Effect of Estrogen on Serum Total and Free Thyroxine and Triiodothyronine in a Thyroxine-binding Globulin Deficient Family

TOSHIRO SAKURADA, TORU YAMAGUCHI, MAKIKO YAMAMOTO, REIKO DEMURA, MITSUYASU AIDA, SEIJU ONODERA, KATSUMI YOSHIDA, SHINTARO SAITO, HIROSHI OHUCHI* and SHOZO MINAKUCHI*

Department of Internal Medicine and Department of Surgery,
Tohoku University School of Medicine, Sendai*

SAKURADA, T., YAMAGUCHI, T., YAMAMOTO, M., DEMURA, R., AIDA, M., ONODERA, S., YOSHIDA, K., SAITO, S., OHUCHI, H. and MINAKUCHI, S. *Effect of Estrogen on Serum Total and Free Thyroxine and Triiodothyronine in a Thyroxine-binding Globulin Deficient Family.* Tohoku J. exp. Med., 1974, 112 (1), 35-46 — In a family with X-chromosome-linked inheritance of thyroxine (T_4)-binding globulin (TBG) deficiency, serum free T_4 values were low in three of four members, but free triiodothyronine (T_3) values were normal in all four of them. Binding capacities of T_4 -binding prealbumin (TBPA) were high in three of four members. In the propositus, a 47-year-old male, whose T_4 -binding capacity of TBG was null, half-time of serum T_4 was shortened, turnover rate, distribution space and clearance rate all increased, extrathyroidal organic iodine pool decreased and degradation rate of T_4 was unchanged compared with normal values. While half-time of his serum T_3 was prolonged, turnover rate, extrathyroidal pool and degradation rate of T_3 decreased, and T_3 distribution space and clearance rate increased compared with normal values. When 0.24 mg of ethinylestradiol-3-methylester was administered daily by mouth to the propositus for 1 month, half-time of serum T_4 was prolonged, total T_4 increased and T_4 -binding capacity of TBPA decreased but free T_4 , T_4 -binding capacity of TBG and the degradation rate of T_4 were unchanged. Meanwhile half-time of his serum T_3 was shortened, total and free T_3 levels and degradation rate of T_3 increased. ——— T_3 radioimmunoassay; estrogen; free T_3 and T_4 ; TBG-deficiency

The first euthyroid man with deficient TBG was reported by Tanaka and Starr (1959 a). In the present paper, the metabolism of T_4 and T_3 and binding capacities of TBG and TBPA and the effect of estrogen on them are studied in a TBG-deficient family.

The case studied was: H.T., 47-year-old man, an office employee.

Present illness: There were family histories of hepatoma and hypertension. In May 1969, he was found to have albuminuria and hypertension, and admitted to a hospital for about a month. In September, he was readmitted to the hospital for one month for the treatment of Raynaud's disease. In June 1971, he complained of palpitation and fatigue. Because the resin sponge ^{131}I - T_3 uptake value

was abnormally high, he was thought to have hyperthyroidism and was treated with antithyroid drug for two months. In September 1971, he was admitted to the Surgery Department of the Tohoku University Hospital for the treatment of Raynaud's disease, and received a bilateral lumbar sympathetic ganglionectomy. After the operation, he became free from symptoms, but was referred to our clinic for the examination of hypertension in October. No excessive sweating, shortness of breath and loss of weight were noticed.

Physical examinations: His height was 140.7 cm and weight 40.5 kg, somewhat smaller than normal stature, but he was well developed and nourished. His blood pressure was 130/90 mmHg, pulse rate was 82/min and regular. The skin was normally moist and no edema was observed. No signs of the ophthalmopathies of Graves' disease were noticed. The thyroid gland was not palpable and no murmur was heard on it. The heart and the lungs were normal by the physical and radiological examinations. There were operation scars in both lumbar regions. Fine tremor of fingers was observed.

Laboratory findings (Table 1): Routine laboratory findings were within normal limits except for a slightly low value of serum iron-binding capacity. The fundusoscopic examination showed KW-1 grade.

