Original

Retrospective Analysis of Infants Designated as Positive on Mass-Screening for Congenital Hypothyroidism at Kagoshima University

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Abstract. Mass-screening for congenital hypothyroidism has identified cases of mild hypothyroidism, transient hypothyroidism, and transient hyperthyrotropinemia as well as typical hypothyroidism. In this paper, we examine the clinical data of the cases found positive in the screening test at our hospital. From 1989 to 1999 there were 72 patients with positive screening tests who started levothyroxine sodium (l-T₄; Thyradin-S) as supplement therapy. At the age of 3 to 4 yr the patients were re-evaluated to determine whether treatment should be continued. Thyroid scintigraphies were done at the same time. We divided these cases into 4 groups. Those in group 1A started l-T₄ in early infancy without a TRH test because of obvious clinical evidence of hypothyroidism, and treatment was continued after re-evaluation (n=37). Those in group 1B also started treatment in early infancy without a TRH test, but treatment was discontinued after re-evaluation (n=20). Patients in group 2A started l-T₄ after evaluation by a TRH test and treatment was continued after re-evaluation (n=14), while those in group 2B started treatment after a TRH test, but after re-evaluation, treatment was discontinued (n=1). In group 2A, only a low dose of l-T₄ was needed, and a slightly elevated TSH and slightly decreased free T₄ (fT₄) were observed after the drug washout period. However, these patients had an exaggerated response to the TRH test at re-evaluation. These findings indicate that this group, forming not a small part of whole screening-positive subjects, had mild hypothyroidism. Such patients require careful follow-up and repeated evaluation to determine whether treatment should be continued.

Key words: congenital hypothyroidism, mass screening, TRH test, mild hypothyroidism, transient hypothyroidism

Introduction

Received: September 17, 2004

Accepted: June 4, 2005

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Mass-screening for congenital hypothyroidism began throughout Japan in 1979. It has not only enabled early detection, but has also facilitated early treatment for typical congenital

hypothyroidism. A guideline for neonatal mass-screening for congenital hypothyroidism was published in 1998. However, in this guideline, a consensus for the management of transient hyperthyrotropinemia, transient hypothyroidism, and mild hypothyroidism was not established. In the present study, we reviewed the clinical management of neonates with positive results on mass-screening from 1989 to 1999 in Kagoshima Prefecture to determine appropriate diagnostic criteria and treatment strategies for these cases.

Subjects and Methods

The protocol used in Kagoshima Prefecture calls for cases with a TSH of whole blood (filter paper) value over $30 \mu\text{U/ml}$ at mass-screening to be evaluated further. Cases with a TSH of whole blood value over $9 \mu\text{U/ml}$ and under $30 \mu\text{U/ml}$ at mass-screening in whom a repeat TSH is over $9 \mu\text{U/ml}$ are also evaluated further. Neonates with a birth weight under 2000 g have repeat tests at one month of age or when their body weight reaches 2500 g.

Subjects

From 1989 to 1999, 189 positive cases found by mass-screening were evaluated at the Department of Pediatrics of Kagoshima University. The subjects of this study were 72 patients who were treated with thyroid hormone up to age 3 to 4 yr in whom I-123 thyroid scintigraphy was performed. Patients with Down's syndrome, other underlying complications (such as a cardiac anomaly), or cases whose follow-up was discontinued (such as a change of residence) were excluded.

Methods

The patients were divided into 2 groups: those who started treatment at the first visit or early without having a TRH test (non-TRH group, group 1); and those who started treatment after the TRH test due to persistent slightly high TSH values

(post-TRH group, group 2). The TRH test was performed using TRH $10 \mu\text{g/kg}$ given by intravenous injection. A baseline serum TSH value greater than $4 \mu\text{U/ml}$ and a peak serum TSH value over $30 \mu\text{U/ml}$ indicates an exaggerated response, and those who developed such responses received treatment. At age 3 to 4 yr, before thyroid scintigraphy, an equivalent dose of liothyronine sodium (l-T₃; Thyronamin) was substituted for l-T₄. After a washout period, diagnostic I-123 thyroid scintigraphy was performed. At the same time, the serum TSH and FT₄ values were measured. Based on the results of these tests, a decision was made whether to continue treatment. In our facility, an iodine uptake of 10% to 40% is normal. A normal or high uptake and a value of over 20% on potassium thiocyanate discharge testing indicates a defect in organification. A low uptake and a saliva/blood ratio of I-123 under 10, indicates a concentration defect. Groups 1 and 2 were subdivided into subgroups depending on whether treatment was continued following the post-thyroid scintigraphy re-evaluation. Groups 1A and 2A continued treatment, while groups 1B and 2B discontinued treatment. The data that was gathered and analyzed for these 4 treatment groups included birth weight, gestational age at birth (weeks), TSH at mass-screening, TSH and FT₄ at initial evaluation, TSH and FT₄ at the time of re-evaluation after the washout period for thyroid scintigraphy, findings of thyroid scintigraphy, dose of thyroid hormone, and TRH test results. We also reviewed the standard set for starting and discontinuing treatment at our University.

