Central Hypothyroidism in Infants Who Were Born to Mothers With Thyrotoxicosis Before 32 Weeks' Gestation: 3 Cases

Ryuzo Higuchi, PhD*; Masakazu Miyawaki, MD‡; Takeshi Kumagai, MD§; Takahiro Okutani, PhD*; Yuko Shima, MD‡; Megumi Yoshiyama, MD‡; Hiroshi Ban, MD‖; and Norisige Yoshikawa, PhD‡

ABSTRACT. We describe 3 infants who were born to mothers with Graves' disease and developed central hypothyroidism that persisted for >6 months after birth. Two were preterm infants, and the other was a term infant who was born to a euthyroid mother who had been treated with an antithyroid drug since week 31 of gestation. These cases suggest that passage of thyroid hormones can occur from a thyrotoxic mother to the fetus and that the gestational period earlier than 32 weeks may be the critical time for development of central hypothyroidism. ***Pediatrics*** **2005;115:e623–e625. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2128;** ***central hypothyroidism, Graves' disease, midgestation, preterm infant, thyrotoxicosis.***

ABBREVIATIONS. T_4, thyroxine; TSH, thyrotropin; T_3, triiodothyronine; FT_4, free T_4; TRAb, TSH receptor antibody; TSAb, thyroid-stimulating antibody; FT_3, free T_3; TRH, thyrotropin-releasing hormone; G*n*P*n*, gravida *n*, para *n*.

Only a minority of newborns from mothers with Graves' disease develop central hypothyroidism.[1] In these cases, free thyroxine (T_4) levels at birth were higher than those at 5 days of age, suggesting that the fetal T_4 level was higher than that in the period immediately after birth, probably as a result of passive transfer from the mother during the last trimester.[2] The major negative feedback effect of thyroid hormones on thyrotropin (TSH) secretion is mediated by serum free T_4, which is monodeiodinated to triiodothyronine (T_3) by type II deiodinase in the hypothalamus and pituitary thyrotroph cells. Undetectable TSH in the fetal cord serum in the presence of markedly elevated free T_4 (FT_4) suggests pituitary negative feedback at as early as 20 weeks' gestation.[3] The exposure of the fetal hypothalamic-pituitary-thyroid system to a higher-than-normal thyroid hormone concentration might impair its physiologic maturation, because there is a continuous significant decrease in the TSH/FT_4 ratio during development from the midgestational fetus to the young adult.[4] Since 1997, we have experienced 3 cases of central hypothyroidism, as described below, and on the basis of these cases, we conclude that the gestational period earlier than 32 weeks may be the critical time for development of central hypothyroidism in offspring.

From the Departments of *Perinatal Medicine and ‡Pediatrics, Wakayama Medical University, Wakayama, Japan; §Department of Neonatology, Tokushukai Hospital at Kishiwada, Osaka, Japan; and ‖Department of Pediatrics, Kinan General Hospital, Tanabe, Japan.

Accepted for publication Dec 2, 2004.
doi:10.1542/peds.2004-2128
No conflict of interest declared.

Reprint requests to (R.H.) Department of Perinatal Medicine, Wakayama Medical University, 811-1 Kimiidera, Wakayama City 641-0012, Japan. E-mail: rhiguchi@wakayama-med.ac.jp

CASE REPORTS

Case 1

A male infant was born at 27 weeks of gestation with a birth weight of 1152 g (0.3 SD). His 27-year-old gravida 2, para 0 (G2P0) mother had received a diagnosis of Graves' disease at the age of 13 years. However, she had been noncompliant with medication, and premature rupture of membranes occurred at 27 weeks and 2 days of gestation. A nonstress test revealed fetal tachycardia >200 beats/min. The mother was transferred to our hospital because of the possibility of preterm labor and abruptio placenta. Her thyroid function was as follows: free T_3 (FT_3) 21.1 pg/mL, FT_4 8.1 ng/dL, and TSH <0.03 μIU/mL on the day when premature rupture of membranes occurred. The TSH receptor antibody (TRAb) level was 52% (normal: <15%), and the thyroid-stimulating antibody (TSAb) level was 294% (normal: <180%).

The infant was born via cesarean section on the day the mother was transferred to our hospital. TRAb in the cord blood was 16%, and the infant showed tachycardia at ~200 beats per minute after birth, with the following hyperthyroid function 1 hour after birth: FT_3 7.0 pg/mL, FT_4 4.7 ng/dL, and TSH 0.12 μIU/mL. Tachycardia and hyperthyroid function normalized 2 days and 5 days after birth, respectively. Subsequently, hypothyroid function was observed at 12 days of age: FT_3 2.1 pg/ml, FT_4 0.4 ng/dL, and TSH 0.03 μIU/mL (Table 1). The TSH response to TSH-releasing hormone (TRH; 10 μg/kg) was low, 0.04 μIU/ml after 30 minutes, and administration of oral L-thyroxine (5 μg/kg per day) was started at 2 weeks of age. The TRH test normalized (increase of TSH to >10 μIU/mL) at 6 months of age, and thyroxine supplementation was stopped.

