration of their eye signs, which needed treatment including steroids or orbital irradiation¹³; in

37 patients spontaneous improvement occurred, and 12 patients remained unchanged (table I).

CHANGES IN EYE SIGNS AND THYROID FUNCTION BETWEEN 1972 AND 1975

Six of the seven patients who developed overt hypothyroidism between 1972 and 1975 had exaggerated responses in TRH tests in 1972 (four with raised basal TSH concentrations), while the remaining one had TSH responses that progressed from impaired to normal in 1972 and finally to exaggerated in 1975. The eye signs deteriorated in one patient during the transition from subclinical to clinical hypothyroidism but improved with thyroxine and concomitant steroid treatment by mouth. The eye signs in four of the six remaining patients improved with thyroid hormone replacement, while two patients reported no change. (The one patient who developed clinical hyperthyroidism had an absent TSH response to TRH previously; the eye signs were unchanged during the intervening period.)

Among the 19 euthyroid patients the important changes in the TSH response to TRH (table II)—namely, the reversion from absent or impaired responses to normal responses—were associated with improvement in the ocular manifestations. The greater suppressibility of thyroid radioiodine uptake in 1975 (table II) was similarly related to the eye signs. The titre of cytoplasmic antibodies tended to increase with time, suggesting, perhaps, progression to a more severe degree of autoimmune thyroiditis; nevertheless, the total number of patients with thyroid antibodies remained the same from 1972 to 1975. Of all 56 patients studied, 29 had thyroglobulin antibodies (titre 1/20 or more) or cytoplasmic antibodies (titre 1/64 or more) or both. Of the 10 hypothyroid patients, eight had strong titres of cytoplasmic antibodies (1/256 to 1/1600), one a weak titre of thyroglobulin antibody (1/80), and one no detectable thyroid antibodies.

SERUM TOTAL T₃ AND T₄, TSH RESPONSE, AND T₃ SUPPRESSIBILITY

Of the 46 clinically euthyroid patients, 45 were tested with TRH: 18 (40%) had an impaired or absent TSH response, and 3 (6.7%)—one with subclinical hypothyroidism and a raised basal TSH concentration—an exaggerated response (table III). The T₃S test was performed on 37 of the 46 patients (one of the 37 was not tested with TRH); 11 (29.7%) had abnormal results. There was a significant correlation between T₃ suppressibility and TSH response ($r=0.43$, $P<0.01$). Total serum concentrations of both T₃ and T₄ correlated well with T₃ suppressibility and TSH response (T₃/T₃S: $r=0.39$, $P<0.05$; T₃/TSH: $r=0.62$, $P<0.001$; T₄/T₃S: $r=0.38$, $P<0.05$; T₄/TSH: $r=0.5$, $P<0.001$).

SERUM fT₃ AND fT₄, TSH RESPONSE, AND T₃ SUPPRESSIBILITY

Serum fT₃ and fT₄ were studied in 37 euthyroid patients. Fifteen had normal responses to T₃S and TRH, and 22 an impaired or absent TSH response or T₃ non-suppressibility or both. Serum fT₃ was raised in three patients in the second group (17.4, 19.4, and 22.4 pmol/l (11.3, 12.6, and 14.6 pg/ml) respectively) (normal 4.5-15.7 pmol/l; 2.9-10.2 pg/ml).¹⁰ The remaining patients in both groups had fT₃ and fT₄ concentrations within the normal ranges with no significant differences between the means in both groups. For the overall population in the two groups, fT₃ and fT₄ did not show significant correlations with T₃ suppressibility and TSH response (fT₃/T₃S: $r=0.343$, $P>0.05$; fT₃/TSH: $r=0.066$, $P>0.1$; fT₄/T₃S: $r=0.082$, $P>0.1$; fT₄/TSH: $r=0.136$, $P>0.1$).