Results

The populations of each group

In the non-TRH group (group 1, n=57), 37 patients (65%) continued treatment following post-thyroid scintigraphy re-evaluation, and 20 patients (35%) discontinued treatment after re-evaluation. In the post-TRH group (group 2, n=15), 14 patients

Table 1 Body weight and gestational age at birth

	gestational term (weeks)	birth weight (g)
group 1A n=37	39.5 ± 1.6 (34.4~43)	2939 ± 475 (1665~3883)
group 1B n=20	39.2 ± 1.6 (36.7~42.1)	2912 ± 319 (2215~3412)
group 2A n=14	39.1 ± 1.3 (37~41)	2759 ± 281 (2254~3362)
group 2B n=1	40.2	2860

mean ± 1 SD. (minimum~max.)

(93%) continued treatment following post-thyroid scintigraphy re-evaluation, and only 1 patient discontinued treatment after re-evaluation.

Birth weight and gestational age at birth

Birth weight and gestational age at birth (weeks) did not significantly differ among the 4 groups (Table 1).

Criteria for starting therapy

1) TSH at mass-screening, TSH and FT4 at initial evaluation (Table 2)

Table 2 summarizes the TSH values at mass-screening and the initial evaluation data of the 4

groups. The mean of the first TSH value at the time of mass-screening (on whole blood) was 56.39 μ U/ml in group 1A and 36.46 μ U/ml in group 1B. Both results were significantly higher than the value in group 2A (14.98 μ U/ml; $p < 0.01$, 2A vs. 1A and 2A vs. 1B). There were no significant differences in the mass-screening TSH values between groups 1A and 1B, and the initial evaluation serum TSH values were also similar ($p < 0.001$: 1A vs. 2A, and 1B vs. 2A). However, the serum FT4 values in group 1A (0.87 ng/dl) and 1B (0.60 ng/dl) were significantly lower than the values in group 2A (1.62 ng/dl; $p < 0.0001$, 2A vs. 1A and 2A vs. 1B). The serum FT4 value was significantly lower in the group that discontinued treatment, group 1B, than in the group that continued treatment, group 1A ($p < 0.05$).

2) The criteria for starting therapy in group 1 (non-TRH group)

Cases with a first TSH value greater than 30 μ U/ml or a second TSH value greater than 15 μ U/ml at mass screening, and cases with initial evaluation serum TSH values greater than 15 μ U/ml and a serum FT4 value less than 1 ng/dl, were referred for clinical evaluation, including physical examination (for jaundice and inactivity) and X-rays of the distal femoral epiphysis, before starting treatment. If the initial evaluation TSH value was less than 15 μ U/ml, then the case was followed for

Table 2 TSH at mass-screening, TSH and FT4 at initial evaluation

	First MS TSH (μ U/ml) ¹⁾	Initial evaluation TSH (μ U/ml)	Initial evaluation FT4 (ng/dl)
group 1A n=37	56.39 ± 55.17 (9.2~228.4)	174.1 ± 250.2 (11.0~968.0)	0.87 ± 0.44 (0.10~1.61)
group 1B n=20	36.46 ± 27.94 (9.6~85.4)	134.1 ± 121.3 (17.0~446.4)	0.60 ± 0.35 (0.12~1.46)
group 2A n=14	14.98 ± 6.23 (9.1~29.5)	8.16 ± 2.89 (4.2~14.1)	1.62 ± 0.82 (1.01~1.38)
group 2B n=1	14.6	5.05	1.21

1) μ U/ml of whole blood, other units are expressed as "of serum". ***: $p < 0.0001$, **: $p < 0.01$, *: $P < 0.05$.

