Transient Hypothyroidism or Persistent Hyperthyrotropinemia in Neonates Born to Mothers with Excessive Iodine Intake

Soroku Nishiyama,1 Tomohiro Mikeda,1 Toshihisa Okada,2 Kimitoshi Nakamura,1 Tomio Kotani,3 and Akira Hishinuma 4

Perinatal exposure to excess iodine can lead to transient hypothyroidism in the newborn. In Japan, large quantities of iodine-rich seaweed such as kombu (Laminaria japonica) are consumed. However, effects of iodine from food consumed during the perinatal period are unknown. The concentration of iodine in serum, urine, and breast milk in addition to thyrotropin (TSH), free thyroxine (FT4), and thyroglobulin was measured in 34 infants who were positive at congenital hypothyroidism screening. Based on the concentration of iodine in the urine, 15 infants were diagnosed with hyperthyrotropinemia caused by the excess ingestion of iodine by their mothers during their pregnancy. According to serum iodine concentrations, these infants were classified into group A (over 17 μg/dL) and group B (under 17 μg/dL) of serum iodine. During their pregnancies these mothers consumed kombu, other seaweeds, and instant kombu soups containing a high level of iodine. It was calculated that the mothers of group A infants ingested approximately 2300–3200 μg of iodine, and the mothers of group B infants approximately 820–1400 μg of iodine per day during their pregnancies. Twelve of 15 infants have required levo-thyroxine (LT4) because hypothyroxinemia or persistent hyperthyrotropinemia was present. In addition, consumption of iodine by the postnatal child and susceptibility to the inhibitory effect of iodine may contribute in part to the persistent hyperthyrotropinemia. We propose that hyperthyrotropinemia related to excessive iodine ingestion by the mother during pregnancy in some cases may not be transient.

Introduction

Neonatal screening programs for congenital hypothyroidism resulted in the early detection and effective therapy for children with congenital hypothyroidism (1). In addition, screening revealed transient disorders of thyroid function, such as transient congenital hypothyroidism with elevated thyrotropin (TSH) and decreased thyroxine (T4) levels and transient hyperthyrotropinemia with elevated TSH without a decrease in T4 (2). Before the start of neonatal screening for hypothyroidism, most of these disorders remained unidentified because of the unknown clinical course. Recently, borderline congenital hypothyroidism (3) or subclinical hypothyroidism (4) has been proposed. Perinatal exposure to excessive iodine may cause transient hypothyroidism or hyperthyrotropinemia in the newborn (2). Direct iodine overload in the newborn is caused by either disinfection agents or contrast medium studies done during the perinatal period (5,6). The fetus and newborn can be exposed to high maternal iodine concentrations either by crossing the placenta perinatally or postnatally by secretion of iodine into breast milk (7,8). Because of antithyroid effects of an iodine excess, the so-called Wolff-Chaikoff effect, which blocks the uptake of iodine by the thyroid gland, leads to reduced T4 and increased TSH. Rare cases of transient congenital hypothyroidism and hyperthyrotropinemia are the transplacental passage of antithyroid antibodies or antithyroid drugs (9–11).

Japan is considered to be an iodine-sufficient area because of the ingestion of large quantities of iodine-rich seaweed (12) such as kombu (tangle weed, Laminaria japonica), hijiki (Hizikia fusiformis), and wakame (Undaria pinnatifida). Kombu contains a high level of iodine (1.3 mg per gram of kombu) (13). However, the effect of iodine contained in foods has not been thoroughly examined, and the iodine content of many kombu products are unknown. The present study was done to measure the concentrations of iodine in the daily Japanese diet consumed by the people of Japan and we investigated the clinical course of newborn infants of mothers who ingested large quantities of iodine during pregnancy.