TABLE I—Change in eye signs in patients with OGD

	No of patients	Mean ophthalmopathy index	Mean duration of symptoms (years) ± SD
Eye signs improved	37	1.11	6.19 ± 3.33
Eye signs unchanged	12	2.00	5.65 ± 3.87
Eye signs deteriorated	7	4.43	2.10 ± 1.45

TABLE II—Mean thyroid function values (± SD) in 19 patients with euthyroid OGD in 1972 and 1975

	1972	1975	P
PBI (nmol/l) (normal 315-630)	522 ± 121	523 ± 95	NS
FTI (normal 270-680)	478 ± 101	475 ± 83	NS
T ₃ (nmol/l) (normal 1.0-2.6)	2.56 ± 0.63	1.93 ± 0.56	0.0025
Rise in TSH 20 min after TRH (mU/l) (normals: men 4.2-16.1; women 5.9-18.2)	4.83 ± 5.06	6.51 ± 4.8	0.025
% fall in ¹³¹ I uptake after T ₃ (normal ≥50)	41.51 ± 26.66	60.16 ± 27.88	0.005

NS = Not significant.

Conversion: SI to traditional units—PBI: 1 nmol/l ≈ 0.013 µg/100 ml. T₃: 1 nmol/l ≈ 0.65 ng/ml.

TABLE III—Mean thyroid function values (± SD) in 45 patients with euthyroid OGD in 1975. (Only 36 of these patients were tested for both TSH response to TRH and percentage fall in ¹³¹I uptake after T₃)

	PBI (nmol/l)	FTI	T ₃ (nmol/l)	T ₄ (nmol/l)*	% fall in ¹³¹ I uptake after T ₃
Absent TSH response (n=4)	540 ± 83	464 ± 63	2.34 ± 0.39	131 ± 8	36.33 ± 40.84 (n=4)
Impaired TSH response (n=14)	524 ± 85	476 ± 81	2.03 ± 0.47	129 ± 23	55.0 ± 22.26 (n=8)
Normal TSH response (n=24)	489 ± 93	439 ± 76	1.86 ± 0.34	117 ± 32	62.47 ± 27.57 (n=21)
Exaggerated TSH response (n=3)	358 ± 78	339 ± 84	1.09 ± 0.52	92 ± 43	94.74 ± 0.88 (n=3)

*Normal range 60-150 nmol/l.

Conversion: SI to traditional units—PBI: 1 nmol/l ≈ 0.013 µg/100 ml. T₃: 1 nmol/l ≈ 0.65 ng/ml. T₄: 1 nmol/l ≈ 0.078 µg/100 ml.

Discussion

It is well recognised that some euthyroid patients with OGD have abnormalities of thyroid function, including exaggerated, impaired, or absent responses of TSH to TRH,⁴ lack of suppression of thyroidal radioiodine uptake by T3,^{2,4} and an increased prevalence of thyroid autoantibody,^{3,4} as shown again in this study. Liddle *et al*¹⁴ suggested that limited thyroidal reserve with inability to respond to thyroid-stimulating agents was responsible for patients with OGD not becoming hyperthyroid, although this was subsequently challenged by Hall *et al*,² who thought that it was valid for only a few patients. Only one of our 27 patients first studied in 1972 progressed to frank hyperthyroidism, which confirms the impression that only a few of these patients develop clinical hyperthyroidism.⁴ Overt hypothyroidism, on the other hand, occurred more often in this study, presumably as a result of autoimmune thyroid disease, as evidenced by the presence of thyroid antibodies. The rising titres of thyroid antibodies with time was similar to that observed in a non-hospital population.¹⁵ Hall *et al*² reported that a third of their patients with OGD had high titres of thyroglobulin or complement-fixing antibodies or both, similar to those in Hashimoto's disease; in addition the frequency of high titres of thyroglobulin antibodies was greater in patients with OGD than in thyrotoxic patients with Graves's disease. These observations were confirmed by Ormston *et al*.⁴ Graves's ophthalmopathy has also been described in 10 patients with histologically proved Hashimoto's thyroiditis.³ The improvement in eye signs associated with a return to normal of T3S or TSH response or both is interesting and suggests a relation between the pathogenesis of the ocular manifestations and the degree of thyroid autonomy in OGD. The possibility that the concentration of circulating thyroid hormones may influence the activity of established eye signs cannot be excluded.

