

Iodide Transport Defect and Breast Milk Iodine

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What Is Known about This Topic?

- Iodide transport defect (ITD) is a dyshormonogenetic congenital hypothyroidism caused by sodium/iodide symporter (*NIS*) gene mutations. In the lactating mammary gland, iodide is concentrated by *NIS*.

What Does This Case Report Add?

- The iodine concentration in an ITD patient's breast milk is low. Possible iodine deficiency in the infant breast-fed by an ITD patient should be kept in mind.

Key Words

Iodide transport defect · Sodium/iodide symporter · *NIS* mutation · Breast milk iodine

Abstract

Background: Iodide transport defect (ITD) is a dyshormonogenetic congenital hypothyroidism caused by sodium/iodide symporter (*NIS*) gene mutations. In the lactating mammary gland, iodide is concentrated by *NIS*, and iodine for thyroid hormone synthesis is thereby supplied to the infant in the breast milk. **Case Description:** A 34-year-old Japanese woman was diagnosed with ITD caused by a homozygous *NIS* gene mutation T354P. She had begun treatment of primary hypothyroidism with levothyroxine at the age of 5. She

delivered a baby at the age of 36. The iodine concentration in her breast milk was 54 µg/l. She took a 50-mg potassium iodide tablet daily to supply iodine in the breast milk, starting on the 5th day postpartum. Her breast milk iodine concentration increased to 90 µg/l (slightly above the minimum requirement level). The patient weaned her baby and stopped taking the daily potassium iodide tablet 6 weeks postpartum, and the baby began to be fed with relatively iodine-rich formula milk. The baby's thyroid function remained normal from birth until 6 months of age. **Conclusion:** Possible iodine deficiency in the infant breast-fed by an ITD patient should be kept in mind. Prophylactic iodine supplementation is essential for such infants in order to prevent severe iodine deficiency.

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Introduction

Iodide transport defect (ITD) is a dysmorphogenetic congenital hypothyroidism caused by sodium/iodide symporter (*NIS*) gene mutations [1]. *NIS* mediates active iodide transportation, and plays an important role in concentrating iodide in the thyroid. *NIS* is also expressed in several other tissues, including the salivary glands, placenta, and lactating mammary gland [1]. In the lactating mammary gland, *NIS* concentrates iodide, and the infant is thereby supplied with iodine in the breast milk. We herein report on a pregnant ITD patient homozygous for an *NIS* mutation. She took potassium iodide tablets after delivery to supply iodine to her baby in the breast milk. This is the first report, to our knowledge, to focus on measurement of the breast milk iodine concentration (BMIC) in a patient with ITD.

Materials and Methods

Breast milk samples of 13 lactating Japanese women served as controls, with their consent. Three women had hypothyroidism treated with levothyroxine (LT_4) (2 due to post ^{131}I therapy of Graves' hyperthyroidism, and one due to postsurgical treatment of Graves' hyperthyroidism). One patient had euthyroid Hashimoto's thyroiditis and one had no thyroidal abnormalities. Eight patients with Graves' hyperthyroidism were treated with potassium iodide (5 at 50 mg per day, and 3 at 50 mg every other day).

BMIC was determined by Hitachi Chemical Clinical Laboratory (Tokyo, Japan). Breast milk was ultracentrifuged with a molecular weight cutoff of 50,000 Da. The iodine concentration in the clear fluid of the whey layer was measured employing a commercial iodine measurement kit (Hitachi Chemical Co., Ltd., Tokyo, Japan) [2]. This kit has adopted an ammonium persulfate digestion microplate method using the Sandell-Kolthoff reaction in a sealing cassette [3]. The coefficient of variation was less than 15%, the detection limit 25 $\mu\text{g/l}$, and the range of measurement 25–500 $\mu\text{g/l}$ [2]. The accuracy of the kit was 80–120% of the value determined by inductively coupled plasma mass spectrometry [2]. Samples showing values over the measurement range were remeasured after dilution to obtain quantitative results.