Table 3 TSH and FT4 at re-evaluation

	TSH (μ U/ml)		FT4 (ng/dl)	
group 1A n=37	52.9 $\pm$ 68.0 (4.29~297.2)	*** **	0.89 $\pm$ 0.45 (0.1~1.9)	*** **
group 1B n=20	3.39 $\pm$ 1.25 (1.34~5.37)		1.36 $\pm$ 0.21 (1.01~1.71)	
group 2A n=14	6.93 $\pm$ 2.0 (4.86~11.87)		1.23 $\pm$ 0.16 (0.96~1.49)	
group 2B n=1	4.56		1.17	

***: $p < 0.0001$, **: $p < 0.01$.

several months. When the TSH value remained greater than 10 μ U/ml on repeat testing, then treatment was started without a TRH test.

3) The criteria for the TRH test in group 2 (post-TRH group)

When the serum TSH value fell below 10 μ U/ml on repeat testing, and when the TSH value remained above the normal range, or if the value fell under the normal range once and then rose above the normal range, a TRH stimulation test was performed. The TRH tests were performed on children ranging from 5 to 17 mo (mean 9.5 mo) of age.

Re-evaluation after the washout period prior to thyroid scintigraphy

1) TSH and FT4 at re-evaluation (Table 3)

Table 3 summarizes the re-evaluation data of the 4 groups. The serum TSH value in group 1A (52.9 μ U/ml) was significantly higher than in the other groups (1B, 3.39 μ U/ml, $p < 0.0001$; 2A, 6.93 μ U/ml, $p < 0.01$). The FT4 value in group 1A (0.89 ng/dl) was significantly lower than in the other groups (1B, 1.36 ng/dl, $p < 0.0001$; 2A, 1.23 ng/dl, $p < 0.01$). After the washout period, there was a slight TSH increase and slight FT4 decrease in group 2A.

2) The criteria for restarting treatment after re-evaluation

After the washout period, if the serum TSH

value was greater than 8 μ U/ml, the FT4 value and the thyroid scintigraphy findings were reviewed before treatment was restarted with the pre-washout dose. However, if the TSH value after the washout period was less than 8 μ U/ml, then a TRH test was performed to determine whether treatment was necessary. In group 1A, 30 patients restarted treatment without TRH tests, and 7 patients restarted treatment after TRH tests. In group 1B, all 20 patients discontinued treatment after TRH tests. In group 2A, 7 patients restarted treatment without TRH tests, and 7 patients restarted treatment after TRH tests. Only 1 group 2B patient discontinued treatment after TRH test.

3) Comparison between the TRH test data at the first evaluation and at re-evaluation in group 2 (Table 4)

Table 4 shows the individual data for 8 patients in group 2 who underwent repeat TRH stimulation tests due to a slightly elevated TSH value (4.56 to 6.10 μ U/ml) at re-evaluation. Of the 7 patients in group 2A, Patients 1 and 4 showed a minimally elevated TSH value after the washout period prior to thyroid scintigraphy, but showed a clearly elevated TSH value at the baseline in the TRH test, which was performed within 1 mo after thyroid scintigraphy. In Patients 2 and 6, the TSH values were only minimally elevated at the baseline in the TRH test, but the peak values were markedly elevated. In 7 cases re-evaluation TRH

Table 4 Comparison between the data at first evaluation and at re-evaluation

		At first evaluation TSH response of TRH test			After washout period	At re-evaluation TSH response of TRH test		
		baseline	peak	120'	TSH	baseline	peak	120'
group 2A	1	5.2	35.3	16.9	4.86	10.1	38.0	15.2
	2	4.3	65.3	31.4	5.02	4.2	71.0	23.8
	3	4.4	48.2	26.6	5.80	6.1	45.9	14.1
	4	9.2	47.7	17.2	5.94	9.7	41.4	15.8
	5	7.8	45.1	14.5	5.49	8.3	51.1	18.1
	6	4.9	65.6	18.9	5.34	5.2	63.2	13.9
	7	6.8	47.8	20.5	6.10	6.6	52.5	17.8
group 2B	1	8.8	87.0	49.8	4.56	2.5	46.1	15.8

(μ U/ml)

Table 5 Findings on I¹²³ Thyroid Scintigraphy

	ectopic	organification defects	concentration defects	hypo uptake	hyper uptake	no remarks	poor examination*
group 1A	9	1	2	3	5	15	2
group 1B	0	0	0	0	4	14	2
group 2A	0	0	0	0	2	11	1
group 2B	0	0	0	0	0	1	0

*: The cases who couldn't swallow potassium thiocyanate etc.

test patterns were similar to those obtained during the first test. In 1 group 2B patient, there was an exaggerated response to the TRH test. However, since the baseline TSH value was not elevated (2.5 μ U/ml), the patient was followed without restarting treatment.

