The Significance of Human Serum Thyrotropin Levels for the Diagnosis and Treatment of the Primary Hypothyroidism

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INTRODUCTION

Since a radioimmunoassay technique for human thyrotropin (TSH) was described by Utiger, Odell and Condliffe,[1] many informations concerning physiology of pituitary-thyroid gland axis have been obtained. But only little attention has been paid to their clinical usefulness. The significance of human serum thyrotropin levels for the diagnosis and treatment of the primary hypothyroidism was described.

MATERIALS AND METHOD

Most of the patients were hospitalized and treated at our clinic.

They were treated at out-patient clinic after euthyroid had been established. Human thyrotropin (TSH) and rabbit anti-HTSH were obtained from the National pituitary Agency (USA). These materials were further diluted with phospho-saline, containing 1 % bovine serum albumin (ARMOUR, USA) and stored frozen in small aliquots until use. Human Thyrotropin Research Standard A was a gift of Medical Research Council, National Institute for Medical Research (London) and used for assay standard.

Iodination

^{125}I was purchased from Dainabot Laboratories (Tokyo, Japan) and HTSH was iodinated according to the methods of Hunter and Greenwood.[2] After preliminary gel filtration with Sephadex G-75 column, ^{125}I-HTSH was repurified with Sephadex G-200 (1.5×40cm) and frozen in small aliquots until use.

RESULTS

The physical appearances and laboratory findings were summarized in Table I.

Table 1. Summary of data on patients with primary hypothyroidism.

patient	age	sex	type	T_3%	PBIμg%	TSHμu/ml	^{131}I-uptake test before, after TSH		thyroid test microsome
1. H. Y.	15	F	J	24	3.0	938	32%	9%	(-) 40^2
2. S. N.	23	F	J	18	2.7	10,000	2	0	(-)
3. H. M.*	18	F	J	28	4.5	950	7	7	(-)
4. Y. F.	44	F	A	21	2.3	720	-	-	(-) 10^2
5. K. S.	47	F	A	17	5.0	150		2	10^3 80^2
6. T. F.	34	F	A	30	1.8	325	81	78	20^2 320^2
7. N. M.	20	M	J	25	2.5	222	-	-	
8. Y. N.	33	F	A	21	3.0	436	2	-	(-) 40^2

* Case 3; Accompanied with congenital heart disease. M; male, F; female, A; adult, J; juvenile

Common complaints of these cases were puffy face, dry skin, cold intolerance, constipation and slow movement. Retarded physical development were observed in 3 of 4 cases in juvenile type. There were rare objective pretibial edema and cornification of the arms.

Moderate gynecomastia was noted in case 7, cardiac effusion in case 2 and enlarged pituitary fossa also in case 2.

Generally the duration of the disease was hardly determined retrospectively. Low levels of T_3 resin sponge uptake (T_3-RSU) and PBI were recorded in all cases except case 3. Elevated serum TSH levels were noted in all cases and especially juvenile type hypothyroidism showed higher levels of the hormone.

^{131}I-uptake (24hr) was markedly depressed in 4 cases but not in the other 2 cases. The TSH test was negative in all patients tested. Therapy was started after detailed examinations, containing ^{131}I-uptake (24hr), TSH determination, insulin and arginine tolerance test, TSH test and TRF test (Thyrotropin Releasing Factor test) as well as T_3-RSU and PBI. All of them were prescribed desiccated thyroid and/or synthetic ℓ-thyroxine, initially 10 to 50mg or 50μg respectively. These hormones were gradually increased with careful observations for their response. Five μg ℓ-triiodothyronine was administered orally during 3 days prior to administration of these hormones and serum levels of TSH was not changed in this periods. Moderate suppression of serum TSH levels were noted by oral administration of 100 μg ℓ-triiodothyronine in 24 hours (345 to 130 μu/ml, case 8). Serum levels of TSH were gradually decreased to normal level after administration of the thyroid hormones.