Case Report

Our patient was the sister of a previously reported Japanese man with ITD with the same homozygous *NIS* mutation [4]. Their parents were cousins, the mother being heterozygous for the *NIS* mutation. The patient was diagnosed with primary hypothyroidism at age 5. She was treated with LT_4 , but her medication adherence was poor. Soon after her brother's hypothyroidism was attributed to ITD due to the *NIS* mutation, she visited our clinic to undergo a detailed thyroid examination at age 34. She was 154 cm in height and 60 kg in weight. She had no apparent mental deficits. On ultrasonography, the thyroid was small and contained several small hypoechoic nodules. Serum free T_4 and thyrotropin (TSH) levels were 13.0 pmol/l (reference interval: 11.6–23.2) and 160.35 mIU/l (refer-

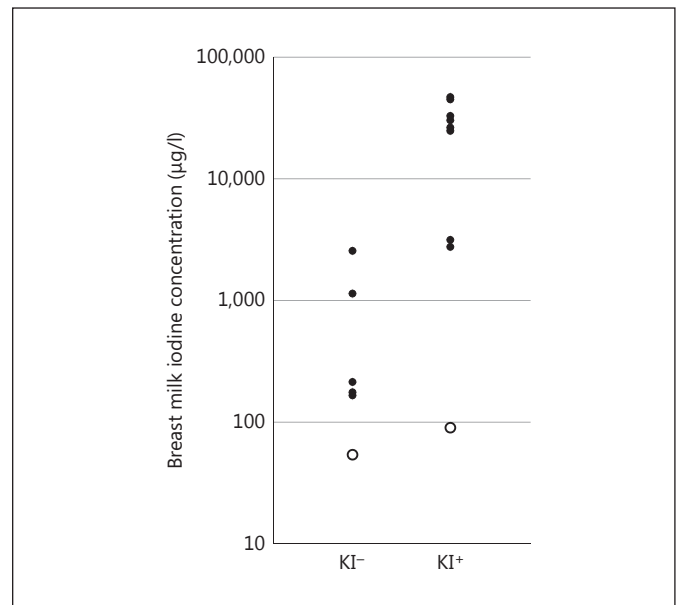


Fig. 1. BMICs of control subjects ($n = 13$) and the present patient. KI⁻: group without intake of potassium iodide ($n = 5$) and the present patient. KI⁺: group with Graves' disease treated with potassium iodide ($n = 8$) and the present patient during intake of potassium iodide. Circles: the present patient; dots: controls.

ence interval: 0.22–3.30), respectively, with prescription of LT_4 150 $\mu\text{g/day}$. Serum antithyroid peroxidase and antithyroglobulin antibodies were negative. The serum thyroglobulin level was 82.8 ng/ml. Neither the thyroid nor the salivary glands were visualized by $^{99m}\text{TcO}_4^-$ scintigraphy. We genetically tested for the *NIS* gene mutation with her consent. ITD due to homozygous *NIS* mutation T354P was diagnosed. She became pregnant at age 36 and gave birth to a baby girl weighing 2,270 g by caesarean section at 38 gestational weeks. Free T_4 and TSH levels were 18.0 pmol/l and 3.49 mIU/l in the umbilical cord serum, and the baby's serum levels were 24.5 pmol/l and 2.93 mIU/l on the 5th day after birth. The patient's BMIC was 54 $\mu\text{g/l}$. To manage the baby's iodine state, we administered potassium iodide to the patient to supply iodine in the breast milk. She began taking a tablet containing 50 mg of potassium iodide daily on the 5th day postpartum, and BMIC rose to 90 $\mu\text{g/l}$ 3 days thereafter. The patient ceased breast feeding and stopped taking the potassium iodide tablet 6 weeks after delivery, and the baby began to be fed with a relatively iodine-rich commercial formula. The baby's thyroid functions were confirmed to be normal at 2 and 6 months after birth. The patient's serum free T_3 , free T_4 , and TSH levels were 3.36 pmol/l (reference interval: 3.38–6.61), 13.0 pmol/l, and 2.660 mIU/l, respectively, with 175 $\mu\text{g/day}$ of oral LT_4 .

