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Original Article

Treatment of Hypothyroidism due to Iodine Deficiency Using Daily Powdered Kelp in Patients Receiving Long-term Total Enteral Nutrition

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Abstract. We investigated thyroid function and urinary iodine concentration (UIC) in seven patients with severe motor intellectual disabilities. All seven received total enteral nutrition (TEN) for more than three years with a daily iodine intake of less than 20 µg. They were diagnosed as hypothyroidism due to iodine deficiency (HID) because of high TSH levels (7.6–82.3 µIU/ml), lower free T4 (FT4 0.4–1.5 ng/dl), negative anti-thyroid antibodies (anti-thyroglobulin antibody, anti-thyroidal peroxidase antibody) and extremely low UIC (<25–58 µg/l) levels. We gave them 1–2 g powdered kelp (200–400 µg as iodine) once a day, which restored their thyroid function and normalized their UICs. We proposed that daily powdered kelp would be effective and safe to treat HID in patient receiving long term TEN.

Key words: hypothyroidism due to iodine deficiency, enteral nutrition, urinary iodine concentration, severe motor intellectual disabilities

Introduction

Iodine is an essential trace element for synthesis of thyroid hormones and normal brain development requires thyroxine (T4). Iodine deficiency (ID) may cause hypothyroidism which results in severe developmental delay in infants and stillbirth in pregnant women (1). In iodine deficient areas, which are distributed in fifty-four countries of the world, iodine supplementation programs using iodized salt have been implemented (2–5).

Patients on long term enteral nutrition (EN) develop ID because of the low iodine content of EN formula. A few domestic reports describing ID in subjects on long term total EN (TEN) have been published since early 1990s (6, 7). In this report, we present seven patients who developed hypothyroidism due to iodine deficiency (HID) during long-term TEN. We also discuss the efficacy of treatment using powdered kelp.

Patients

Seven patients (five male, two female) were studied, including four outpatients living with their families who provided their daily care and three inpatients living in a nursing home (Table 1). They were all diagnosed as having severe

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Table 1 Seven cases

Case	Onset age/Sex	Diagnosis	EN formula	Duration of TEN (yr)	Iodine intake (μg /d)	Clinical manifestation
1	15/M	Sequela of encepalitis	Racol	5	19.2	constipation, goiter
2	17/M	Sequela of HIE*	Ensure	16	12.0	constipation, goiter
3	26/M	Spasistic quadriplegia	Ensure	7	9.6	–
4	13/M	Sequela of HIE	Racol	8	18.4	–
5	41/M	Sequela of HIE	Ensure H	4	12.0	extension of sleeping time
6	3/F	Sequela of HIE	Enterud	3	Very low	goiter
7	2/F	Toluene embryopathy	Elental-P/E-3	2/5	49.6/21.0	bradycardia, low body temperature

*HIE: hypoxic ischemic encephalopathy.

motor and intellectual disabilities (SMID) and all seven were on medication for epilepsy. There was no specific choice of antiepileptics. All seven had received TEN for more than three years because of their swallowing disorders with an average duration of TEN was 7.1 (3–16) yr. Hypothyroidism was diagnosed at 16.7 (2–41) yr of age. Labels of EN formula used were the following: Ensure® (Abbott) in 2, Ensure High® (Abbott) in 1, Racol® (Otsuka) in 2, Enterud® (Terumo) in 1, Elental® (Ajinomoto) was changed to E-3® (Clinico) in 1 case. Their daily iodine intake was calculated to be less than 20 μg per day. In three cases, goiter (III/IV: Shichijo's classification) was found and two of them also had constipation. In four cases without goiter, two had other clinical manifestations of hypothyroidism, specifically, bradycardia with low body temperature in one, and extension of sleeping time in the other. No significant symptoms were present in the remaining two cases.

Methods

TSH and freeT4 (FT4) were measured by CLIA. Anti-thyroglobulin (Tg) - antibody and anti-thyroid peroxidase (TPO) - antibody were measured by EIA. Urinary iodine concentration (UIC) was measured using the morning spot urine sample by the Sandell-Kolthoff reaction using 96-well micro plates (HITACHI) (8). When a patient had goiter, we investigated the thyroid gland to detect tumors or nodules by ultrasound scanning. Hypothyroidism in patients with TSH>4.0 μIU/ml or FT4<0.8 ng/dl without elevation of anti-Tg/TPO-antibody and low level of UIC (less than 100 μg/l), was attributed to ID. We provided 1–2 g/d (200–400 μg/d iodine) of powdered kelp dissolved in EN formula or a small amount of water and fed through their nutritional tubes. After starting powdered kelp, TSH and FT4 were measured 1–2 mo later. UIC was also measured 3–11 mo later.

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

Results

The patient's thyroid function and UICs before and after treatment by powdered kelp are presented in Table 2. Before treatment, TSH was 7.6–82.3 (median 9.2) μIU/ml and FT4 was 0.4–1.5 (median 0.66) ng/dl. Anti-Tg/TPO-antibody was negative in all cases. In five cases (Case 1–5), UICs were measured before treatment and extremely low (less than 25 μg /l in 4, 58 μg/l in one case). Thyroid function {TSH: 0.7–4.7

Table 2 Thyroid function and UIC before/after iodine supplementation

Case	Before supplementation				After supplementation					Powdered kelp (g/d)
	TSH (μIU/ml)	FT4 (ng/dl)	UIC (μg/l)	Goiter	TSH (μIU/ml)	FT4 (ng/dl)	UIC (μg/l)	Goiter	Prognosis of clinical manifestation	
1	16.8	0.4	< 25	III	0.7	1.2	362	I	Remained constipation	2.0
2	4.6	0.8	< 25	IV~III	2.0	1.1	180	I	Remained constipation	1.0
3	9.2	0.5	58.0	I	2.1	1.2	224	I	–	1.0
4	7.7	0.9	< 25	I	3.8	0.8	261	I	–	1.6/1.0
5	82.3	0.5	< 25	I	4.7	1.0	367	I	All improved	2.0/1.6
6	7.6	0.7	N.D.	III	3.5	1.5	282	II~I	All improved	1.0
7	24.0	1.5	N.D.	I	1.6	0.9	648	I	All improved	2.0/1.6

N.D.; not done.

