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Case Report

Two Japanese Infants With Hypothyroidism Following Exposure to Iodinated Contrast Media

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Abstract

We report 2 Japanese infants with hypothyroidism requiring levothyroxine (LT4) replacement therapy following exposure to iodinated contrast media (ICM). Patient 1 was born at 32 weeks gestation. He had congenital heart disease and underwent contrast-enhanced computed tomography (CT) on day 22 (estimated amount of iodine: 600 mg/kg/dose). The newborn mass screening showed normal thyrotropin (thyroid-stimulating hormone; TSH) levels at day 4, but high TSH and low free thyroxine levels on retest at day 44. LT4 replacement therapy was administered on days 46 to 74. No hypothyroidism requiring LT4 replacement therapy was observed afterward. The ultrasonography showed a hypoplastic thyroid gland. Patient 2 was born full-term. She had congenital heart disease and underwent contrast-enhanced CT on day 52 (estimated amount of iodine: 1500 mg/kg/dose). The newborn mass screening showed normal TSH levels on day 4, but high TSH levels on retest on day 62. LT4 replacement therapy was administered from day 65 to 3 years of age. Genetic analysis showed a heterozygous variant of *DUOX2*. Exposure to ICM can result in hypothyroidism, requiring LT4 replacement therapy. The severity of hypothyroidism may depend on risk factors, such as genetic predisposition, preterm birth, thyroid hypoplasia, or early exposure to ICM.

Key Words: hypothyroidism, iodinated contrast media

Abbreviations: CH, congenital hypothyroidism; CT, computed tomography; ICM, iodinated contrast media; LT4, levothyroxine; TSH, thyrotropin (thyroid-stimulating hormone).

Hypothyroidism is a congenital or acquired condition of thyroid hormone deficiency that can lead to profound mental retardation in newborns or infants unless treated. Hypothyroidism is caused by various factors, including iodine excess. It is well known that iodine excess inhibits organification of iodine, thereby diminishing thyroid hormone synthesis; this phenomenon is called the Wolff-Chaikoff effect [1]. Hypothyroidism due to iodine excess occurs in children, including newborns, but the dosage of iodine and risk factors related to hypothyroidism are not clear.

Iodinated contrast media (ICM) for medical imaging contains high-dose iodine and are used in contrast-enhanced CT or cardiac catheterization especially in patients with congenital heart disease. In March 2022, the Food and Drug Administration (FDA) recommended [2] that "thyroid function monitoring should be performed on children under 3 years old who receive injections of ICM within 3 weeks because of potential cognitive and developmental impairments associated with hypothyroidism. In particular, newborns, premature infants, infants requiring intensive care, and infants with underlying diseases such as heart disease are considered at higher risk and require special attention. Iodine-induced hypothyroidism in most children is transient and does not require replacement therapy." However, the natural course or predisposing factors of iodine-induced hypothyroidism in children receiving ICM have not yet been elucidated. We report here 2 Japanese infants with hypothyroidism requiring levothyroxine (LT4) replacement therapy following exposure to ICM.

Patient 1

Case Presentation

The patient was the first child of healthy and non-consanguineous parents who had achieved spontaneous conception. He had no family history of thyroid disorders. His mother had no maternal history of thyroid disease and no history of receiving contrast medium before conception. He was born by emergency cesarean section due to maternal hypertension at 32 weeks and 6 days of gestation. His birth length was 37.5 cm (−2.2 SD), and birth weight 1148 g (−2.9 SD). Apgar scores at 1 and 5 minutes were 4 and 6, respectively. The patient required intratracheal intubation and ventilatory support. In addition, right bronchial stenosis, a right cleft lip, and softening of the larynx were observed. Cardiac malformations, right ventricular origin of both large blood vessels, ventricular septal defect, right aortic arch, right pulmonary artery transection, and bilateral ductus arteriosus were also observed. He was fed a milk-based formula and did not take any medications related to thyroid function.

