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Transient infantile hyperthyrotrophinaemia

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SUMMARY Sixteen cases of transient infantile hyperthyrotrophinaemia were followed up for two to seven years. Concentrations of serum triiodothyronine, thyroxine, and free thyroxine were maintained within the normal range in all cases. All but one child, who had a hearing disturbance, showed normal mental development with normal physical and skeletal maturation. Eleven children had normal concentrations of serum thyroid stimulating hormone and no signs or symptoms of thyroid dysfunction; in three children, diffuse small goitres developed and two further children showed relapse with slightly raised concentrations of thyroid stimulating hormone.

It is concluded that 'transient infantile hyperthyrotrophinaemia' is a syndrome, which differs from typical transient neonatal hypothyroidism, and that careful follow up is necessary because some children show signs of mild pituitary-thyroid dysfunction in later childhood.

Transient infantile hyperthyrotrophinaemia was first reported by Miyai *et al* in 1979.[1] Since then many similar cases have been reported[2 3] with a total of 98 cases in Japan by 1986.[4]

Differentiation of transient infantile hyperthyrotrophinaemia from mild congenital hypothyroidism or transient neonatal hypothyroidism is difficult unless suspected cases are carefully followed up. No long term studies have been made on this syndrome, however, so confirmatory diagnosis has not been possible and the prognosis for physical and psychomotor development is uncertain.

In this paper we report follow up studies on 16 children with transient infantile hyperthyrotrophinaemia.

Patients and methods

During eight years from November 1975 to November 1983, 281 468 infants born in the Osaka area were screened by measuring thyroid stimulating hormone in filter paper blood samples, and 257 neonates were recalled according to the programme reported previously.[5] There were 84 infants with a high concentration of thyroid stimulating hormone (>17 mU/l), and of these 16 infants (10 boys and six girls) were diagnosed as having transient infantile hyperthyrotrophinaemia by the criteria shown in table 1. All were delivered normally at full term and had normal birth weights and lengths. None had clinical features of congenital hypothyroidism[6] and bone age was normal in the infants where radiography was performed. None had a maternal history of excessive or low iodine intake or of amniofetography.

Maternal antithyroglobulin haemagglutination antibodies (TGHA) and antithyroid microsome haemagglutination antibody (MCHA) were negative as was thyroid stimulating hormone binding inhibitor immunoglobulin (TBII) in the cases examined.

These 16 infants were followed up from two to

Table 1 *Criteria for the diagnosis of transient infantile hyperthyrotrophinaemia*

1	Serum thyroid stimulating hormone concentration (2–8 weeks of age) >4 SD above mean for normal controls (mean (SD) 7·4 (2·3) mU/l; mean+4 SD 17 mU/l)
2	No contamination with heterophilic antibodies (linear relationship in dilution experiment)
3	Serum thyroid stimulating hormone concentration (2–9 months of age) decreases to normal and remains normal until 1 year of age
4	Serum thyroxine, triiodothyronine, and free thyroxine concentrations are maintained within the normal range
5	No goitre or sublingual mass due to an ectopic thyroid (normal thyroid radioiodine uptake and scintigram)
6	No signs or symptoms of congenital hypothyroidism and normal bone maturation
7	No maternal history of thyroid disorder, intake of antithyroid agents, or excessive or deficient iodide intake

seven years with reference to growth and clinical progress. Mental development was assessed by the Tsumori-Inage or Tsumori-Isobe developmental scales, which are usually used in Japan to evaluate psychomotor development of infants and children.[7] In some cases the IQ was assessed by the Wechsler intelligence scales for children.[8]

Hormones were measured by radioimmunoassay using commercial kits: thyroid stimulating hormone (Daiichi Radioisotope Laboratory), thyroxine and triiodothyronine (Eiken Immunochemical Laboratory), and free thyroxine (Gamma Coat RIA kit, Clinical Assays Inc or Amerlex Free T_4 RIA Kit, Amersham Radiochemical Centre).