Findings of thyroid scintigraphy (Table 5)

Table 5 shows the findings of thyroid scintigraphy for each group. Group 1A contained all cases with an ectopic thyroid gland, cases with a defect in organification, and those with low uptake, including a concentration disorder. Four patients with a high uptake were in group 1B.

The l-T4 dose (Table 6)

The l-T4 dose per body weight at the initiation of treatment was 6.9 μ g/kg/day in group 1A and 7.8

μ g/kg/day in group 1B. Each of these l-T4 doses was significantly higher than the doses given to group 2A (2.5 μ g/kg/day, $p < 0.0001$ for both). There were no significant differences between groups 1A and 1B with respect to the l-T4 dose per body weight. At the time of re-evaluation, just before the washout period prior to thyroid scintigraphy, the l-T4 dose per body weight in group 1A (3.0 μ g/kg/day) was significantly higher than in group 1B (1.7 μ g/kg/day, $p < 0.01$) and in group 2A (1.9 μ g/kg/day, $p < 0.01$). There were no significant differences between groups 1B and 2A with respect to the l-T4 dose per body weight.

The actual l-T4 dose given at the initiation of treatment was 27.0 μ g/day in group 1A and 28.7 μ g/day in group 1B. Each of these l-T4 doses was significantly higher than that given to group 2A (21.4 μ g/day, $p < 0.05$ vs. 1A and $p < 0.01$ vs. 1B). At

Table 6 The dose of L-T4 at initiation of treatment and at re-evaluation

	Dose at initiation of treatment		Dose at re-evaluation	
	($\mu\text{g/day}$)	($\mu\text{g/kg/day}$)	($\mu\text{g/day}$)	($\mu\text{g/kg/day}$)
Group1A n=37	27.0 $\pm$ 7.4 (20~50)	6.9 $\pm$ 2.2 (2.9~12.0)	43.4 $\pm$ 18.9 (20~95)	3.0 $\pm$ 1.3 (1.2~5.4)
Group1B n=20	28.7 $\pm$ 7.2 (15~40)	7.8 $\pm$ 2.1 (4.0~10.5)	24.5 $\pm$ 6.9 (10~40)	1.7 $\pm$ 0.5 (0.7~2.8)
Group2A n=14	21.4 $\pm$ 3.6 (20~30)	2.5 $\pm$ 0.5 (2.1~3.9)	25.4 $\pm$ 6.3 (20~40)	1.9 $\pm$ 0.5 (1.4~2.8)
Group2B n=1	20	2.3	20	1.5

***, $P < 0.0001$, **, $P < 0.001$, *, $P < 0.05$.

the time of re-evaluation, the actual l-T4 dose in group 1A (43.4 $\mu\text{g/day}$) was significantly higher than that given to group 1B (24.5 $\mu\text{g/day}$, $p < 0.0001$) and that given to group 2A (25.4 $\mu\text{g/day}$, $p < 0.01$). In groups 1A and 2A, the groups in which treatment was continued, the l-T4 dose tended to increase with age. However, in groups 1B and 2B, the groups in which treatment was discontinued, the l-T4 dose tended to remain unchanged or decrease over the course of treatment.

Summary

1. In the non-TRH group (group 1, $n=57$), a high percentage of patients (35%, 20 patients) discontinued treatment after re-evaluation.
2. In the non-TRH group, the initial evaluation TSH values did not significantly differ between group 1A (the group in which treatment was continued) and group 1B (the group in which treatment was discontinued).
3. In group 2A, a slightly elevated TSH level and a slightly decreased FT4 level were observed after the washout period. However, these patients had an exaggerated response to the TRH test at re-evaluation. Therefore, except for 1 patient, they were restarted on treatment.
4. All cases with evidence of thyroid dysplasia were in group 1A.

5. In the non-TRH groups (groups 1A and 1B), the initial l-T4 dose was significantly higher than that in the post-TRH group (groups 2A and 2B). In groups 1A and 2A, the l-T4 dose tended to increase with age, while in groups 1B and 2B, the l-T4 dose tended to remain unchanged or decrease over the course of treatment.