Clinical course of case I was shown in Figure I. Patient's families noticed that she was shorter than her classmates 3 years ago. Her growth appeared to be

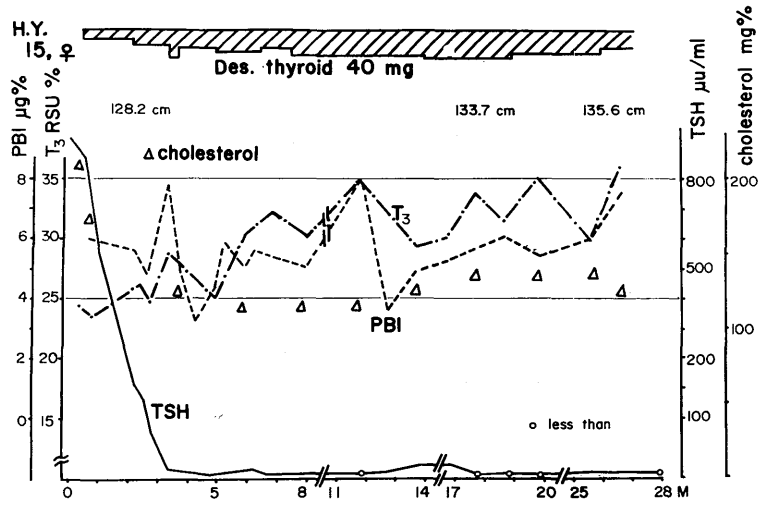

Fig. 1. Clinical course of case 1. Good response was obtained following replacement therapy in juvenile type of hypothyroidism.
T_3-RSU rose parallel with PBI, otherwise TSH declined gradually.

stopped during these several years.

High serum TSH levels (more than 900 μu/ml) were suppressed to normal level after administration of desiccated thyroid with gradual increase of T_3-RSU and PBI. Her serum TSH levels were kept in normal range during the treatment. Also serum cholesterol levels were dropped to near 140mg percent from 200mg percent.

Her height increased 2.5cm in 6 months and 5.5cm in the first year of therapy. Her axillary and pubic hairs were first noticed at 16 weeks of the treatment.

Clinical course of case 2 was shown in Fig. 2. Although retrospective estimation of her physical development could not made, it seems that she was the shortest girl among her classmates at the age of 9. Striking high TSH level of 10,000 μu/ml was noted before treatment and was confirmed by repeated determinations.

Sella turcica enlarged moderately in this case. Diurnal pattern of serum TSH levels showed variable change (2,800 to 8,300 μu/ml). High serum levels of TSH were dropped gradually to normal level after administration of synthetic ℓ-thyroxine and T_3-RSU and PBI rose slowly up to upper normal range. She felt more comfortable in somewhat higher levels of T_3-RSU and PBI rather than euthyroid.

In case 3, her complaints were the same as other juvenile type hypothyroid patients (case 1 and case 2). T_3-RSU and PBI remained within normal range despite of increased TSH levels (Fig. 3). Correlation among TSH, T_3-RSU and PBI was not observed during initial stage of replacement therapy. Although serum TSH levels decreased gradually, paradoxical decrease in T_3-RSU was noted. As

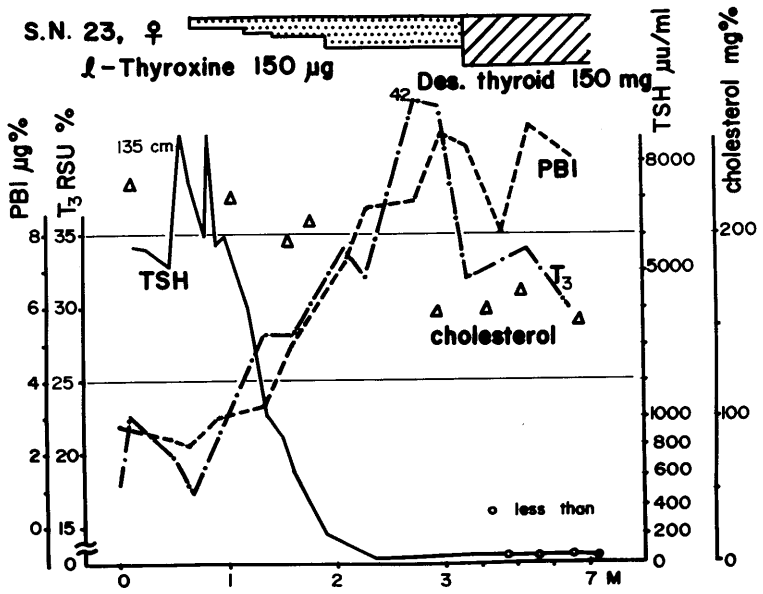

Fig. 2. Clinical course of case 2. Showing rapid decline of high TSH levels to normal range. She felt more comfortable in somewhat hyperthyroid condition rather than in euthyroid.
Initial TSH level was 10,000 μu/ml.