TABLE 1. *Laboratory findings*

Urine and stool: no abnormal findings	Serum total protein: 7.1 g/100 ml
E.S.R.: 12 mm/hr	Albumin 63.8%
RBC: 443×10^4 , 14.7 g/100ml, WBC: 6,200	α_1 -globulin 3.8 "
Differential count: no abnormalities	α_2 -globulin 10.3 "
Serologic test for syphilis: negative	β -globulin 8.1 "
Fasting blood sugar: 110 mg/100 ml	γ -globulin 14.0 "
Serum total cholesterol: 225 mg/100 ml	Liver function tests: no abnormal findings
Serum electrolytes:	ECG: no abnormalities
Na 142, K 4.6, Cl 103 mEq/L	
Ca 10.4, P 3.0 mg/100 ml, Fe 115 μ g/100 ml,	

Endocrinological examinations (Table 3): Histamine test was negative. Urinary 17-OHCS, estrogen and catecholamine values were all within normal limits. Binding capacity of corticosteroid-binding globulin in the serum was normal.

Thyroid function tests (Table 3): Basal metabolic rate (BMR) and thyroidal 24-hour uptake of ^{131}I were normal, but resin sponge ^{131}I - T_3 uptake (Abbott Co.) was extremely high. Serum total T_4 , measured by Tatrastorb Kit (Abbott Co.) was low. The elutable fraction of T_4 , measured by microcolumn chromatography of Sephadex G-25 (Sakurada et al. 1969) corresponding to percent of free T_4 (Sterling and Hegedus 1962) was high and the calculated serum free T_4 was low. Total serum T_3 measured by radioimmunoassay (Sakurada et al. 1973) was low, but the elutable fraction of T_3 (Sakurada et al. 1969) corresponding to percent of free T_3 (Oddie et al. 1971) was high and calculated serum free T_3 was normal. Plasma thyroid-stimulating hormone (TSH) levels measured by radioimmunoassay

TABLE 2. *Endocrinological findings*

Urine 17-OHCS	3.42 mg/m ² /day
Urine 17-KS	5.6 mg/day
Serum cortisol	16.7 μ g/100ml
Binding capacity of transcortin	18.1 μ g/100ml
Urine estrogens	37.8 μ g/100ml
estron	13.3 μ g/100ml
estradiol	10.5 μ g/100ml
estriol	14.0 μ g/100ml
Urine pregnanediol	0.18 mg/day
Urine adrenaline	2.1 μ g/day
Urine noradrenaline	14.5 μ g/day
Histamin test	Negative

TABLE 3. *Thyroid function tests*

BMR	-2.5%
24-hour uptake of ¹³¹ I	16 %
Resin-sponge ¹³¹ I- T_3 uptake (Triosorb kit)	60 %
PBI	2.8 μ g/100ml
Serum thyroxine (Tetrasorb kit)	2.5 μ g/100ml
TSH test	Positive
Tanned-red-cell hemagglutination test	0

(Demura et al. 1969) and the TSH response to synthetic thyrotropin-releasing hormone (TRH) were nearly normal. Thyroidal ¹³¹I uptake responded to the intramuscular injection of TSH (10 U.S.P. per day) for 3 days. T_4 -binding capacity of TBG, measured by the method of Tanaka and Starr (1959 b) (reverse-flow paper electrophoresis, barbital buffer, pH 8.6), was null.

As shown in Table 4 and Fig. 1, his younger brother (M.T.) was proved to be TBG deficient and his mother (S.T.) and eldest sister (I.T.) to have a decreased TBG. Serum total T_4 in Case M.T. was low. Serum free T_4 in Case S.T. was normal, but those in Cases M.T. and I.T. were low. Serum total T_3 in Case M.T. was low, but serum free T_3 was normal in all four members. When T_4 -binding capacity of TBPA was measured by the method of the present author (Sakurada et al. 1967) (polyacrylamide gel electrophoresis, borate buffer, pH 8.2) and by the

Fig. 1. Pedigree of the present family (the arrow indicates the proband, H.T.).

TABLE 4. *Thyroid function tests of a TBG-deficient*

		Propositus (H.T.)		T.T.	
		Administration of estrogen			
		Before	After	Before	After
RSU	(%)	60.0	54.0	24.6	18.4
Total T ₄	(μg/100 ml)	2.50	2.75	11.0	12.25
EF of T ₄	(× 10 ⁻⁴)	6.65	4.65	4.65	3.53
Free T ₄	(ng/100 ml)	1.66	1.28	5.10	5.30
Total T ₃	(ng/100 ml)	48	70	107	218
EF of T ₃	(× 10 ⁻³)	6.43	8.88	3.72	1.74
Free T ₃	(pg/100 ml)	309	622	398	379
TBG*	(T ₄ μg/100 ml)	0	0	22.8	34.2
TBPA†	(T ₄ μg/100 ml)	421	315	330	232
TBPA‡	(T ₄ μg/100 ml)	310	229	240	215

