Investigation of iodine deficient state and iodine supplementation in patients with severe motor and intellectual disabilities on long-term total enteral nutrition

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Abstract. Iodine concentrations of enteral nutrition (EN) formulae available in Japan are very low and long-term total EN (TEN) might result in hypothyroidism due to iodine deficiency (HID). Our aim of this study was to determine the degree of iodine deficiency (ID) and need for iodine supplementation (IS) in patients with severe motor and intellectual disabilities (SMID) on long-term TEN. Thyroid function including urinary iodine concentration (UIC) was monitored, and powdered kelp was provided as a source of iodine supplement. Thirty-five SMID on TEN participated in our study. UIC less than 100 μg/L, representing ID, were detected in 97% of them. Their TSH ranged from 0.5 to 90 μIU/mL. IS using powdered kelp raised their UIC to the normal range. Thyroid function also recovered in the five hypothyroidism cases, which were diagnosed as HID, was also detected. In Japan, there must be many cases with ID associated with long term TEN. We also discuss the regulation of thyroid function in the iodine deficient state.

Key words: Hypothyroidism due to iodine deficiency, Total enteral nutrition, Urinary iodine concentration, Powdered kelp

IODINE is an essential trace element for synthesis of thyroid hormones and thyroxine (T4) is also essential for brain development. Iodine deficiency (ID) might cause hypothyroidism resulting in severe developmental delay in infants and stillbirth in pregnant women [1, 2]. Patients on long-term total enteral nutrition (TEN) are at risk of ID because of the low iodine content of EN formulae (Table 1) [3-5]. We measured urinary iodine concentration (UIC) in patients with severe motor and intellectual disabilities (SMID) receiving long-term TEN. We also provided iodine supplementation (IS) for ID cases in the form of powdered kelp and monitored their thyroid function, UIC, biochemical parameters and vital signs.

Subjects

We enrolled 35 SMID (Male 24, Female 11, 2-82 years, average 21.4 ± 18.4 years) patients living in an Otaru city nursing home from June 2009 to May 2010 in this study. All of the patients had been receiving TEN at this nursing home for over one year because of their swallowing disorder. Labels of EN formulae used were: Ensure® (Abbott) in 10, Racol® (Ostuka) in 8, E-3® (Clinico) in 11, and other preparations in 6 cases. Their average daily iodine intake was calculated to be 19.8 ± 15.1 μg. Excepting two cases, all patients were on medication for epilepsy including carbamazepine and phenytoin which could suppress thyroid function [6]. There was no specific choice of antiepileptics. Two were formally diagnosed as being hypothyroid.

Methods

Chart of the investigation

We divided our investigation into three stages (Fig. 1);

Stage 1 (Investigation of baseline UIC and thyroid function)

We measured UIC, thyroid function (TSH, free triiodothyronine (FT3), freeT4 (FT4)), and anti-thyroid-antibodies (Anti-thyroglobulin-antibody (ATA), anti-
The diagnosis of HID depended on the WHO criteria of ID (UIC < 100 μg/L), and hypothyroidism (TSH > 4.0 μIU/mL or FT4 < 0.8 ng/dL) without elevation of ATA and APA (Table 2) [1, 2]. Low UIC and hypothyroidism which remitted after IS were also considered as HID.

**Method of IS**

When participants had a UIC < 100 μg/L, we provided them with 1-2 g/day (200-400 μg/day iodine) of powdered kelp dissolved in EN formula or in a small amount of water and fed through their nutritional tubes. During IS, we did not alter their daily calorie intake, labels of their nutrition, or their medications for epilepsy.