TGHA and MCHA were measured by a commercial kit (Fujizoki Co); the basal metabolic rate was measured with an open circuit indirect calorimeter.[9]

Statistical analyses were performed by the two sample Student's *t* test.

Results

The initial thyroid function test results are shown in table 2. None of the infants had appreciable clinical features of cretinism on the score of Smith *et al*,[6] and in the infants studied for bone age none had abnormal bone maturation. Concentrations of serum thyroxine, triiodothyronine, and free thyroxine were all normal as were the basal metabolic rates of those infants examined. Thyroid uptake of ^{123}I was also within the normal range, and scintigrams showed a normal shape, size, and location of the thyroid.

Changes in the concentrations of serum thyroid stimulating hormone, thyroxine, and triiodothyronine during follow up for two to seven years are shown in fig 1. Five infants (cases 5, 6, 12, 13, and 15) were given L-thyroxine for two to six months after birth; the other infants received no medication.

According to outcome we have tentatively classified the 16 infants into three groups (table 3). Group A had normal thyroid function (cases 1–11; fig 1A) and concentrations of serum thyroxine, triiodothyronine, and free thyroxine were within the normal range of age matched controls. Group B had relapse of hyperthyrotrophinaemia (cases 12 and 13; fig 1B), concentrations of serum thyroid stimulating hormone were >17 mU/l at 5·9 years (case 12) and 5·4 years (case 13), but concentrations of serum thyroxine, triiodothyronine, and free thyroxine were within the normal ranges throughout the follow up period. Group C (cases 14–16; fig 1C) developed small diffuse goitres (2–3 cm width) at the ages of 3 years (case 14), 4·1 years (case 15), and 5·3

Table 2 *Initial results of thyroid function tests in patients with transient infantile hyperthyrotrophinaemia at 2 to 7 weeks of age*

Case No	*Age (weeks)*	*Thyroid stimulating hormone (mU/l)*	*Thyroxine (nmol/l)*	*Free thyroxine* (pmol/l)*	*Triiodothyronine (nmol/l)*	*% Basal metabolic rate*	*^{123}I uptake (3 hours)*
1	3	43·0	190	47·3 (G)	3·35	−3	17·7
2	3	19·5	110	35·9 (G)	3·21	+10	21·8
3	7	22·0	141	11·3 (A)	3·69	ND	ND
4	4	19·7	128	49·1 (G)	2·90	−11	ND
5	4	29·7	209	22·1 (G)	3·84	−10	36·6
6	3	18·4	217	29·7 (G)	4·09	+6	26·4
7	5	23·6	97	13·2 (A)	3·20	+16	28·3
8	5	24·1	146	21·2 (A)	3·13	ND	ND
9	5	27·0	136	20·5 (A)	3·43	ND	ND
10	3	18·3	129	ND	3·59	+4	ND
11†	5	26·4	141	14·7 (A)	4·93	ND	ND
12‡	2	29·4	160	23·5 (G)	3·89	−1	36·4
13‡	3	22·4	186	32·1 (G)	3·32	−8	31·6
14§	5	17·2	156	44·6 (G)	2·93	−12	37·6
15§	5	33·3	133	21·2 (A)	3·61	−5	26·1
16§	3	77·4	195	23·1 (A)	3·21	+14	ND
Normal range		2·8–12·0	90–187	22·8–47·2 (G) 8·08–25·5 (A)	2·43–4·52	−15 to +15	10·0–35·0

ND: not done.
*Gamma Coat RIA (G) or Amerlex Free T4 RIA (A).
†Child with hearing disturbance; ‡child with relapsed hyperthyrotrophinaemia; §child with goitre that appeared later.