* Reverse-flow paper electrophoresis (barbital buffer, pH 8.6)

† Reverse-flow paper electrophoresis (glycine acetate buffer, pH 8.6)

TABLE 5. *Effect of estrogen on T₄ kinetics of TBG-deficient (H.T.) and normal (T.T.) subjects*

		H.T.		T.T.		Normal range	Ingbar's euthyroid	
		Administration of estrogen						
		Before	After	Before	After			
T ₄ half-time	(days)	3.3	3.6	7.0	8.8	5.7 ~ 7.2	6.6±	0.62*
Turnover rate	(%/day)	21.0	19.3	9.9	7.9	9.6 ~ 12.2	10.6±	0.9
T ₄ distribution space	(L)	16.3	16.4	9.6	9.9	6.4 ~ 10.1	9.4±	2.0
Extrathyroidal organic iodine pool	(μgI)	266	295	690	792	516 ~ 690	508	±146
Clearance rate	(L/day)	3.42	3.17	0.95	0.78	0.78~ 1.08	1.0±	0.25
Degradation rate	(μgI/day)	55.9	56.9	68.3	62.6	55.1 ~ 68.3	53.6±	16.5

* Calculated from Ingbar's turnover rate

TABLE 6. *Effect of estrogen on T₃ kinetics of*

		H.T.		T.T.
		Administration of estrogen		
		Before	After	Before
T ₃ half-time	(hrs)	26.4	22.8	21.6
Turnover rate	(%/day)	63	73	77
T ₃ distribution space	(L)	42.8	42.9	34.2
Extrathyroidal T ₃ pool	(μg)	20.5	30.0	36.6
Clearance rate	(L/day)	27.0	31.3	26.3
Degradation rate	(μg/day)	13.0	21.9	28.2

family and effects of estrogen on them

M.T.	S.T.	I.T.	J.T.	T.M.	E.T.	Normal range
53.5	42.6	44.0	26.0	26.4	22.0	25 ~ 40
2.3	7.2	5.8	8.2	9.2	9.0	5 ~ 15
8.40	4.54	2.83	3.91	3.16	3.92	3.6~ 6.4
1.93	3.27	1.64	3.20	2.91	3.53	2.0~ 3.5
47	87	120	90	98	111	70 ~180
—	3.32	3.40	2.93	3.20	3.78	2.8~ 4.2
—	289	408	264	314	420	260 ~450
0	4.0	8.6	26.5	22.8	29.4	15 ~ 30
353	331	378	363	326	302	260 ~330
341	262	270	290	254	275	220 ~280

† Polyacrylamide gel electrophoresis (borate buffer, pH 8.2)

method of Sterling and Tabachnick (1961) (reverse-flow paper electrophoresis, glycine acetate buffer, pH 8.6), the values in Cases H.T., M.T. and I.T. were high.

T₄-kinetics (Table 5): T₄-kinetics in Case H.T. was studied by the method of Ingbar and Freinkel (1955). Half-time of the serum T₄ was shortened, the turnover rate, distribution space and the clearance rate of T₄ increased, but the degradation rate was within normal limits.

T₃-kinetics (Table 6): T₃-kinetics in Case H.T. was studied by the single-injection method of Cavalieri et al. (1971). Half-time of the serum T₃ was prolonged, the turnover rate and T₃ distribution space increased, the extrathyroidal T₄ pool decreased, the clearance rate unchanged and degradation rate decreased.

Effects of estrogen: The effects of the ethinylestradiol-3-methylester, 0.24 mg of which were given orally every day for one month, were studied on the T₄- and T₃-kinetics in Cases H.T. and T.T. (Tables 5 and 6).