**Definition of HID**

The diagnosis of HID depended on the WHO criteria of ID (UIC < 100 μg/L), and hypothyroidism (TSH > 4.0 μIU/mL or FT4 < 0.8 ng/dL) without elevation of ATA and APA (Table 2) [1, 2]. Low UIC and hypothyroidism which remitted after IS were also considered as HID.
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**Results**

**Stage 1**

Thirty-four (97.1 %) of the thirty-five subjects on long-term TEN had a UIC less than 100 μg/L. UIC in twenty-two (62.8%) was below the lower limit level (< 25 μg/L) (Fig. 2). Six (17.1%) were hypothyroid (Table 3) and two of them had clinical manifestations of hypothyroidism such as prolonged sleeping time (about

### Table 2

Epidemiological criteria for assessing iodine nutrition based on median urinary concentration of school-age children (≥ 6 years) [1]

<table>
<thead>
<tr>
<th>Median urinary iodine concentration (μg/L)</th>
<th>Iodine intake</th>
<th>Iodine status</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>Insufficient</td>
<td>Severe deficiency</td>
</tr>
<tr>
<td>20 ~ 49</td>
<td>Insufficient</td>
<td>Moderate deficiency</td>
</tr>
<tr>
<td>50 ~ 99</td>
<td>Insufficient</td>
<td>Mild deficiency</td>
</tr>
<tr>
<td>100 ~ 199</td>
<td>Adequate</td>
<td>Adequate iodine nutrition</td>
</tr>
<tr>
<td>200 ~ 299</td>
<td>Above requirements</td>
<td>Likely to provide adequate intake for pregnant /lactating women, but may pose a slight risk of more than adequate intake in the overall population</td>
</tr>
<tr>
<td>&gt; 300</td>
<td>Excessive</td>
<td>Risk of adverse health consequence (iodine-induced hyperthyroidism, autoimmune thyroid disease)</td>
</tr>
</tbody>
</table>

### Table 3

Six cases with hypothyroidism

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex (Age)</th>
<th>Original diagnosis</th>
<th>EN formulae</th>
<th>Duration of TEN (Years)</th>
<th>Iodine (µg/day)</th>
<th>UIC (µg/L)</th>
<th>TSH (µIU/mL)</th>
<th>FT3 (pg/mL)</th>
<th>FT4 (ng/dL)</th>
<th>Diagnosis of HID</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M (4)</td>
<td>Epilepsy</td>
<td>Racol</td>
<td>4</td>
<td>12.8</td>
<td>&lt;25</td>
<td>5.1</td>
<td>4.1</td>
<td>0.8</td>
<td>+ (subclinical)</td>
</tr>
<tr>
<td>2</td>
<td>M (6)</td>
<td>Campomelic dysplasia</td>
<td>Racol</td>
<td>3</td>
<td>6.4</td>
<td>&lt;25</td>
<td>4.3</td>
<td>3.8</td>
<td>1.0</td>
<td>+ (subclinical)</td>
</tr>
<tr>
<td>3</td>
<td>M (13)</td>
<td>Cerebral palsy, Epilepsy</td>
<td>Racol</td>
<td>7</td>
<td>18.4</td>
<td>&lt;25</td>
<td>7.7</td>
<td>3.7</td>
<td>0.9</td>
<td>+ (subclinical)</td>
</tr>
<tr>
<td>4</td>
<td>M (42)</td>
<td>Cerebral palsy, Epilepsy</td>
<td>Ensure H</td>
<td>4</td>
<td>12.0</td>
<td>&lt;25</td>
<td>90.0</td>
<td>1.8</td>
<td>0.4</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>F (9)</td>
<td>Toluene embryopathy</td>
<td>E-3</td>
<td>5</td>
<td>21.0</td>
<td>&lt;25</td>
<td>24.0</td>
<td>3.6</td>
<td>1.5</td>
<td>+</td>
</tr>
<tr>
<td>6*</td>
<td>M (38)</td>
<td>Hypoxic ischemic encephalopathy, Epilepsy</td>
<td>E-3, Glucerna</td>
<td>5 unknown</td>
<td>25.0</td>
<td>8.4</td>
<td>2.6</td>
<td>0.8</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Cases 1 to 3 were diagnosed as subclinical HID. Cases 4 and 5 were diagnosed as clinical HID. *Case 6 was not diagnosed as HID because his hypothyroidism remained during IS.