Case 2

A male infant was born at 34 weeks' gestation with a birth weight of 2445 g (0.53 SD). His 23-year-old G1P1 mother had received a diagnosis of Graves' disease at the age of 21 years. However, she had been noncompliant with medication and was transferred to a local hospital because of the possibility of preterm labor complicated with thyrotoxicosis at 31 weeks' gestation, when her thyroid function was as follows: FT_3 of 21.1 pg/mL, FT_4 of 7.65 ng/dL, and TSH of <0.05 μIU/mL, with TRAb and TSAb at 41.9% and 504%, respectively. Propylthiouracil was administered orally at a dose of 300 mg/day, and her serum FT_4 had decreased to 3.23 ng/dL at week 34 of gestation, when the infant was spontaneously delivered vaginally after PROM. TRAb in the cord blood was 42.7%. Radiography demonstrated formation of distal femoral epiphyses. The infant showed poor sucking and hyperbilirubinemia from 2 days after birth and was treated with phototherapy. Thyroid function at 4 days of age was as follows: FT_3 of 1.05 pg/mL, FT_4 of 0.65 ng/dL, TSH of 0.25 μIU/mL, and a neonatal screening test based on TSH levels performed at 8 days of age was normal. Subsequently, constipation appeared. Hypothyroid function was still observed at 4 weeks of age: FT_3 of 3.16

TABLE 1. Thyroid Function Tests and Autoantibodies in Samples Collected at Birth and Before Starting L-Thyroxine Administration in 3 Infants Who Were Born to Mothers With Thyrotoxicosis Before 32 Weeks of Gestation

Case	Gestation, wk	Age, d	FT_3, pg/mL	FT_4, ng/dL	TSH, μIU/mL	TRAb, %*	TSAb, %†
1	27	0	7	4.7 (0.6–2.2)	0.12 (0.2–30.3)	16	370
		12	2.1	0.4	0.03		
2	34	0	ND	ND	<0.005 (1.2–21.6)	42.7	ND
		4	1.05	0.65 (1.2–4.4)	0.025 (1.2–21.6)		
3	37	0	0.82	1.00 (2.0–5.3)	0.84 (1.0–39)	20.3	384
		2	0.98	0.66 (2.0–5.3)	0.40 (1.0–39)		

ND indicates not determined. Reference ranges for thyroid function tests during the first week of life are indicated in parentheses.[5]
* Normal range: <15%.
† Normal range: <180%.

pg/mL, FT_4 of 0.75 ng/dL, and TSH of 1.33 μIU/mL (Table 1), with the maximal TSH response to the TRH test ranging from 1.79 to 5.55 μIU/mL after 30 minutes. Hence, oral L-thyroxine (10 μg/kg per day) supplementation was started. The TRH test normalized at 13 months of age, and thyroxine supplementation was stopped.

Case 3

A male infant was born at 37 weeks' gestation with a birth weight of 3244 g (1.2 SD). His 26-year-old G0P0 mother had received a diagnosis of thyrotoxicosis attributable to Graves' disease at 31 weeks' gestation. Her thyroid function was as follows: FT_3 of 16.04 pg/mL, FT_4 of 3.92 ng/dL, TSH of 0.01 μIU/mL, and TRAb at 62.3%. Propylthiouracil was administered orally to the mother at a dose of 300 mg/day, and, as a result, she became euthyroid: FT_4 of 1.74 ng/dL, TSH of 0.03 μIU/mL, and TRAb at 50%, 2 days before an elective cesarean section.

Thyroid function in the cord blood was as follows: FT_4 of 1.00 ng/dL, TSH of 0.84 μIU/mL, and TRAb at 20.3%. Radiography demonstrated formation of distal femoral epiphyses. Two days after birth, the infant's thyroid function decreased: FT_3 of 0.98 pg/mL, FT_4 of 0.66 ng/dL, and TSH of 0.4 μIU/mL, and oral L-thyroxine (5 μg/kg per day) supplementation was started (Table 1). The maximal TSH response to the TRH test ranged from 0.18 to 1.58 μIU/mL after 30 minutes at 3 months of age. The TRH test normalized at 20 months of age, and L-thyroxine supplementation was stopped.

DISCUSSION

Transient hypothyroxinemia in infants who are born to mothers with poorly controlled Graves' disease was first reported in 1988.[1] The FT_4 levels at birth in such infants were higher than those at 5 days of age, suggesting that the fetal T_4 level was higher than that in the period immediately after birth, probably as a result of passive transfer during the last trimester.[2] However, the time during pregnancy when maternal thyrotoxicosis might lead to the development of central hypothyroidism in offspring is unknown.