As for T₄-kinetics in both Cases of H.T. and T.T., the estrogen administration caused an increase in serum total T₄, a prolongation of half-time and increase of

TBG-deficient (H.T.) and normal (T.T.) subjects

	Normal range	McConnon's euthyroid	Cavalieri's euthyroid
After			
18.0	20.4~21.6	—	22.2±3.6
92	77 ~82	68 ±2.9	—
35.1	26.9~34.2	37.8±1.35	35.1±6.4
76.5	32.3~36.6	—	—
32.3	26.3~28.9	25.4±1.42	27.2±7.1
70.4	21.9~28.2	57.3±2.29	—

TABLE 7. *Effect of oral administration of ethinylestradiol (0.18~0.3 mg per day for 7 days) on serum total protein and its fractions*

Age and sex	Before estrogen administration						After estrogen administration					
	Serum total protein (g/100ml)	Percent of fractions (%)					Serum total protein (g/100ml)	Percent of fractions (%)				
		Albu- min	Globulin					Albu- min	Globulin			
			α_1	α_2	β	γ			α_1	α_2	β	γ
Euthyroid												
28 f	7.2	55.3	5.3	15.1	11.5	12.8	8.4	59.9	3.4	15.5	11.1	10.1
19 f	7.2	56.7	5.1	11.2	11.2	15.8	8.7	61.4	3.6	9.6	11.0	14.4
24 f	7.2	54.1	5.7	10.5	10.1	19.6	9.4	61.0	2.9	11.9	9.7	14.5
Hyperthyroid												
36 f	7.3	50.5	3.5	11.0	10.5	24.5	8.0	60.3	3.7	8.7	8.7	18.6
43 f	7.0	55.3	3.8	8.7	9.1	23.1	7.4	66.7	2.2	5.8	8.6	16.7
30 f	7.4	52.6	5.5	11.0	8.8	22.1	8.2	59.9	5.1	9.1	9.1	16.8
17 f	6.5	61.9	3.4	9.7	9.1	15.9	7.8	57.0	3.8	11.1	10.6	17.5
49 m	5.6	62.4	4.0	8.0	9.6	16.0	7.8	57.4	3.8	9.8	10.4	18.6
47 f	6.8	61.5	5.2	8.3	9.9	15.1	7.7	66.7	1.9	6.2	8.0	17.2
18 m	8.0	66.7	4.3	8.6	10.7	9.7	7.5	71.1	3.3	8.0	9.3	8.3
36 f	6.0	56.5	4.7	10.7	10.3	18.4	8.2	58.3	4.1	12.3	8.9	16.4
30 m	6.8	68.3	2.8	6.7	7.8	14.4	6.8	62.7	3.5	8.0	9.7	16.1
58 f	7.0	54.8	3.4	8.2	10.1	23.5	8.2	59.4	3.2	8.7	8.3	20.4
43 f	6.2	60.4	4.0	9.4	7.9	18.3	7.2	60.6	4.1	9.0	9.2	17.1
31 f	6.3	47.1	5.8	12.2	10.6	24.3	8.8	55.4	3.4	9.5	11.7	20.0
45 f	6.8	60.5	4.2	9.0	11.9	14.4	7.6	68.4	2.1	7.8	9.2	12.5
Hypothyroid												
60 f	7.6	59.8	3.5	9.0	7.8	19.9	9.0	59.1	3.2	8.7	8.0	21.0
37 f	7.7	64.5	1.9	8.4	7.9	17.3	8.2	64.5	2.1	8.4	8.0	17.0
60 m	7.4	50.9	3.4	12.0	12.4	21.2	8.0	56.7	4.4	8.5	10.0	20.4
Mean	7.0	57.9	4.2	9.9	9.9	18.2	8.0	61.4	3.4	9.3	9.0	16.5
S.D.	± 0.6	± 5.5	± 1.0	± 1.9	± 1.4	± 4.1	± 0.6	± 4.2	± 0.8	± 2.2	± 1.6	± 3.3
The present family												
H.T.	7.1	63.8	3.8	10.3	8.1	14.0	7.0	66.2	3.8	9.3	8.7	12.0
T.T.	6.2	59.7	5.4	11.5	8.0	15.4	6.4	58.0	6.4	11.9	11.5	12.2

turnover rate and extrathyroidal T_4 pool, but there was no change in free T_4 , T_4 distribution space and degradation rate. T_4 -binding capacity of TBG did not change in Case H.T., but increased in Case T.T. T_4 -binding capacity of TBPA decreased in both of them.

As for T_3 -kinetics in both cases of H.T. and T.T., the serum total T_3 increased, the half-time was shortened, the T_3 distribution space unchanged, the turnover rate, extrathyroidal T_3 pool, clearance rate and degradation rate increased after estrogen administration. Serum free T_3 did not change in Case T.T., but increased in Case. H.T.