Diagnostic Assessment

The newborn mass screening on day 4 showed normal TSH levels. A contrast-enhanced CT was performed on day 22 to evaluate the vascular run (estimated amount of iodine exposure: 900 mg; approximately 600 mg/kg/dose). Iodine disinfectant

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Table 1. The results of subsequent serum thyroid function tests of patient 1 from day 46 to day 88

Day of life	46	50	53	60	67	74	81	88
Free triiodothyronine (pmol/L [pg/mL]) (normal range, 4.0–7.8 [2.6–5.1])	3.2 [2.1]	4.6 [3.0]	4.9 [3.2]	4.1 [2.7]	3.4 [2.2]	3.1 [2.0]	4.0 [2.6]	3.8 [2.5]
Free thyroxine (pmol/L [ng/dL]) (normal range, 12.9–23.2 [1.0–1.8])	5.1 [0.4]	23.2 [1.8]	29.6 [2.3]	15.4 [1.2]	16.7 [1.3]	18.0 [1.4]	12.9 [1.0]	12.9 [1.0]
TSH (mIU/L) (normal range, 0.27 - 4.20)	150.4	11.77	1.64	4.58	2.95	0.73	3.06	3.22
Urinary iodine excretion (μg/L)	1770	131			139			

Abbreviation: TSH, thyrotropin (thyroid-stimulating hormone).

Table 2. The results of subsequent serum thyroid function tests of patient 1 from day 129 to day 161

Day of life	129	131	134	137	141	147	154	161
Free triiodothyronine (pmol/L [pg/mL]) (normal range, 4.0–7.8 [2.6–5.1])	5.8 [3.8]	4.8 [3.1]	6.1 [4.0]	6.6 [4.3]	6.1 [4.0]	4.3 [2.8]	5.2 [3.4]	4.5 [2.9]
Free thyroxine (pmol/L [ng/dL]) (normal range, 12.9–23.2 [1.0–1.8])	15.4 [1.2]	14.2 [1.1]	15.4 [1.2]	15.4 [1.2]	15.4 [1.2]	11.6 [0.9]	14.2 [1.1]	12.9 [1.0]
TSH (mIU/L) (normal range, 0.27 - 4.20)	4.06	4.24	6.4	5.65	3.52	8.44	13.44	5.5
Urinary iodine excretion (μg/L)	700	133000	8900					

Abbreviation: TSH, thyrotropin (thyroid-stimulating hormone).

was also used to insert a central venous catheter on day 30 (estimated amount of iodine exposure: 50 mg at maximum). A retest of the newborn mass screening at day 44 showed high TSH level (63.3 mIU/L; normal range, 0.27-4.20) and low free thyroxine (fT4) level (3.35 pmol/L [0.26 ng/dL]; normal range, 12.9-23.2 [1.0-1.8]) (filter paper blood, serum equivalent). The results of subsequent serum thyroid function tests and urinary iodine excretion from day 46 are shown in Table 1. There was no reference range for urinary iodine excretion. Because urinary iodine excretion increased after exposure to contrast-enhanced CT, we diagnosed the patient with hypothyroidism due to iodine excess.

Thyroid ultrasonography and genetic analysis were performed to identify the cause of congenital hypothyroidism (CH). The thyroid ultrasonography on day 58 showed an orthotopic and hypoplastic thyroid gland with a maximum transverse diameter of 21 mm (−2.9 SD). No pathogenic variants were identified in 11 known responsible genes causing CH (*TSHR, PAX8, NKX2-1, FOXE1, TG, TPO, DUOX2, DUOXA2, SLC26A4, SLC5A5,* and *ITD*).

Treatment

LT4 replacement therapy (8.8 μg/kg/day) was initiated on day 46. The dose of LT4 was reduced to 4.0 μg/kg/day at day 50. LT4 replacement therapy was discontinued on day 74.

Outcome and Follow-up

The patient underwent another contrast-enhanced CT on day 129 (estimated amount of iodine exposure: 1500 mg; approximately 600 mg/kg/dose). We intensively monitored thyroid function before and after CT (Table 2). Serum TSH level increased 18 and 25 days after CT, but spontaneously normalized without LT4 replacement therapy. Furthermore, no severe hypothyroidism was observed afterward in case of medical imaging using ICM. His TSH levels hovered at approximately 5 mIU/L. His latest blood test, at age 8 years, was consistent with subclinical hypothyroidism (TSH 6.680 mIU/L; fT4 20.6 pmol/L [1.6 ng/dL]; and thyroglobulin 106.0 ng/mL) (normal range, TSH 0.27-4.20; fT4 12.9-23.2 [1.0-1.8]; and thyroglobulin 3.0-33.7). He had heart failure and underwent endocardial repair. He attended elementary school but required special support because of his developmental disability.