**Laboratory analysis**

Early morning spot urine samples were obtained, and rapidly frozen at -20 °C until they were analyzed. UIC was measured by the Sandell-Kolthoff reaction using 96-well micro plates (HITACHI) [7].

**Statistical analysis**

We compared thyroid function, biochemical data, average vital data of three days before and after iodine supplementation, using Students t-test for Stage 2 and 3 data. We also compared UIC using McNemar’s analysis in Stage 2. Significance was set at $p < 0.05$ in both analyses.

**Informed consent**

Before the investigation, informed consent for all biochemical testing including thyroid function and UIC measurement was obtained from family members or guardians of all patients according to Helsinki declaration. We provided the results if requested by the family.

**Fig. 2** The UIC level of all subjects

More than 90% showed ID and over 60% of them had ID, out of the lower limit level.

![Fig. 2](image-url)
twelve hours) in case 4, and morning hypothermia (34.7°C) in case 5. ATA and APA were negative in all thirty-five subjects. None of the patients had a goiter.

Stage 2

Twenty-eight subjects reached Stage 2. There was no significant difference in the means of most parameters before and after short-term IS (Table 4). However, UIC after IS rose significantly (*p* < 0.001) (Fig. 3). Improvement of TSH level was confirmed in five (14.7%) of six hypothyroidism cases (Fig. 4). They were finally diagnosed as HID. One patient showed no change in his TSH and hypothyroidism persisted (case 6). His hypothyroidism was considered to result from medication for epilepsy or pituitary TSH secreting disorder.

### Table 4 Thyroid function, biochemical items, and vital signs before and after one-month IS (*N* = 28) at Stage 2

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (µIU/mL)</td>
<td>6.46 ± 16.66</td>
<td>2.84 ± 1.83</td>
<td>0.25</td>
</tr>
<tr>
<td>FT4 (ng/dL)</td>
<td>1.06 ± 0.29</td>
<td>1.04 ± 0.28</td>
<td>0.59</td>
</tr>
<tr>
<td>FT3 (pg/mL)</td>
<td>3.39 ± 0.73</td>
<td>3.17 ± 0.81</td>
<td>0.05</td>
</tr>
<tr>
<td>Tcho (mg/dL)</td>
<td>150.89 ± 30.49</td>
<td>154.36 ± 31.47</td>
<td>0.15</td>
</tr>
<tr>
<td>CPK (IU/L)</td>
<td>75.39 ± 47.13</td>
<td>96.57 ± 72.71</td>
<td>0.05</td>
</tr>
<tr>
<td><em>Body temperature (°C)</em></td>
<td>36.21 ± 0.35</td>
<td>36.18 ± 0.26</td>
<td>0.67</td>
</tr>
<tr>
<td><em>Pulse (/minute)</em></td>
<td>85.41 ± 13.13</td>
<td>85.00 ± 13.83</td>
<td>0.84</td>
</tr>
</tbody>
</table>

*Average for three days

![Fig. 3](image-url) Recovery of UIC after one-month IS
This figure represents McNemar’s analysis of UIC at Stage 2. The limit is set at 50 µg/L, that is a lower-criterion as Moderate ID [1]. One dot represents one participant. UIC less than 50 µg/L, elevated more than the limit after one-month IS, black dots (●); elevated UIC but in the range of 25-50 µg/L, meshed dots (○); UIC was more than 50 µg/L before IS and elevated more after IS, white dots (□). The results of McNemar’s analysis gave a *p* < 0.001.

![Fig. 4](image-url) Course of UIC, TSH and FT4 in five HID (cases 1 to 5) during 1M and 5M IS
Their thyroid function recovered as UIC rose.
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urging some company to add iodine to its formulae.