In three euthyroid, thirteen hyperthyroid and three hypothyroid patients,

serum total protein was determined by a biuret method and fractions of serum protein were estimated by cellulose-acetate membrane electrophoresis (barbital buffer, pH 8.6) before and after the oral administration of 0.18–0.3 mg of ethinyl-estradiol-3-methylester per day for 7 days (Table 7). Mean values of total serum protein and the percent of albumin fraction tended to increase by estrogen administration.

DISCUSSION

In regard to the T_4 kinetics of the present case, the half-time was shortened, the fractional turnover rate and distribution space increased, but the extrathyroidal T_4 pool was reduced, so degradation rate was normal as in the case reported by Ingbar (1961). The normal degradation rate of T_4 in this case would account for the fact that the patient remained euthyroid even though his TBG was deficient.

It is assumed that, if serum TBG decreases, the percentage and absolute amount of serum free T_4 increase (Rosenbaum et al. 1968). The increased free T_4 causes a suppression of TSH secretion, accordingly the circulating T_4 (protein bound iodine, PBI) will decrease so as to restore the absolute amount of free T_4 to normal, although the percentage may remain increased. Thus, the patient with decreased TBG is euthyroid with low PBI and normal free T_4 . Indeed, PBI values in subjects with decreased TBG are reported to be low (Ingbar 1961; Nikolai and Robert 1969; Refetoff et al. 1972). But, if TSH secretion is suppressed, thyroidal uptake of ^{131}I is to be suppressed, too. However, except for the case of Beisel et al. (1962), cases with decreased TBG have not shown any decrease in thyroidal uptake of ^{131}I . The TSH level in the present case, measured by radioimmunoassay, was high normal. And an intravenous administration of 500 μg of synthetic TRH caused a response of plasma TSH. Therefore it may be presumed that there is not always hyposecretion of TSH in TBG-deficient subjects.

The serum free T_4 values in three of four members of the present family were lower than normal value. And free T_4 values in euthyroid subjects with decreased TBG are observed to be normal or low (Cavalieri and Seale 1966; Bayley et al. 1969; Heinonen et al. 1970; Nusynowiz et al. 1971; Hennemann and Dolman 1971; Refetoff et al. 1972). On the other hand, serum free T_4 values in euthyroid subjects with elevated TBG are reported to be normal or high (Katz and Oppenheimer 1963; Jones and Seale 1967; Shane et al. 1971; Thomson et al. 1972). Moreover, increase in serum free T_4 has been reported in normal individuals in response to stress such as surgical operations (Bernstein and Oppenheimer 1966). From these results, the authors would agree with Heinonen et al. (1970) and Thomson et al. (1972) who retain some doubts that serum free T_4 is the main factor to control the thyroid metabolism.

T_4 -binding capacities of TBPA in three of four members of this family were higher than normal. Recent papers indicated that the T_4 -binding capacity of TBPA were high in 14–20 percent of the subjects with decreased TBG (Bayley et al. 1969; Nusynowiz et al. 1971; Refetoff et al. 1972). Heinonen et al. (1970)

reported that a mean value of the T_4 -binding capacity of TBPA in subjects with decreased TBG was higher than normal. On the other hand, T_4 -binding capacity of TBPA are found to be low in many cases with increased TBG (Florsheim et al. 1962; Ingbar et al. 1964; Thomson et al. 1972). In the present case, T_4 -binding capacity of TBG was increased and that of TBPA was decreased by estrogen administration (Table 4). It is interesting that, when a binding capacity of TBP varies in the subjects with decreased or increased TBG, there is a reciprocal change in the T_4 -binding capacity of TBPA, while when a secretion of thyroid hormone changes in hyper- or hypothyroidism, the binding capacities of TBG and TBPA show concordant changes, both increasing in hyperthyroidism and decreasing in hypothyroidism (Cavalieri 1961; Sakurada et al. 1968). However, the change of binding capacity of TBPA is not always observed in the subjects with decreased or increased TBG, so that further studies are waited on this aspect.

TBPA is said to contribute significantly to the hormonal binding in vivo (Ingbar and Freinkel 1960), but other evidence suggests that it may not be so (Christensen and Litonjua 1961). In the present members with TBG deficiency, the serum total T_3 was low or low normal, but the serum free T_3 was normal in all. There may be a possibility of competition between T_4 and T_3 for binding sites of TBP other than TBG in TBG deficiency. The fact that free T_3 was normal in the present case might be another reason why he was euthyroid, but free T_3 did not increase so as to compensate sufficiently the deficit of serum free T_4 .