Patient 2

Case Presentation

The patient was the first child of healthy and nonconsanguineous parents who had achieved spontaneous conception. She had no family history of thyroid disorders. Her mother had no maternal history of thyroid disease and no history of receiving contrast medium before conception. She was born via cephalic vaginal delivery at 38 weeks and 0 days of gestation. Her birth length was 45.5 cm (−1.3 SD), and weight was 2056 g (−2.1 SD). Pulmonary atresia with intact ventricular septum was diagnosed after birth. She was fed a milk-based formula and did not take any medications related to thyroid function.

Diagnostic Assessment

The newborn mass screening on day 4 showed normal TSH levels. A contrast-enhanced CT on day 52 evaluated the vascular run (estimated amount of iodine exposed: 3500 mg; approximately 1500 mg/kg/dose). A retest of the newborn mass screening on day 62 reportedly showed increased serum TSH levels (data were unavailable). The results of subsequent serum thyroid function tests from day 65 are shown in Table 3. We diagnosed her with hypothyroidism due to iodine excess.

Table 3. The results of subsequent serum thyroid function tests of patient 2 from day 65 to day 104

Day of life	65	69	77	80	91	104
Free triiodothyronine (pmol/L [pg/mL]) (normal range, 4.0–7.8 [2.6–5.1])	2.3 [1.5]	7.1 [4.6]	2.8 [1.8]	2.8 [1.8]	5.4 [3.5]	5.1 [3.4]
Free thyroxine (pmol/L [ng/dL]) (normal range, 12.9–23.2 [1.0–1.8])	3.9 [0.3]	23.2 [1.8]	21.9 [1.7]	10.3 [0.8]	29.6 [2.3]	32.2 [2.5]
TSH (mIU/L) (normal range, 0.27–4.20)	358.6	156.3	1.13	30.75	5.76	0.79

Abbreviation: TSH, thyrotropin (thyroid-stimulating hormone).

Thyroid ultrasonography and genetic analysis (*DUOX2*, *TSHR*, and *PAX8*) were performed to identify the cause of CH. The thyroid ultrasonography on day 73 showed an orthotopic thyroid gland with a maximum transverse diameter of 27 mm (+0.9 SD). Genetic analysis showed a heterozygous variant of *DUOX2* (c.4232G>A, p.Cys1411Tyr), and this variant had already been reported [3]. The frequency of p.Cys1411Tyr in gnomAD was 1.77e-5. Cys1411 is conserved across species and determined to be pathogenic by in silico analysis (Polyphen2, 0.986; Mutation Taster, disease causing).

Treatment

Because of severe hypothyroidism with TSH of 358.6 μIU/mL (normal range, 0.27-4.20) and fT4 of 3.87 pmol/L [0.3 ng/dL] (normal range, 12.9-23.2 [1.0-1.8]), LT4 replacement therapy (10 μg/kg/day) was started at day 65. After 12 days of treatment, serum TSH level decreased to 1.13 mIU/L, and LT4 replacement was discontinued. One week later, the TSH increased to 30.75 mIU/L, and LT4 replacement resumed. Thereafter, she continued to receive LT4 until the age of 3 years.

Outcome and Follow-up

Since then, her thyroid function tests showed subclinical hypothyroidism, although LT4 replacement was not required. Her latest blood test at 17 years of age showed TSH 5.640 mIU/L, fT4 25.7 pmol/L (2.0 ng/dL), and thyroglobulin 46.6 ng/mL (normal range, TSH 0.27-4.20; fT4 12.9-23.2 [1.0-1.8]; and thyroglobulin 3.0-33.7). She studied in high school without any support.

Discussion

We here reported 2 cases of hypothyroidism following exposure to ICM during infancy. Both patients had no hypothyroidism on newborn mass screening on day 4 but developed hypothyroidism requiring LT4 replacement. Urinary iodine excretion increased after exposure to contrast-enhanced CT, indicating that both infants had developed iodine-induced hypothyroidism.