---

1Department of Pediatrics, Kumamoto University School of Medicine, Kumamoto, Japan.
2Department of Pediatrics, Saisyunso National Hospital, Kumamoto, Japan.
3Department of Laboratory Medicine, Miyazaki Medical College, Miyazaki, Japan.
4Department of Clinical Laboratory Medicine, Dokkyo University School of Medicine, Tochigi, Japan.
Subjects and Methods

Screening for congenital hypothyroidism

In Japan, mass screening for congenital hypothyroidism is nationwide (14). Blood samples are collected within the first 4–7 postnatal days and TSH values are measured using blood filter papers. The value of blood filter paper TSH is shown to be a whole blood index (in the case of serum indication, a value of whole blood indication should be multiplied by 1.6). Among the primary collected samples, in cases where the value of TSH is in excess of 30 μIU/mL (in the case of serum indication, 48; hereafter omitted), a request for a thorough confirmation test should immediately be made at a medical institution. In cases where the value is in excess of 10 μIU/mL, a request for a second blood sample should be made to the institution responsible for the blood collection (obstetric and so forth). In cases where the value of TSH is in excess of 30 μIU/mL (in the case of serum indication, 48: hereafter omitted), a request for a thorough confirmation test should immediately be made at a medical institution. In cases where the value is in excess of 10 μIU/mL, a request for a second blood sample should be made to the institution responsible for the blood collection (obstetric and so forth). In cases where the TSH value of the second sample exceeds 10 μIU/mL, a request for a thorough confirmation test should be made.

Patients

From April 2000 to March 2002, 37,724 Japanese infants were screened for congenital hypothyroidism in Kumamoto Prefecture and 34 (1:1109) underwent confirmation tests. In all cases and controls, informed consent to enter the study was obtained from the parents. Over 20% of newborns who were negative at congenital hypothyroidism screening and whose mother ingested excess iodine of 1500–2500 μg per day during pregnancy. Kombu intake was restricted for 4 days before sampling. We also measured concentrations of iodine in serum, urine, and breast milk under the same restriction technique. The combination of maternal and paternal intake of kombu is achieved. The amount of iodine that the mothers consumed during pregnancy was calculated (Table 1 and see Yamaguchi [13]). Intake of iodine from other foods was negligible.

TSH and FT4 were measured using electrochemiluminescence detection for development of immunoassay, using Modular Analytics (Roche Diagnostics, Mannheim, Germany). Sensitivity of the TSH assay was 0.002 μIU/mL; intra-assay and interassay variations were 0.33–0.62 and 1.09–1.52%, respectively. Normal values for TSH at 15 days, 30 days, 100 days, 1 year, and 2 years were 2.9 ± 0.9, 2.7 ± 0.9, 2.3 ± 0.8, 1.6 ± 0.6, and 1.3 ± 0.4 μIU/mL. Sensitivity of the FT4 assay was 0.13 pmol/L; intra-assay and interassay variations were 0.90–1.64 and 2.24–2.99%, respectively. Normal values for FT4 at 15 days, 30 days, 100 days, 1 year, and 2 years were 20.6 ± 2.6, 19.4 ± 2.4, 18.7 ± 2.3, 18.0 ± 2.3 and 16.7 ± 2.1 pmol/L. Over 27 μIU/mL (normal controls ± 2SD) of TSH values was identified as an excess reaction to the thyrotropin-releasing hormone (TRH) test. Peak TSH in normal controls ages 2–8 years was 18.0 ± 4.4 μIU/mL (n = 14). Thyroglobulin was measured using radioimmunoassay (Eiken Co., Tokyo, Japan). Sensitivity of the thyroglobulin assay was 5 ng/mL. TPOAb and TgAb were measured using radioimmunoassay (Cosmic Co., Tokyo, Japan). Concentrations of iodine in serum, urine, breast milk, and foods with a precision of 3%–4% was achieved.

Genetic analysis of thyroperoxidase and TSH receptors

Genomic DNA was isolated from peripheral white blood cells using GenTLE (Takara Bio, Otsu, Japan). Polymerase