On the other hand, five subjects (14.7%) among them were diagnosed as having HID. The incidence of HID is surprisingly low in view of the extremely low iodine intake but may actually be in line with other data from population studies [9-14] or may reflect difficulty in recognizing hypothyroid state in these patients or may be due to thyroid adaptive processes [15-18]. Possibly SMID patients, the targets of this study, might be at risk of developing disorders with a poor response of TSH that renders their hypothyroidism difficult to diagnose. In fact the majority of them have hypothalamus-pituitary disorders resulting from hypoxic episodes in their early childhood. Furthermore, in 5 subjects with HID except case 4, the TSH response may be insufficient to correspond to their lower FT4.

A thyroid adaptation mechanism exists in some subjects with iodine deficiency. Some experimental reports document that early thyroid adaptation develops after short-term (about one month) iodine deficiency, e.g. angiogenesis in the thyroid gland to increase iodine absorption without TSH stimulation, or tissue-selective acceleration of deiodinase activity resulting in T4 to T3 conversion [15-18]. Therefore, modest increase TSH, high normal or increased T3, and low normal or decreased T4 might be detected in iodine deficient state [19]. In the present study, there was a significant decrease of FT3 after five-month IS. This could represent elevation of FT3 before IS, suggesting the existence of an adaptive mechanism such as deiodinase activation. However, the correlation of T3 and ID varied in different reports [13, 14, 20]. It remains to be elucidated whether same thyroid adaptation occurs

**Stage 3**

In this group, consisting of twenty-two subjects, a significant reduction of FT3 were detected ($p < 0.05$), however, changes of TSH and FT4 were not significant (Fig. 5). TSH in five HID cases improved after one month IS and remained at normal throughout five-month IS (Fig. 4). Clinical manifestations in cases 4 and 5 remitted.

**Discussion**

Worldwide, approximately 30% of the population, which is about 1,900 million people, has an inadequate iodine intake. The diagnosis of ID depended on UIC [1, 2]. This is the first survey of iodine status involving an “at risk” SMID population receiving long-term TEN who were living a nursing home in Japan. A few case reports on ID in subjects on long-term TEN have been published since the early 1990’s [4, 5], however, there has been no systematic investigation of iodine status in large SMID populations receiving long-term TEN. Iodine status in such patients depends entirely on the iodine content of the EN formulae. When they take 1,500 Cal of the EN solutions available in our country, their daily iodine intakes are far below the level of the Ministry of Health, Labor and Welfare recommendation, which is 35-140 μg for children and adolescents, and 95-270 μg for adults [5, 8].

In the present study, with one exception, all participants were iodine deficient. This highlights the fact that ID is a common major adverse effect of long-term TEN in our country. Recently, the Japanese Society for Pediatric Endocrinology issued a special statement urging some company to add iodine to its formulae.

On the other hand, five subjects (14.7%) among them were diagnosed as having HID. The incidence of HID is surprisingly low in view of the extremely low iodine intake but may actually be in line with other data from population studies [9-14] or may reflect difficulty in recognizing hypothyroid state in these patients or may be due to thyroid adaptive processes [15-18]. Possibly SMID patients, the targets of this study, might be at risk of developing disorders with a poor response of TSH that renders their hypothyroidism difficult to diagnose. In fact the majority of them have hypothalamus-pituitary disorders resulting from hypoxic episodes in their early childhood. Furthermore, in 5 subjects with HID except case 4, the TSH response may be insufficient to correspond to their lower FT4.

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even in the chronic and severe ID which develops in SMID on long-term TEN.

Several investigators concluded that significant remission of thyroid function was brought about after IS, especially in iodine status [11-14, 20]. In our study, however, statistically significant alteration of thyroid function in the iodine deficient state might act to maintain their thyroid hormone synthesis.

SMID in our investigation seldom had any specific clinical symptoms including goiter. Symptoms which improved after IS were found in only two cases. Hypothyroidism in SMID might have been difficult to detect and we should increase our awareness of possible HID in SMID.

**Conclusion**

We investigated the iodine status of SMID on long-term TEN. Most had ID. Simple powdered kelp supplementation was effective for SMID. Only five were diagnosed as HID. Adaptive mechanisms in thyroid function in the iodine deficient state might act to maintain their thyroid hormone synthesis.

**References**