Contrary to T_4 , half-time of T_3 in the present case was longer than normal, but not so long as in the case reported by Bayley et al. (1969). This might be due to the difference of the method used for estimation; they counted the radioactivity of the plasma containing $^{131}\text{I}-T_3$, but in our experiment, serum proteins were precipitated with trichloroacetic acid, the precipitate was extracted three times with acidbutanol and the butanol-extractable ^{131}I was determined as $^{131}\text{I}-T_3$ (Cavalieri et al. 1971; McConnon et al. 1972). According to Woeber et al. (1970), half-time of T_3 was prolonged when T_3 was administered intravenously to saturate TBG. Binding capacity of TBG in the subjects with decreased TBG is reported to be unsaturated (Kraemer and Wiswell 1968; Nikolai and Roberts 1969) and it seems likely that T_4 and T_3 compete for binding at the binding site of decreased TBG.

By estrogen administration, as Dowling et al. (1960) and Ingbar (1961) reported, turnover rate of T_4 and extrathyroidal T_4 pool increased, clearance rate of T_4 decreased and degradation rate of T_4 remained unchanged. After estrogen administration, T_4 -binding capacity of TBG was increased in Case T.T. but unchanged in Case H.T., while T_4 -binding capacity of TBPA was decreased in both cases. On the other hand, Braverman et al. (1971) reported that T_4 -binding capacity of TBPA was found to be increased by androgen administration.

As to the effects of estrogen on T_3 kinetics, half-time was slightly shortened and serum total T_3 , turnover rate, extrathyroidal pool and degradation rate of T_3 were increased in both Cases T.T. and H.T. as Zaninovich et al. (1969) observed in normal subject.

As shown in Table 7, serum total protein and percent of albumin fraction tended to be increased by estrogen administration. Since the binding capacities of TBG and TBPA depend upon their respective protein concentrations (Oppenheimer et al. 1966; Sakurada et al. 1968; Levy et al. 1971), if concentration of albumin increases, the binding capacity of albumin for T_4 and T_3 might increase and this change of binding capacity may influence the amount of total and free T_4 and T_3 . Especially, in cases of TBG deficiency like the present one, increase of serum total T_3 may partly be due to the increase of albumin fraction.

The decrease of concentration of serum albumin is observed in pregnancy as a result of blood dilution (Dickmann 1952), and the total T_4 and T_3 values in pregnant women are reported to increase in parallel with the increase of TBG (Hotellung and Sherwood 1971). Therefore, TBG may be related more closely to the increase of total T_4 and T_3 than albumin in pregnancy. It has been postulated that the increase of serum total T_4 after estrogen administration is due to the shift of T_4 from intracellular site to extrathyroidal site (Musa et al. 1969), which is contrary to the changes observed in the idiopathic TBG-deficiency (Cavalieri and Searle 1966) and in a decreased binding capacity of TBG after administration of diphenylhydantoin (Oppenheimer et al. 1967). Moreover, as estrogen is supposed to increase the TSH secretion (Adams and Maloof 1970), there is a possibility that the increased TSH may play a role in these changes.

Estrogen administration did not change the serum free T_3 level in Case T.T., but increased free T_3 in the present case from 309 to 621 pg/100 ml without causing hyperthyroidism. The reason why increased free T_3 did not cause hypermetabolism in the present case remains obscure. But there are interesting reports that thyrotoxicosis does not occur in pregnancy in spite of the increase of human chorionic thyrotropin (Hennen et al. 1969) and further, an increased serum free T_4 does not always induce thyrotoxicosis (Katz and Oppenheimer 1963; Bernstein and Oppenheimer 1966; Thomson et al. 1972). In normal subjects, estrogen administration might not cause any change in serum free T_3 , because the effects of estrogen on T_3 -binding capacity of TBP and those on T_3 -kinetics would cancel each other. In the present case, however, estrogen administration increased the serum free T_3 level probably by inducing competition between T_4 and T_3 for the binding site of TBP. Moreover, there might also be a competition for binding sites between T_4 and T_3 at intracellular site (Cavalieri et al. 1970). If T_4 shifts from the intracellular site to the extracellular site when estrogen was administered, the residual T_3 might be more easily metabolized and the degradation rate of T_3 may increase.

Chromosome abnormality could not be found in the present case. As shown in Fig. 1, X-chromosome-linked inheritance was strongly suggested in the present family.

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