<table>
<thead>
<tr>
<th>Group</th>
<th>Samples</th>
<th>Number of samples</th>
<th>Concentrations μg/dL</th>
<th>Minimum μg/dL</th>
<th>Maximum μg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Instant soups of dried bonito</td>
<td>10</td>
<td>16.8 ± 25.5</td>
<td>0.9</td>
<td>114</td>
</tr>
<tr>
<td>B</td>
<td>Instant soups of dried sardines</td>
<td>5</td>
<td>15.3 ± 26.5</td>
<td>1.5</td>
<td>62.4</td>
</tr>
<tr>
<td>C</td>
<td>Mixed soups with or without kombu</td>
<td>14</td>
<td>95.3 ± 105.3</td>
<td>1.4</td>
<td>356</td>
</tr>
<tr>
<td>D</td>
<td>Instant kombu soups</td>
<td>5</td>
<td>943.6 ± 998.9</td>
<td>218</td>
<td>2650</td>
</tr>
<tr>
<td>E</td>
<td>Instant udon soups (stock for noodles) with kombu</td>
<td>9</td>
<td>1317.4 ± 775.1</td>
<td>323</td>
<td>3100</td>
</tr>
<tr>
<td>F</td>
<td>Instant udon soups without kombu</td>
<td>7</td>
<td>5.8 ± 6.7</td>
<td>1.2</td>
<td>17.4</td>
</tr>
<tr>
<td>G</td>
<td>Self-cooked kombu soups</td>
<td>6</td>
<td>1200.3 ± 330.9</td>
<td>66</td>
<td>1510</td>
</tr>
<tr>
<td>H</td>
<td>Instant cup noodles</td>
<td>24</td>
<td>16.1 ± 31.2</td>
<td>0.8</td>
<td>133</td>
</tr>
</tbody>
</table>

Concentrations of iodine were represented as mean ± standard deviation (SD).
chain reaction (PCR) primer site for the thyroperoxidase (TPO) and TSH receptor gene and the condition for sequencing have been previously described (15–18).

**Statistics**

Data are given as the mean ± standard deviation (SD). A nonparametric analysis was used as statistics.

**Results**

**Concentration of iodine in foods**

As previously determined, foods with kombu in group E and G contain excess amounts of iodine (Table 1). While bonito and sardine soups contain low levels of iodine (0.9–6.5 μg/dL and 1.5–8.2 μg/dL, respectively), a few samples contained a trace of kombu. The presence of kombu was not labeled on the foods in group C. The variation as shown in standard deviations in Table 1 is so high that it is difficult to conclude which groups contain the highest or lowest iodine.

**Laboratory findings at birth and amounts of iodine intake**

Concentrations of serum and urinary iodine under various diagnosis are given in Table 2. Of the 34 infants who were positive at congenital hypothyroidism screening, 6 were thought to be cases of congenital hypothyroidism, (2 normal site thyroid, 3 abnormal site thyroid, and 1 left lobe defect), 1 was diagnosed with transient hypothyroidism caused by thyroid dysfunction and concentration of iodine in breast milk at diagnosis in group A and B are given in Table 3. Concentrations of TSH and thyroglobulin in infants of group A and B were higher than those in controls (p < 0.01), although concentrations of FT4 did not differ among the three groups. Concentrations of TSH and thyroglobulin in group A were higher than those in group B (p < 0.01, p < 0.05). Concentrations of iodine in breast milk in group A were higher than those in group B and controls (p < 0.01).

Based on the concentrations of iodine in foods consumed daily, we calculated the amount of iodine consumed by 5 women in group A and 10 women in group B during pregnancy. The concentrations of iodine in kombu, hijiki, wakame, fish, and other items were recorded according to Japanese Dietary Reference Intake (13). The amount of iodine ingested by 5 mothers in group A and 10 mothers in group B were calculated to be 2280–3180 μg and 820–1400 μg per day during pregnancy (Table 3).

Iodine-containing drugs or disinfection-related medicines were not used. Concentrations of iodine in serum, urine, and breast milk in 5 infants 15 days old whose mothers ingested excessive iodine during pregnancy were 24.1 ± 8.2, 31.2 ± 10.2, and 29.8 ± 8.1 μg/dL, respectively. Concentrations of iodine in these infants did not differ from those in group A. These infants were negative at screening for congenital hypothyroidism, and concentrations of TSH and FT4 were 3.1 ± 0.8 mIU/mL and 19.4 ± 3.1 pmol/mL at 15 days old.