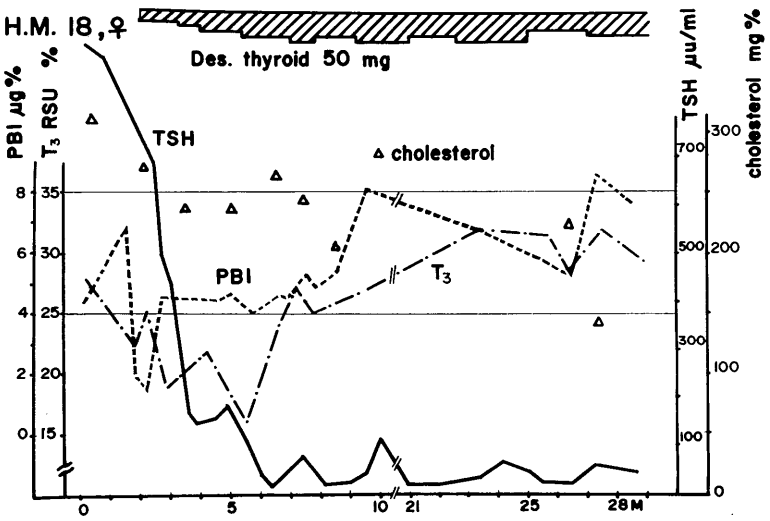

Fig. 3. Clinical course of case 3. T_3-RSU and PBI remained within normal range, although serum TSH elevated highly. Good controle was difficult because she had congenital disease.

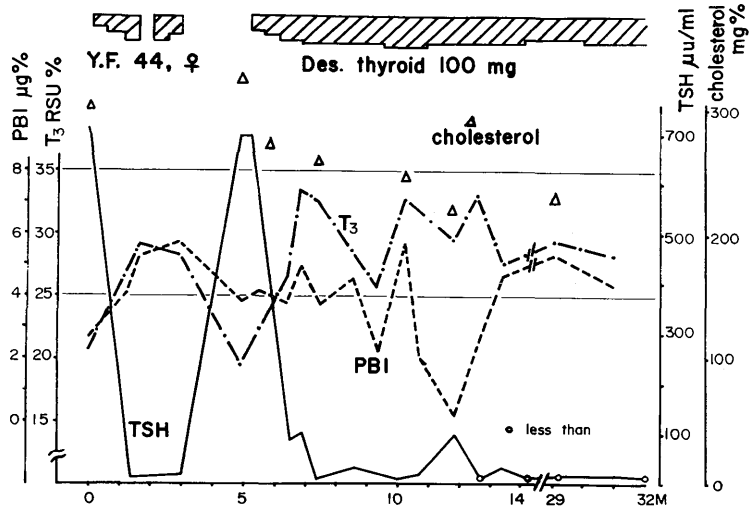

Fig. 4. Clinical course of case 4. Serum TSH levels rose rapidly after desiccated thyroid was discontinued suddenly. Two months were needed for gaining the prior condition.

she had congenital heart disease, sufficient quantity of desiccated thyroid was hardly administered. Sometimes dosis of above medication had to be decreased, because palpitation, arrythmia and slight elevation of TSH were observed occasionally.

In case 4, moderately elevated TSH level were noted before treatment (Fig. 4). T_3-RSU and PBI rose gradually to normal levels after starting of the treatment with sharp drop of TSH levels. After 2 months of treatment this patient stopped her medicine and rapid rise of TSH was observed again.

Readministration of the medication led to decline of serum TSH levels again and her TSH levels were kept in normal range most of the time thereafter.

In one juvenile type hypothyroidism, it was difficult to control the thyroid function as he was not cooperative (case 7).

DISCUSSION

Recent hypothyroid patients, seem not to have far advanced symptoms compared with those described in textbooks. Abnormally low levels of both T_3-RSU and PBI were observed in 4 out of 8 cases and only one case showed normal values of both of these tests. Normal PBI with lower T_3-RSU and normal T_3-RSU with lower PBI were noted in case I and 2 respectively. Despite of variable T_3-RSU and PBI, abnormally high TSH levels were noted in all of the cases. These results may suggest technical errors in determinations of T_3-RSU and PBI. Al-

though all cases had no struma or history of struma, so called thyroiditis chronica may listed in our cases, because they were hardly diagnosed before biopsy and their thyroidal functions were low sometimes in such conditions. Thus poor clinical manifestations and variable T_3-RSU and PBI values may lead to misdiagnosis of hypothyroidism without TSH determination.

It will be noteworthy that TSH levels are always high in hypothyroid patients except secondary hypothyroidism due to anterior pituitary insufficiency or hypothalamic lesions.