BMIC in the Present Patient and Control Subjects

Figure 1 shows the BMIC of our present patient and the control subjects ($n = 13$). The BMIC in the lactating Japanese women ($n = 5$) ranged from 166 to 2,560 $\mu\text{g/l}$ (median 214). The BMIC ranged from 3,150 to 47,000 $\mu\text{g/l}$ (median 28,350) in the patients with Graves' disease treated with 50-mg potassium iodide tablets every 1 or 2 days ($n = 8$).

Discussion

Our patient had the T354P *NIS* mutation, which is the most common mutation in Japan. Although this patient did not begin treatment with LT₄ during the neonatal period, she had no apparent neurodevelopmental deficits. The clinical features of ITD patients with *NIS* mutations are heterogeneous, and their broad spectrum of manifestations range from extremely small goiters to huge goiters, and from euthyroidism to overt hypothyroidism [5]. The Japanese people generally consume rather large amounts of iodine in traditional foods. Substantial iodine intake may have compensated for impaired active iodide transport due to the mutated *NIS* in our present patient. Moreover, there might be partial compensation for the functions of the mutated *NIS* due to iodide transport through nonspecific channels or carriers, or even via diffusion [6].

The baby is probably heterozygous for the *NIS* mutation. No patients were reported in her husband's pedigree. Since *NIS* is located at the apical membrane (maternal side) of placental syncytiotrophoblasts, the efficacy of iodide transport across the placenta is assumed to be decreased in ITD patients with *NIS* mutations. However, in this case, the baby's thyroid function was normal at birth. Substantial maternal iodine supplementation and the following placental characteristics may have compensated for impaired iodide transport due to the mutated *NIS*. Although its capacity is much lower than that of the thyroid, the placenta stores iodine to be supplied to the fetus [7]. Additionally, type 3 iodothyronine deiodinase, which is present in the placenta, plays a role in supplying iodine to the fetus [8]. While autoregulation of *NIS* in the lactating mammary gland seems minimal or absent [9], it is suggested that *NIS* in the placenta is autoregulated to keep iodide transport unaltered [10]. Finally, several iodide transporters are presumed to be involved in placental transport [10].

The reported median BMIC in lactating women ranges from 35 to 155 µg/l in the United States [11]. BMIC less

than 50 µg/l is considered to indicate iodine deficiency [12], and BMIC exceeding 80 µg/l is required for an infant before the commencement of weaning foods [13]. Since the lactating mammary gland with the inactivating *NIS* mutation is not able to effectively concentrate iodide in breast milk, the BMIC of ITD patients would presumably be low. In fact, our patient's BMIC was 54 µg/l, clearly lower than that of lactating Japanese women in general. Our patient's BMIC increased modestly to 90 µg/l after taking a daily 50-mg potassium iodide tablet, a level just above the minimum iodine requirement. Although *NIS* is not regulated by TSH in the breast [1], the BMIC in patients with Graves' hyperthyroidism may differ from that in euthyroid or hypothyroid patients. Nevertheless, the BMIC during potassium iodide intake was much lower in this patient than in control subjects with Graves' hyperthyroidism. Infants breast-fed by ITD patients are at risk for developing severe iodine deficiency, especially in iodine-deficient geographic areas. Prophylactic iodine supplementation is essential for such infants in order to prevent severe iodine deficiency. In spite of *NIS* mutation, the BMIC of ITD patients can be increased above the minimum requirement level by supplying high doses of iodine.

Commercial infant formulas generally contain much lower amounts of iodine than breast milk. The iodine contents of commercial formulas vary considerably among manufacturers as well as among branded product lots. Japanese commercial formulas are not iodized by law. The iodine content in these formulas also warrants attention as some infants are fed only such formulas.

In conclusion, clinicians need to be aware of possible iodine deficiency in the infant breast-fed by an ITD patient.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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