According to a recommendation issued by the FDA in 2022 [2], hypothyroidism is transient and does not require treatment in most cases. In contrast, our 2 cases had severe hypothyroidism and required LT4 replacement therapy. The amount of iodine in the ICM used in the 2 cases was not significantly different from that commonly used. Thus, our patients may have a predisposition to iodine-induced hypothyroidism. The monoallelic *DUOX2* variant was previously reported to be a risk factor for the development of CH rather than a monogenic cause of CH [4]. After exposure to excess iodine, hypothyroidism did not occur in 16 adults without thyroid disease [5], but it did occur in cases after partial thyroidectomy [6, 7]. This is consistent with the notion that thyroid hypoplasia can be another risk factor for iodine-induced hypothyroidism. In addition, 8.3% of term infants and 18.3% of premature infants develop hypothyroidism after exposure to ICM, suggesting that preterm infants have an increased risk of hypothyroidism compared with term infants [8]. Based on these data, possible predisposing factors for ICM-induced hypothyroidism in our 2 cases include monoallelic *DUOX2* variant, thyroid hypoplasia, or preterm birth.

Earlier exposure to excessive iodine could result in greater adverse effects on thyroid function. Consistent with this hypothesis, 29% of newborns [9] and 4.3% of adults [4] have been reported to show elevated TSH. In a report of 2320 pediatric patients aged < 4 years who underwent a diagnostic procedure with ICM in the United States, the rate of hypothyroidism, including subclinical hypothyroidism, was highest in children aged < 3 months and decreased with increasing age [10]. Patient 1 received multiple ICM administrations. He developed overt hypothyroidism during early infancy. However, as he grew older, he no longer exhibited hypothyroidism with multiple ICM administrations. Thus, the adverse effect of iodine excess on thyroid function could have a critical period, especially in the neonatal period or early infancy.

Learning Points

- Exposure to excessive iodine by ICM can cause severe hypothyroidism requiring LT4 replacement therapy.
- The severity of hypothyroidism may depend on predisposing factors, such as genetic predisposition, thyroid hypoplasia, or preterm birth.
- Earlier exposure to excessive iodine could result in greater adverse effects on thyroid function.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

References

1. Wolff J, Chaikoff IL. Plasma inorganic iodide as a homeostatic regulator of thyroid function. *J Biol Chem*. 1948;174(2):555-564.
2. U.S. Food and Drug Administration. FDA recommends thyroid monitoring in babies and young children who receive injections of iodine-containing contrast media for medical imaging. March 30, 2022. Accessed January 10, 2023. https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-thyroid-monitoring-babies-and-young-children-who-receive-injections-iodine-containing
3. Kim Y-M, Jin HY, Lee BH, Heo S-H, Kim G-H, Yoo H-W. Clinical and molecular characteristics of congenital hypothyroidism with DUOX2 mutations. *Int J Pediatr Endocrinol*. 2013;2013(Suppl 1):O54.
4. Rhee CM, Bhan I, Alexander EK, Brunelli SM. Association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism. *Arch Intern Med*. 2012;172(2):153-159.
5. Gartner W, Weissel M. Do iodine-containing contrast media induce clinically relevant changes in thyroid function parameters of euthyroid patients within the first week? *Thyroid*. 2004;14(7):521-524.
6. Markou K, Georgopoulos N, Kyriazopoulou V, Vagenakis AG. Iodine-Induced hypothyroidism. *Thyroid*. 2001;11(5):501-510.
7. Braverman LE, Ingbar SH, Vagenakis AG, Adams L, Maloof F. Enhanced susceptibility to iodide myxedema in patients with Hashimoto's disease. *J Clin Endocrinol Metab*. 1971;32(4):515-521.
8. Ahmet A, Lawson ML, Babyn P, Tricco AC. Hypothyroidism in neonates post-iodinated contrast media: a systematic review. *Acta Paediatr*. 2009;98(10):1568-1574.
9. Linder N, Sela B, German B, *et al*. Iodine and hypothyroidism in neonates with congenital heart disease. *Arch Dis Child Fetal Neonatal Ed*. 1997;77(3):F239-F240.
10. Jick SS, Hedderson M, Xu F, Cheng Y, Palkowitsch P, Michel A. Iodinated contrast agents and risk of hypothyroidism in young children in the United States. *Invest Radiol*. 2019;54(5):296-301.