Low FT_4 concentrations in combination with suppressed TSH levels and the blunted TSH response after TRH administration confirmed that the thyroid regulatory system was impaired in the 3 cases described in this report. We hypothesize that maternal hyperthyroidism during pregnancy leads to a hyperthyroid fetal environment, as seen in case 1, which has previously been reported as "short-term hyperthyroidism followed by transient pituitary hypothyroidism in a very low birth weight infant born to a mother with uncontrolled Graves' disease."[6] Another report describes an infant in whom central hyperthyroidism developed after neonatal hyperthyroidism and persisted for only a few days after birth, with the condition thought to be attributable to passive transfer of maternal thyroxine from a mother with thyrotoxicosis.[7] However, in case 3, a term normal birth weight infant was born to a mother who had euthyroid function at the time of delivery, and in case 2, maternal thyroid function was improving at the time of delivery after antithyroid drug therapy had been introduced in week 31 of gestation. Hence, the most unusual maternal thyroid hormone concentration in each of the 3 present cases was concluded to be before 32 weeks of gestation, when the passage of thyroid hormones from thyrotoxic mother to fetus probably occurs. Three other cases of central hypothyroidism have been reported in term or near-term infants who were born to mothers who were noncompliant with medication or in whom Graves' disease was undiagnosed during pregnancy.[8]

Immunoglobulins move transplacentally, mainly during the late-gestational period. TRAb and TSAb both were positive but were not high enough to provoke neonatal hyperthyroidism in the cord blood in the present 3 cases (Table 1). Therefore, it is likely that thyroxine, not autoantibodies transferred from the mother, affected the maturation of the fetal hypothalamic-pituitary-thyroid system. One case has

TABLE 2. Summary of Cases of Central Hypothyroidism Related to Maternal Thyrotoxicosis

Gestational Age, wk	Birth Weight, g	Maternal Graves' Disease, Onset, Control at Delivery	Thyrotoxicosis, Duration	TRAb (TSAb), %	Hypothyroidism, Onset, Recovery	Source
27	1152	Pregestation, poor	2 d	16	12 d, 6 mo	Case 1
30	1620	Pregestation, poor	2 d	88.7	16 d, 15 mo	Ref 7
31	1474	Pregestation, poor	3 mo	(2438)	7 mo, >18 mo	Ref 9
33	2016	23 wk gestation, partial	—	45.2	0 d, 24 mo	Ref 11
34	2455	Pregestation, partial	—	42.7	4 d, 13 mo	Case 2
36	3250	Pregestation, partial	—	ND	4 d, >4 mo	Ref 8
37	3244	31 wk gestation, good	—	20.3	2 d, 20 mo	Case 3
38	2735	Pregestation, poor	—	Negative	4 d, >3 mo	Ref 8
38	3490	Around delivery, poor	—	Negative	7 d	Ref 8

— indicates not applicable; ND, not determined.

been reported of a premature infant who showed central hypothyroidism after 3 months of neonatal hyperthyroidism as a result of TRAb transferred from a mother with Graves' disease,[9] and 1 of 7 premature infants with congenital thyrotoxicosis developed hypothyroidism that required T_4 treatment from day 64.[10] A review of the available case reports (Table 2) indicates that central hypothyroidism may develop in 3 different ways: by way of short-term (a few days) hyperthyroidism as a result of passively transferred thyroxine, by way of long-term (>1 month) hyperthyroidism as a result of passively transferred TRAb, and directly after birth. The high levels of thyroid hormones produced by fetal thyroids as a result of TRAb transferred from the mother may also impair the fetal hypothalamic-pituitary-thyroid system.

The cases shown in Table 2 suggest that maternal thyrotoxicosis before 32 weeks' gestation may be critical for development of central hypothyroidism in offspring, except for the last case[8] in Table 2, whose diagnosis was not confirmed by TRH test. Furthermore, case 3 indicates that the possibility of central hypothyroidism cannot be excluded in cases in which term infants who are born to euthyroid mothers with Graves' disease are exposed to maternal thyrotoxicosis before 32 weeks' gestation. We also note 1 report of a very low birth weight infant who started L-thyroxine treatment at 1 year of age and showed developmental delay,[11] suggesting that both fetal exposure to high thyroxine levels and infantile hypothyroidism may be causes of developmental delay. Therefore, thyroxine supplementation during a period of central hypothyroidism is of importance. However, TSH-based neonatal screening cannot detect congenital central hypothyroidism, as shown in case 2. Although T_4-based screening has been reported to be useful for detecting central hypothyroidism,[12] the preferential strategy to prevent maternal Graves' disease–associated hypothyroidism is control of thyroid function throughout pregnancy.

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Pediatrics 2005;115;e623
DOI: 10.1542/peds.2004-2128 originally published online April 15, 2005;

PEDIATRICS®
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