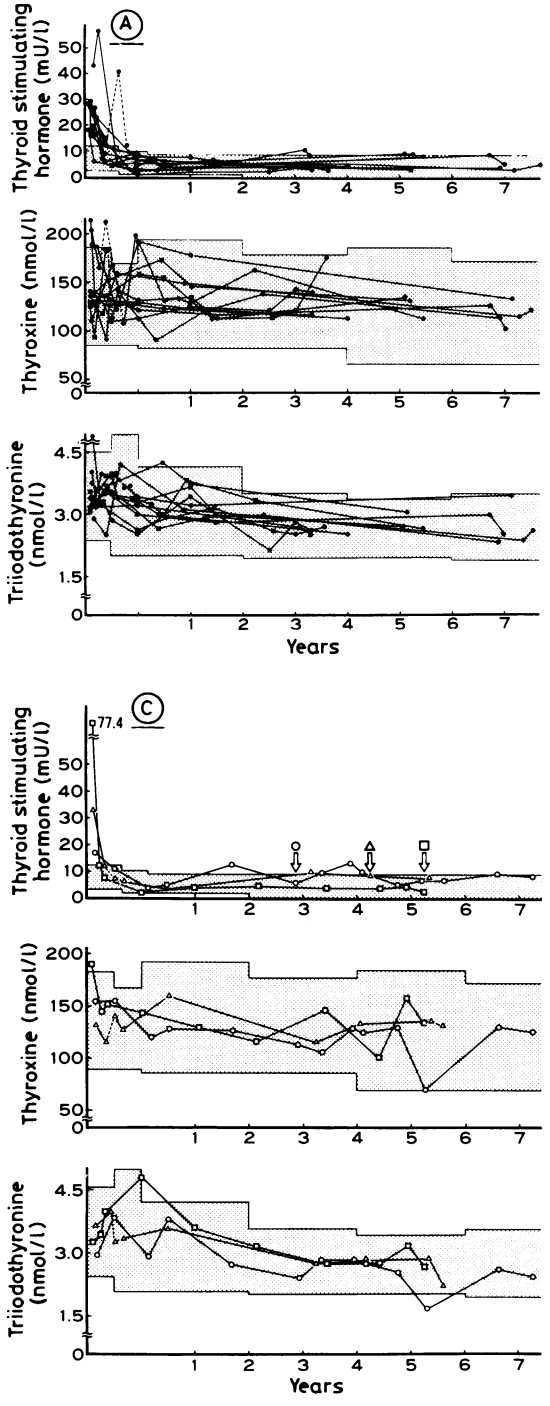

Fig 1 *Changes in serum thyroid stimulating hormone, thyroxine, and triiodothyronine concentrations in patients with transient infantile hyperthyrotrophinaemia. The lines indicate data during no treatment (−) and treatment with L-thyroxine (– –). The shaded area shows the range of normal control values in our hospital. (A) Group A: cases 1–11; (B) Group B: hyperthyrotrophinaemia relapsed cases 12 (○) and 13 (△); and (C) group C: cases who developed goitre (cases 14○, 15△, and 16□).*

Table 3 *Most recent results of thyroid function tests in patients with transient infantile hyperthyrotrophinaemia*

Case No	*Age (years)*	*Thyroid stimulating hormone (mU/l)*	*Thyroxine (nmol/l)* (nmol/l)	*Free thyroxine* (pmol/l)*	*Triiodothyronine (nmol/l)*	*Developmental quotient‖ or IQ*
1	7·1	3·5	133	21·2	3·38	119 (T)
2	6·9	4·1	114	22·2	2·60	97 (T)
3	7·0	5·8	105	22·1	2·60	99 (W)
4	7·6	5·4	124	19·9	2·66	116 (W)
5	5·4	8·7	117	16·7	2·75	90 (T)
6	5·1	4·4	136	19·9	3·07	110 (T)
7	5·3	10·8	127	21·2	3·04	120 (T)
8	3·3	4·5	142	19·9	2·70	127 (T)
9	4·0	5·6	119	25·0	2·72	133 (T)
10	3·2	4·7	121	21·8	2·67	150 (T)
11†	3·5	4·0	183	17·9	2·87	80 (T)
12‡	5·9	20·0	105	18·6	2·75	107 (T)
13‡	5·7	13·6	144	23·1	1·90	112 (W)
14§	7·1	7·6	127	21·2	2·40	110 (W)
15§	5·6	6·1	135	18·6	2·17	110 (T)
16§	5·2	2·6	137	23·1	2·61	126 (T)
Normal range		<1–9·0	73–187	9·2–27·7	1·89–3·50	