**Clinical and laboratory findings after birth**

After the diagnosis of hyperthyrotropinemia, with or without hypothyroxinemia, resulting from excess iodine intake

---

**Table 2. Diagnosis, Concentration of Iodine, and Number of Patients Treated with Levothyroxine**

<table>
<thead>
<tr>
<th>Diagnosis (sub)</th>
<th>Numbers of cases</th>
<th>Iodine in serum μg/dL</th>
<th>Iodine in urine μg/dL</th>
<th>Patients receiving LT4 during 1–2 yr</th>
<th>LT4 μg/d during 1–2 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital hypothyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(normal site thyroid 2)</td>
<td>6</td>
<td>11.2 ± 3.4</td>
<td>18.1 ± 4.5</td>
<td>6/6</td>
<td>6.4 ± 1.6</td>
</tr>
<tr>
<td>(abnormal site thyroid 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(left lobe defect 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient hypothyroidism (TBII)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyrotropinemia caused by iodine excess (group A; serum iodine above 17 μg/dL)</td>
<td>15</td>
<td>16 ± 8.4a</td>
<td>33.1 ± 16.5b</td>
<td>12/15</td>
<td>2.4 ± 0.2</td>
</tr>
<tr>
<td>(group B; serum iodine below 17 μg/dL)</td>
<td></td>
<td>(25.8 ± 7.6b)</td>
<td>(30.0 ± 7.5b)</td>
<td>4/5</td>
<td>3.1 ± 0.2</td>
</tr>
<tr>
<td>Hyperthyrotropinemia of unknown etiology</td>
<td>9</td>
<td>9.6 ± 1.8</td>
<td>11.5 ± 3.9</td>
<td>2/9</td>
<td>1.6 ± 0.3</td>
</tr>
<tr>
<td>False-positive</td>
<td>3</td>
<td>9.5 ± 1.1</td>
<td>12.9 ± 2.4</td>
<td>0/3</td>
<td></td>
</tr>
<tr>
<td>Normal controls</td>
<td>22</td>
<td>10.8 ± 2.8</td>
<td>12.2 ± 3.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis of congenital hypothyroidism was based on findings of the thyroid gland using ultrasonography and the dose of LT4 given during a 1–2 year period. Concentrations of TSH in false-positive subjects were under 4.8 mIU/mL in the confirmation test and during the study. *p < 0.05; **p < 0.01 compared to controls.

TBI, thyrotropin-binding inhibitor immunoglobulin; LT4, levothyroxine.
during pregnancy, we advised 5 mothers in group A to reduce their consumption of iodine and monitored concentrations of serum and urinary iodine in infants and iodine in breast milk. As shown in Figure 1, the concentrations of serum and urinary iodine in infants and iodine in breast milk in cases 1 and 2 decreased to normal levels together with a decrease in TSH. Case 1 received LT4 at the age of 1 year because of a continuation of slightly higher levels of TSH (10–12 μIU/mL).

Case 2 did not receive LT4 by age 2 years. Cases 1 and 2 were fed breast milk for approximately 100 days and did not eat baby foods flavored with kombu and kombu products.

As shown in Figure 2, the concentrations of serum and urinary iodine in infants in cases 3, 4, and 5 did not decrease to normal. Mothers of infants did not reduce consumption of instant kombu soups mostly because of the convenience. Cases 3 and 4 received LT4 because their FT4 levels were decreased (9.6 and 12.3 pmol/L) at the confirmation test and at age 150 days of life, respectively. Case 5 received LT4 at 450 days because of an elevated TSH (27.5 μIU/mL) were normal FT4 (15.9 pmol/L). Subjects were fed breast milk for 60 days in case 3 and for 300 days in cases 4 and 5. They ate baby foods flavored with kombu and kombu products. All were treated with 1.7 ± 0.3 μg/kg of body weight of LT4 during the first 2 years of life (Table 2). We detected no other cause of hypothyrotopeinemia among these 15 infants. TPOAb and TgAb were negative. No mutation was found in the TPO gene and TSH receptor gene analysis of 5 patients in group A (18). The physical and psychomotor development of the infants was normal throughout the follow-up period.