Table 3 Iodine concentration of EN formula (on the market in Japan)

Labels of EN	Ensure liquid® (Abbot)	Racol® (Otsuka)	Elental® (Ajinomoto)	Elental P® (Ajinomoto)	Clinimeal® (Eisai)	E-3® (Clinico)
Iodine (μg/dl)	1.6	1.6	5.0*	8.26*	4.4[7)]	3.0

*concentration of 1kcal/ml solution.

μIU/ml (median 3.52), FT4: 0.8–1.5 ng/dl (median 1.05)} and UIC {180–648 μg/l (median 282)} (N=7) were normalized after treatment. No thyroid tumors or nodules were detected by ultrasound carried out in 3 cases with goiters and the goiters almost completely remitted after treatment. In 2 cases, constipation persisted. Extension of sleeping time of case 5 and bradycardia with low body temperature of case 7, both improved. In the last two asymptomatic cases there was no change during treatment. There was no adjustment or change of antiepileptics, amount or labeling of EN solution during this study.

Discussion

Iodine is an essential micronutrient which is crucial for normal thyroid function. When iodine intake falls below the recommended level, the thyroid may not synthesize sufficient amounts of thyroid hormone. Worldwide, about 30% of the population, which is about 1,900 million people, has an inadequate iodine intake (1). The international council for control of IDD (ICCIDD) formed in 1985 and supported by WHO and UNICEF, has successfully addressed this global problem by establishing a program of regional iodized salt supplementation which involves the distribution of iodized salt to each family and restores people's iodine intake to adequate levels (1, 9, 10). ICCIDD recommended that iodized salt should contain 20–40 mg/kg (20–40 μg/g) of iodine in order to provide 150 μg/day of iodine, the recommended daily intake for an adult. Under these circumstances, median UIC of the population is expected to vary from 100–199 μg/l (1). At present, iodized salt is not available in Japan.

Some foods or plants contain high amounts of iodine, especially seaweeds, fish and other marine products. In Japan, being surrounded by the sea, IDD is rare because of people's frequent consumption of marine products. However, the iodine status of patients receiving long-term TEN depends entirely on the iodine concentration of the EN formula. In Table 3, we

Table 4 Epidemiological criteria for assessing iodine nutrition based on Median urinary concentration of school-age children (≥6 yr[1)])

Median urinary Iodine (μg/l)	Iodine intake	Iodine status
<20	Insufficient	Severe deficiency
20–49	Insufficient	Moderate deficiency
50–99	Insufficient	Mild deficiency
100–199	Adequate	Adequate iodine nutrition
200–299	Above requirements	Likely to provide adequate intake for Pregnant/ lactating women, but may pose a slight risk of more than adequate intake in the overall population
>300	Excessive	Risk of adverse health consequence (iodine-induced hyperthyroidism, autoimmune thyroid disease)

show the iodine concentrations of EN solutions available in Japan. When a patient takes 1,500 Cal of these formulae, the daily iodine intakes are far below the Ministry of Health, Labor and Welfare (MHLW) recommendation, that is 40–150 μg for children and adolescents (7, 12). Recently, The Japanese Society for Pediatric Endocrinology (JSPE) issued a special request for some company (e.g., Abbott, Otsuka) to add iodine to its EN formula.

In the present study, we investigated thyroid function and UICs of seven SMID cases and diagnosed them as HID. We treated them with iodine as powdered kelp (Konbucha in Japanese, which is dried, powdered *Laminaria japonica*) which is inexpensive and easily obtained. Five cases, which had severe low UICs, recovered both UIC and thyroid function after treatment. In the other two cases, thyroid function recovered.

As a cause of hypothyroidism in SMID cases, several other factors should be considered, such as hypothalamus-pituitary disorders, malnutrition, and anticonvulsants and combinations of these. Although in the present study these factors could not be excluded entirely, hypothyroidism in our cases was probably due to ID, because simple iodine treatment improved their thyroid function.

When we started powdered kelp at 1.6–2 g/d in 2 cases, their UICs were too high (1,380 μg/l in case 4, 560 μg/l in case 5, not presenting in Table 2). Therefore we decreased the dosage of powdered kelp between 1 to 1.6 g/d. About one gram powdered kelp per day, which contains about 200 μg iodine (11), (it is slightly above the MHLW recommendation for children and adolescents) was enough to restore ID in our cases. Indeed, powdered kelp contains about ten times the iodine content of iodized salt. Dissolving Konbucha is not so difficult and does not need to be heated (when heated, iodine is volatilized.). Of note was no clinical side effect was observed during treatment by powdered kelp, except high UIC in two patients as described above. We believe powdered kelp is one of the best treatments for SMID with ID in Japan.

We also believe that monitoring UIC is necessary to assess ID. UIC is good marker of very recent dietary iodine intake because more than 90% of ingested iodine is excreted in the urine (10, 13). WHO have defined the epidemiological criterion for iodine deficiency as a UIC of less than 100 μg/l (Table 4).

Two following clinical issues remain to be elucidated. First, four of our cases had no goiter. Second, two cases did not have any symptoms of hypothyroidism.

Conclusion

We report HID in seven SMID cases under long-term TEN. UIC was a good indicator of their iodine status. Powdered kelp was effective for recovery and safe treatment for HID.

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