*Amerlex Free T_4 RIA.
†Child with hearing disturbance; ‡child with relapsed hyperthyrotrophinaemia; §child with goitre that appeared later.
‖Tsumori-Isobe (T) or Wechsler intelligence scales for children (W).

years (case 16). Concentrations of serum thyroxine, triiodothyronine, free thyroxine, and thyroid stimulating hormone were within the normal range except for case 14 who showed a transiently low triiodothyronine concentration at 5·1 years with slight increases in concentrations of thyroid stimulating hormone at 1·7 and 3·9 years.

Thyroid antibodies were not detected in any infant throughout the follow up period. The response of thyroid stimulating hormone to thyrotrophin releasing hormone (10 μg/kg bodyweight; TRH–Tanabe) was examined in some cases in early infancy (1–3 months of age), later infancy (6–12 months of age), and childhood (3·4–7·7 years of age); the results are shown in fig 2. In the seven infants studied in group A, peak thyroid stimulating hormone concentrations in childhood (mean (SD) 33·5 (7·5) mU/l) were significantly lower than those in early infancy (81·3 (49·1) mU/l) ($p<0·05$). Both infants in group B and one infant in group C (case 14) had significantly higher peak thyroid stimulating hormone concentrations in later infancy and childhood than found in normal controls.

The ratio of the increments in thyroid stimulating hormone (TSH) and triiodothyronine (T_3) after stimulation by thyrotrophin releasing hormone ($\triangle T_3$:$\triangle$TSH) of all cases examined in group A (mean (SD): 1·9 (1·5)$\times 10^3$ nmol/mU) were similar to those in normal controls (2·9 (1·8)$\times 10^3$ nmol/mU) in early infancy.

All cases showed normal growth and none were below −1·5 SD for height or weight in normal Japanese children. Bone maturation was also normal in all cases. Developmental quotient or IQ values for all infants were above 90, except for the one child who was deaf who had a score of 80 (table 3).

Discussion

In this paper we have proposed a definition of transient infantile hyperthyrotrophinaemia that is a modification of our previous definition.[2] On the basis of these criteria we found 16 cases in 281 468 newborn babies screened and estimate the incidence of this syndrome to be about 1:17600. During follow up for two to seven years, 11 children (group A) had consistently normal thyroid function and no signs or symptoms of hypothyroidism. The peak values of thyroid stimulating hormone after administration of thyrotrophin releasing hormone decreased gradually with age, becoming almost normal by the ages of 3–7 years.

The results for the $\triangle T_3$:$\triangle$TSH ratio after thyrotrophin releasing hormone indicate that these children respond to endogenous thyroid stimulating hormone, and compensated primary hypothyroidism can be excluded as the residual capacity of the thyroid to secrete triiodothyronine after thyroid stimulating hormone stimulation was the same as that in age matched normal controls. In this respect, transient hyperthyrotrophinaemia can be