**Discussion**

In this survey we found that many Japanese foods contain high concentrations of iodine. The ordinary intake of iodine by the Japanese is 500–1500 μg per day (19,20). These data

---

**Table 3. Thyroid Function and Concentrations of Iodine in Breast Milk in Groups A and B**

<table>
<thead>
<tr>
<th>Group</th>
<th>Postnatal day of confirmation test</th>
<th>Serum TSH μIU/mL</th>
<th>Serum FT4 pmol/L</th>
<th>Serum thyroglobulin μg/L</th>
<th>Iodine in breast milk μg/dL</th>
<th>Intake of iodine during pregnancy μg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>(Mean)</td>
<td>14.2</td>
<td>38.7a,b</td>
<td>18.5</td>
<td>574.0a,c</td>
<td>32.5a,b</td>
</tr>
<tr>
<td>n = 5 (SD)</td>
<td></td>
<td>3.0</td>
<td>13.6</td>
<td>5.6</td>
<td>195.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Group B</td>
<td>(Mean)</td>
<td>20.4c</td>
<td>19.4a</td>
<td>18.8</td>
<td>297.0a</td>
<td>14.4</td>
</tr>
<tr>
<td>n = 10 (SD)</td>
<td></td>
<td>2.7</td>
<td>3.5</td>
<td>3.6</td>
<td>140.0</td>
<td>5.8</td>
</tr>
<tr>
<td>Controls</td>
<td>(Mean)</td>
<td>15.3</td>
<td>2.9</td>
<td>20.6</td>
<td>72</td>
<td>14.4</td>
</tr>
<tr>
<td>n = 22 (SD)</td>
<td></td>
<td>4.2</td>
<td>0.9</td>
<td>2.6</td>
<td>14</td>
<td>2.5</td>
</tr>
</tbody>
</table>

The mother of case 1 in group A reduced the consumption of 250 μg iodine daily from 24 weeks’ gestation.

*p < 0.01 compared to controls.

b*p < 0.01 compared to group B.

*p < 0.05 compared to control S.

d*p < 0.05 compared to group B.

---

**FIG. 1.** Clinical course and concentrations of iodine in subjects 1 and 2. Concentrations of iodine in serum and urine decreased to normal in 2 subjects.
led to the general concept that iodine intake by the Japanese is excessive compared to the recommended daily dietary allowance of 150 μg of iodine for adults as given by the U.S. National Research Council (21). Fifteen infants had hyperthyrotropinemia resulting from an excessive intake of iodine by their mothers during pregnancy, and this occurred in 1 in 2515 live births in this present study. Twelve of 15 patients with excess iodine ingestion received LT₄ because hypothyroxinemia or hyperthyrotropinemia was detected. Only 13 cases of borderline congenital hypothyroidism were found during a 10-year period in New York State (3). Their confirmatory basal TSH was under 20 μIU/mL. In Europe, transient congenital hypothyroidism and hyperthyrotropinemia have a prevalence of 1 in 8260 (22). Calaciura et al. (4) and Daliva et al. (3) suggested that newborns classified as false-positive or borderline at congenital hypothyroidism screening have a high risk of subclinical or persistent hypothyroidism in infancy and early childhood. In that study, 5 of these 48 subjects with subclinical hypothyroidism had a higher than the 20 μg/dL of iodine in urine at the confirmation test (4).

The high incidence of abnormal thyroid function in our study suggests that excess iodine intake during pregnancy might be the cause of persistent hypothyrotoipenia, in some cases. The mother of subjects 3–5 continued to consume 1000–2000 μg of iodine per day after giving birth. Moreover, these 3–5 subjects consumed iodine from baby food to which iodine had been added. Hence, infants who repeatedly ingest iodine derived from placenta, breast milk, and baby food are at a higher risk for hyperthyrotoipenia. Increased urinary iodine concentration as well as elevated serum iodine values found in infants confirmed the hypothesis that alterations in thyroid gland functions resulted from iodine excess. High concentrations of thyroglobulin in 15 infants suggested a mild blockade of thyroid hormone.