Discussion

Mass-screening of infants for congenital hypothyroidism was started throughout Japan in 1979. This improved the prognosis for identified cases and allowed for normal intellectual development. Cases with congenital hypothyroidism often present with few typical clinical manifestations, which makes the differential diagnosis difficult in many cases (1–3). Furthermore, criteria for the diagnosis and treatment varied among medical institutions. Though a guideline for neonatal mass-screening for congenital hypothyroidism was published in 1998 (1, 4), this guideline did not establish a consensus for the management of transient hyperthyrotropinemia, transient hypothyroidism, and mild hypothyroidism. The guideline only stated that such patients required careful specialist treatment. In the present study, we reviewed the clinical management of neonates

with positive results at mass-screening from 1989 to 1999 in Kagoshima Prefecture, so as to review appropriate diagnostic criteria and treatment strategies. There are a variety of opinions as to the appropriate management of persistent mild hyperthyrotropinemia. In our hospital, the TRH stimulation test is actively promoted, and the result helps determine treatment.

In the post-TRH treatment group (group 2), all but 1 patient continued treatment after re-evaluation (group 2A). In group 2A, after the washout period TSH rose slightly, but there was no substantial decrease in FT4. However, there was an exaggerated response to the TRH test in group 2A. These findings indicate that mild hypothyroidism was present in group 2A (5). Thus, the responses to the TRH test at re-evaluation performed at 3 to 4 yr of age were similar to the responses to the TRH test seen during the neonatal period. Therefore, neonatal evaluation using the TRH test was highly reliable. In one group 2B patient, there was an exaggerated response to the TRH test at re-evaluation. However, since the baseline TSH value was not elevated ($2.5 \mu\text{U/ml}$), the patient was followed without restarting treatment. It is possible that this patient will have to restart the treatment.

It has been suggested that re-evaluation to determine whether treatment should be continued must be done before a pathologic diagnosis is obtained by thyroid scintigraphy (2, 6). In our hospital, we also measure TSH and perform a TRH stimulation test after the washout period for thyroid scintigraphy to obtain more detailed information to use in re-evaluation.

In our study, all cases with an ectopic thyroid gland and thyroid hypoplasia, as determined by I-123 thyroid scintigraphy, were in group 1A. In these patients with permanent hypothyroidism, treatment was continued with thyroid hormone. Among the patients who discontinued treatment after re-evaluation (group 1B), some had scintigraphy results that showed a high uptake. Such patients require careful follow-up and

evaluation to determine if treatment should be resumed.

Patients in group 2A appeared to have mild hypothyroidism, and the l-T4 dose was significantly lower than in group 1. Furthermore, the l-T4 dose tended to increase with age (groups 1A and 2A), while the l-T4 dose tended to remain unchanged or decrease in those for whom treatment was discontinued (groups 1B and 2B).

Calaciura *et al.* (7) evaluated a group of 56 children aged 1 to 3 yr who, after a confirmatory re-examination, had been classified as being false-positive at congenital hypothyroidism screening. They found that, in nearly half these patients, a thyroid abnormality was nevertheless identified. In addition, at the 36th Annual Meeting of the Japanese Society for Pediatric Endocrinology, Otsu *et al.* reported that 82% of 33 neonates with slight TSH elevations, whether treated or untreated, were later diagnosed as having a thyroid abnormality (8). Tomita *et al.* evaluated the discontinuation of short term l-T4 therapy in infants who continued to have mildly elevated serum TSH levels without having low serum FT4 concentrations, and who had an exaggerated TSH response to the TRH test (borderline hypothyroidism) (9). They found that the TSH, FT4, and TSH response to the TRH test gradually normalized 6 to 9 mo after the discontinuation of l-T4 therapy, compared to levels obtained immediately after the discontinuation of treatment. These studies suggest that the management of infants with mild hyperthyrotropinemia is not yet well established, and that these patients require careful follow-up and frequent re-evaluations to determine whether treatment should be given (10). In our hospital, patients whose treatment is discontinued are generally monitored up to adolescence, and careful scheduling ensures no loss of patients to follow-up. Among children in whom treatment is continued based on re-evaluation at age 3 to 4 yr, those without further increases of TSH and who do not need to have their l-T4 doses increased are

followed to adolescence, at which time a re-evaluation after a washout period and TRH stimulation tests are done.