Of course all of the patients had high values of TSH in our cases, and we have not a diagnosis of primary hypothyroidism unless high TSH levels in their serum were observed.[3] TSH never rises in euthyroid nor hyperthyroid patients. There are, however, some unusual instances of elevated TSH values in presumably euthyroid individuals.[4] Buttfield, Hetzel and Odell reported that serum TSH leveled up to 79 μu/ml in euthyroid goitrous New Guinea natives who had low extremely iodine intake.[5] TSH stimulation can be evoked temporally during surgical hypothermia.[12]

Maximum level of serum TSH of case 2 was 10,000 μu/ml, and her fasting serum levels of TSH fluctuated between 5,100 to 10,000 μu/ml. In Utiger's report, all 32 patients with primary hypothyroidism had plasma TSH values ranging from 18 to 180 mμg/ml[6] and TSH levels of 61 patients with primary hypothyroidism rose up to 800 μu/ml (range, 24 to 800 μu/ml).[3] High TSH levels presumably suggest inadequate pituitary suppression by low circulating free thyroxine in untreated hypothyroidism.[7] In our cases, higher levels of TSH were noted in juvenile type of hypothyroidism rather than adult type of hypothyroidism, as Utiger mentioned. It seems that the pituitary has a greater capacity for TSH production in younger persons than in older ones.

Factors affecting the TSH levels may be age, duration and degree of the disease. The lack of a significant diurnal variation is a common knowledge nowadas,[7] but Patel et al reported using more sensitive method that a surge of TSH released shortly after the onset of both nocturnal and diurnal variation.[13]

In case 2, however, great diurnal variation (2,800 to 8,300 μu/ml) was noted in our laboratories[14] as others reported.[9][10]

It could be concluded that pituitary had a rather autonomous secreting function during high levels of TSH, being affected by temperature, vasopressin and other factors subtly. Even in longstanding hypothyroid patients, definite sellar enlargements were observed rarely. This may be due to the fact that there is no space to spare in pituitary fossa, because of surrounding bone hardness after maturation. In differentiating the primary hypothyroidism from the secondary one, determination of serum TSH had a greater diagnostic value than any other tests of thyroid function. In the hypothalamic or pituitary hypothyroidism, no elevation of serum TSH level was noted, because of the lesions of these organ.[1]

In almost all cases, the initially elevated TSH levels fell to normal range following replacement therapy. The rapidity of reduction to normal level may dependent on both the type and dose of thyroid hormone used. Acute reduction of serum TSH level may require large dosis of ℓ-triiodothyronine. Single intravenous administration of 500 μg ℓ-triiodothyronine produced a rapid fall in plasma TSH concentration.[11] In the patient who had moderate elevation of initial TSH (100 mμg/ml), 50 % reduction was obtained within 2 hours.[11] Assays performed after the administration of a single oral dosis of 50μg ℓ-triiodothyronine to 4 hypothyroid patients revealed no change in plasma TSH over a 3-day study period.[6] In our study, 5μg ℓ-triiodothyronine administration had not effect on their TSH levels as might have been expected. Moderate reduction was obtained following 100μg ℓ-triiodothyronine administration orally.

It is likely that 100μg ℓ-triiodothyronine would be necessary for gaining TSH reduction.

Utiger reported 3 weeks to 3 months of duration of hormone therapy were needed to produce an euthyroid stadium in 7 cases.[6] Their thyroid functions were evaluated carefully by their clinical feature and laboratory examinations. But clinical decision of euthyroidism was difficult because other thyroid function tests might not reflect correct thyroidal functional state. As TSH always remains beyond upper normal in hypothyroid stadium, the point of euthyroid may be determined with TSH measurement. In some cases, the correlation between the levels of TSH and other thyroid function tests were not so evident. Satisfactory replacement therapy could be achieved easily with occasional determination of their TSH levels.

SUMMARY

Studies were performed in 8 subjects of primary hypothyroidism.

All patients showed variable degree of hypothyroidism in physical features and laboratory tests. Normal value of T_3-RSU and PBI was observed in one patient and abnormally low levels of both tests in 4 patients. The radioimmunoassay of TSH was utmost convenient to establish the diagnosis of primary hypothyroidism.

High levels of serum TSH were noted in all cases. The highest level of TSH was 10,000 μu/ml, which was noted in juvenile type hypothyroidism (female, 23 yrs. old). This is also the highest level of TSH among the previous reports. Young persons had a higher levels of TSH than older ones. Thyroxine and desiccated thyroid were used for replacement therapy. Evaluation of serum TSH was most preferable method to detect the mild hypothyroidism and euthyroid point. There was no correlation between the initial levels of TSH and duration required for euthyroidism.

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