We have confirmed the finding⁴ that euthyroid patients with OGD who have impaired or absent TRH responsiveness or failure of thyroidal suppression by T3 or both have thyroid-function values that, although within "normal" ranges, tend to approach the hyperthyroid level, especially as regards serum total T3. The serum free thyroid hormones, however, were not examined previously. Interestingly, three of our 22 patients had raised fT3 but normal fT4 and total hormone levels. The importance of this finding remains to be established. Serum fT3 and fT4 concentrations would probably be expected to be within normal ranges in patients with normal T3S and TSH responses. The presence of normal free thyroid hormone concentrations, however, in patients with impaired or absent

TSH responses and thyroid non-suppressibility challenges the concept that free thyroid hormones are the sole physiologically active moieties in the feedback control of TSH. The precise bases for these abnormal results in OGD therefore remain to be established, although failure of suppression of thyroidal ¹³¹I uptake by T3 implies that the thyroid-trapping process is controlled by a mechanism other than TSH. The role of thyroid-stimulating immunoglobulins in the control of thyroid function in patients with OGD is discussed elsewhere.¹⁶

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ONE HUNDRED YEARS AGO Initiated in midwifery by my late lamented friend Dr Edward Rigby, I was early taught the importance of the "binder" as a means of preventing *post partum* haemorrhage; and through a period of nearly thirty-three years, during greater part of which I have had a very extensive midwifery practice, I have only had one fatal case in my own practice.

In every case, I myself carefully bandaged the patient as tightly as possible with a shawl or large towel, in which I generally wrapped a book to form a pad over the uterus, with the best results, though I had then sometimes to deal with cases of haemorrhage.

In the year 1861, however, I was engaged to attend one of the largest women I ever saw. She was tall and immensely stout. The labour was natural, but rather tedious; and, after it was over, violent haemorrhage set in. Here any ordinary binder was useless; and to grasp the uterus through the parietes was impossible, from the immense quantity of fat on the wall of the abdomen. I had the advantage of the advice of my old friend Mr S D Fereday, and all the means which we could devise were used without effect. We watched her for some hours, a certain quantity of draining going on in spite of our efforts; and we anticipated a certainly fatal issue. Where art had failed, however, nature came to her assistance, and she ultimately recovered.

In the following year, I was again asked to attend her, and was called to see her one Sunday morning. I had a most lively recollection

of her last labour and a firm reliance on the binder, and was determined, if possible, to bring one to bear on her huge abdomen; so I went to a saddler who lived near, and there extemporised a binder. It consisted of an oval piece of the strongest "butt leather" he had, ten inches long by eight wide, to each side of which a strong strap (nearly as strong as stirrup-straps) with buckle was attached. With this I was able to attain some degree of pressure. Suffice it to say the labour went on well and no flooding took place.

For some time afterwards, I took my "binder" with me only when I had to attend stout persons; but I soon found that the comfort of it was so great and the advantages so signal, that I began to take it with me to every patient I attended, and have continued to do so for the last eight or nine years; and during that period I have not had a single case of haemorrhage that has given me the slightest anxiety.

This is the practical fact I wish to bring forward: I apply the bandage gently before the child is born. I make the nurse press on the pad during the expulsion of the child. I then tighten the bandage pretty firmly; and, after the expulsion of the placenta, which is rarely long delayed, I again tighten it as firmly as the patient can comfortably bear. It is very rarely necessary to do more; but if the pains be sluggish or infrequent, and if pressure by the binder do not increase them, I give a dose of ergot just before the child is born. (*British Medical Journal*, 1877.)