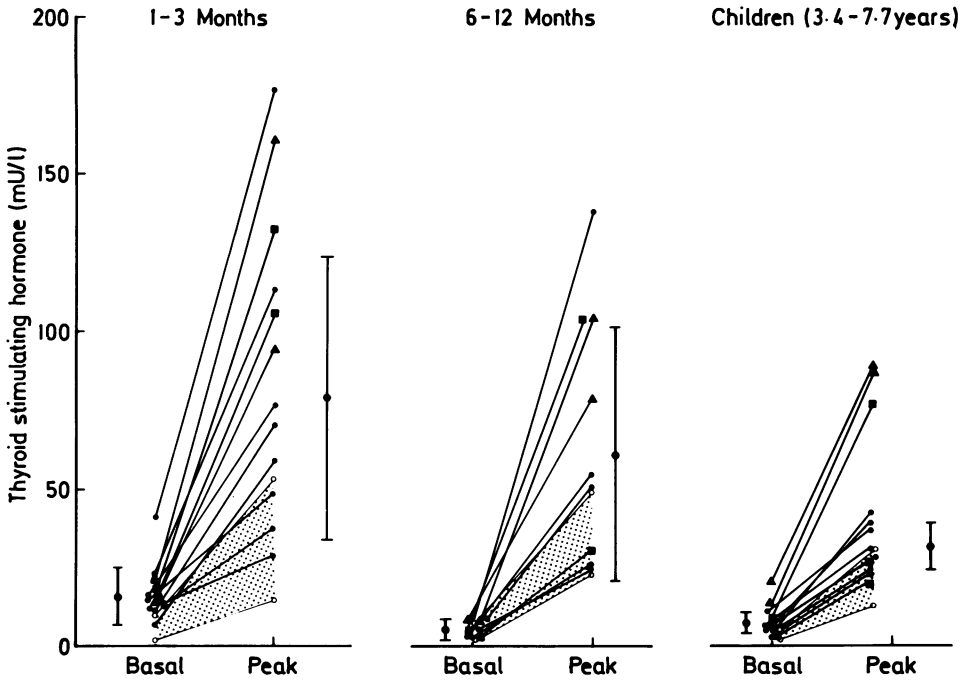

Fig. 2 *Thyroid stimulating hormone response to thyrotrophin releasing hormone stimulation test in group A (●), B (▲), and C (■). the shaded area shows the range of normal control values. Closed circle with vertical bars indicate means (SD) of thyroid stimulating hormone concentrations of group A cases. Peak thyroid stimulating hormone values of group A cases in childhood were significantly lower than those obtained in early infancy ($p<0·05$).*

considered to be a different condition from primary hypothyroidism. The children in group A may have had some form immaturity of the hypothalamic-pituitary-thyroid axis—probably in the negative feedback system—in early life, but this immaturity had disappeared by childhood.

On the other hand, two children in group B showed relapse of hyperthyrotrophinaemia and in three children in group C small soft diffuse goitres developed. The children in group B had slightly higher concentrations of serum thyroid stimulating hormone than normal. We have followed up these cases without medication, and they show good psychosomatic development with normal bone maturation. The reason for hyperthyrotrophinaemia in these cases is unknown. If their concentrations of serum thyroxine decrease in response to increased demands for thyroid hormones in the future, they will have a final diagnosis of mild primary hypothyroidism. On the other hand, if their thyroid stimulating hormone is maintained at a raised concentration or fluctuates without any abnormalities in the concentration of serum thyroid hormones, we may classify them as having sustained or fluctuating hyperthyrotrophinaemia.

One child in group C had a persistently exaggerated thyroid stimulating hormone response to thyrotrophin releasing hormone and one episode of a low triiodothyronine and a low-normal thyroxine concentration. The ^{123}I scinitigram of this girl showed normal location but slight enlargement of the thyroid, and her ^{123}I thyroidal uptake was normal with no discharge of ^{123}I by thiocyanate; mild hypothyroidism due to a defect of hormone synthesis still cannot be excluded in this girl. The other two children (cases 15 and 16) had small soft goitres but their serum thyroid hormones and thyroid stimulating hormone concentrations were normal. These children most likely had diffuse simple goitres. As these three children show good physical and mental development and normal bone maturation, we will continue their follow up without treatment.

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