In adults, acute blockade of iodine uptake, thyroid hormone synthesis, and release occurs when the intrathyroid iodine concentration exceeds a critical level. However, this blockade is limited by an escape phenomenon after 48 hours (23). This effect is caused by a decreased activity of the sodium iodide symporter, and there is decreased iodine transport into the thyroid. Moreover, neonates are particularly sensitive to iodine excess. Transient hypothyroidism or goiter has been observed in newborn infants after the topical application of povidone-iodine or iodine-containing alcoholic solution (3). The membranes of infants are highly permeable, iodine trapping processes in the thyroid gland are active and the iodine renal clearance is low. The fetus can absorb iodine from the amniotic fluid through the skin or gastrointestinal tract and iodine can be from the mother via the placenta (24). Theodoropoulos et al. (25) confirmed that thyroid hormone synthesis in the newborn rat was reduced by virtue of the iodine concentration.

We speculated that 15 infants with hyperthyrotropinemia may have been susceptible to the inhibitory effect of iodine, because 5 other pregnant women, who consumed even 1500–2500 μg of iodine per day were delivered of normal infants associated with high concentrations of iodine in serum, urine, and breast milk. FT₄ levels in group A and B were normal, even if the hyperthyrotropinemia remained after withdrawal of LT₄. Therefore, the persistent hyperthyrotropinemia noted in this study was suggestive of an intrauterine iodine imprinting effect. Thus, it is likely that thyroid homeostasis renders the thyroid of infants with an excess of iodine obtained during the fetal stage susceptible to the inhibitory effects of iodine. In the follow-up of patient with thalassemia major and iron overload for 5 years, 64% of those who developed transient hypothyroidism during iodine administration developed permanent clinical hypothyroidism (26). We also speculated that excess iodine ingestion during early pregnancy disturbs thyroid function, because case 1 subject have been treated with LT₄ despite reduction in the consumption of iodine of 250 μg per day by the mother of case 1 from 24 weeks’ gestation. Maturation of the hypothalamic-pituitary-thyroid axis is a complex process starting from midgestation and ending in adult life (27).
On the other hand, there were 9 cases of hyperthyrotropinemia of unknown cause in our study and many cases of persistent hyperthyrotoptropinemia in infants in the United States without iodine excess (28) and in Japan presumably without iodine excess (14) have been reported, and many of these cases have been persistent. The excess iodine intake in our subjects could well be circumstantial. These children should be more carefully studied to define the thyroid function defect after 3 years when T₄ withdrawal does not threaten central nervous system (CNS) function. A sodium iodide symporter defect might also be considered in the normal serum iodide in 10 cases in group B.

In the United States the iodine intake has gradually increased over 30 years with the subsequent widespread use of iodized salt for decreasing the incidence of goiter (29). The average daily intake in various sections of the United States varies from about 240 to 740 μg daily (29), however, excess iodine intake to the extent that other problems, namely iodine-induced hypothyroidism, autoimmune thyroiditis, and hyperthyrotoptropinemia, became more of a problem than deficiency disorders (30). Because iodine intake has decreased in the United States. National Health and Nutrition Examination Survey found that the median urinary iodine concentration decreased from 32 μg/dL to 14.5 μg/dL over 20 years (31). It is also possible that instant kombu soups may cause hyperthyrotropinemia or transient hypothyroidism in other countries. However, it is difficult to assess the amount of iodine, because these products do not retain odor or color associated with kombu or other seaweed products.

We have emphasized the importance of obtaining an accurate clinical history of iodine exposure. We have often found that mothers are not fully aware of how many iodine products are consumed during pregnancy and after giving birth. To avoid excess consumption of iodine during pregnancy, pregnant women should be checked for their iodine consumption at their first visit to the hospital. Food was not labeled with concentrations of iodine, which was one reason the mothers could not reduce intake of iodine after delivery. For such purpose it is necessary that foods be labeled with their precise amounts of iodine.

References


Address reprint requests to:
Soroku Nishiyama, M.D.
Department of Pediatrics
Kumamoto University
School of Medicine
Honjo 1-1-1
Kumamoto 860-8556
Japan

E-mail: soroku@Kaiju.medic.kumamoto-u.ac.jp