To make a pathologic diagnosis, thyroid ultrasound may be useful at the initial evaluation to non-invasively assess structural abnormalities, and it may be used at later stages to determine the need for continued treatment (1, 11, 12). Ultrasound for diagnosis is also being considered for use in our hospital. In our study, several patients who underwent thyroid scintigraphy had incomplete results, mainly because of their inability to take potassium thiocyanate. Some clinicians recommend that an evaluation, to obtain a pathologic diagnosis, be conducted when the children are 5 to 6 yr of age (6, 13). This issue requires further investigation. In addition, improved detection rates of gene mutations in goitrous congenital hypothyroidism and a genetic disorder in a case with thyroid dysplasia have been reported (6, 14). Therefore, genetic tests are expected to become more routine in the evaluation of infants with congenital hypothyroidism. The use of genetic tests will facilitate more accurate pathologic diagnosis.

Conclusion

In this study, we analyzed the data of infants who were found positive at mass screening for congenital hypothyroidism and were treated at Kagoshima University Hospital. For 35% of the patients in the group not requiring the TRH test at the time of initiating treatment due to elevated serum TSH levels, treatment was discontinued at the time of re-evaluation. These findings show that even among neonates who are diagnosed with hypothyroidism, some cases may later turn out to have been just a transient decrease in thyroid function. In our hospital, we do the TRH stimulation test routinely in cases with persistent mild hyperthyrotropinemia so as to guide treatment. Group 2A seemed to be mostly composed of patients with mild hypothyroidism.

During the neonatal period, the TRH test was found to be very useful for the evaluation of thyroid function in cases with mild hypothyroidism. It remains to be determined whether treatment is needed for infants with mild hypothyroidism. Patients in whom treatment is discontinued at re-evaluation require careful follow-up and evaluation to determine if treatment should be resumed.

References

1. Inomata H. Guideline of therapy for Mass-screening for congenital hypothyroidism. *Jpn J Pediatr* 2002;55:1213-9.
2. Nishi Y. Assignment of diagnosis and treatment for congenital hypothyroidism. *Pediatr Jpn* 2002;43:1487-95.
3. Miyagi H, Nakasone K, Onaga A. Four cases of neonatal hyperthyrotropinemia with various clinical courses. *Jpn J Pediatr* 1991;44:2332-8.
4. Working Group on Congenital Hypothyroidism of Japanese Society for Mass-screening. Guideline for neonatal mass-screening for congenital hypothyroidism. *Clin Pediatr Endocrinol* 1999;8:51-5.
5. Harada S, Matuura N, Fujieda K, Oyanagi K, Okuno A, Ichikawa K, *et al.* Mild hypothyroidism detected by mass-screening for congenital hypothyroidism. *Clin Endocrinol* 1991; 39:85-90.
6. Harada S. Congenital hypothyroidism. *Jpn Pediatr Med* 2002;34:626-34.
7. Calaciura F, Motta RM, Miscio G, Fichera G, Leonardi D, Carta A, *et al.* Subclinical hypothyroidism in early childhood: a frequent outcome of transient neonatal hyperthyrotropinemia. *J Clin Endocrinol Metab* 2002;87:3209-14.
8. Ohtsu S, Takubo K, Kazahari K, Kazahari M, Yokota Y, Oyama Y, *et al.* Diagnosis of mild congenital hypothyroidism—Etiology of the disease and confirmatory test performed by council members of the JSPE for diagnosis of the disease. *Clin Pediatr Endocrinol* 2002;11:112.
9. Tomita Y, Ishiguro H, Shinagawa T, Kubota C, Shinohara O. Persistence of mild hyperthyrotropinemia after discontinuation of

- three-year course of low-dose L-thyroxine therapy in infants with borderline hypothyroidism. *Endocr J* 2003;50:379-84.
10. Miyagawa S, Nishimura H, Nishi Y, Kamino K. Following examination of the infants detected by congenital hypothyroid mass-screening in Hiroshima Prefecture (1984~1996). *Clin Endocrinol* 2003;51:73-6.
 11. Ohnishi H, Inomata H, Watanabe T, Wataki K, Sato H, Noda H, *et al.* High-frequency thyroid ultrasonography in 165 infants detected by congenital hypothyroid screening. *Clin Pediatr Endocrinol* 1998;7:136.
 12. Ichiba Y, Furujyou M. Study of the cases needed detailed evaluation for congenital hypothyroidism mass-screening. *Jpn J Pediatr* 1998;51:1615-9.
 13. Harada S, Matuura N. Diagnosis and treatment for hypothyroidism in infants and children. *Clin Endocrinol* 2002;50:67-71.
 14. Krude H, Biebermann H, Schnabel D, Ambrugger P, Gruters A. Molecular pathogenesis of neonatal hypothyroidism. *Horm Res* 2000;53:12-8.