

# UCSF

## UC San Francisco Previously Published Works

### Title

Iodine Deficiency Hypothyroidism Among Children in the United States - 21st Century Resurgence?

### Permalink

<https://escholarship.org/uc/item/5sb219f3>

### Journal

AACE Clinical Case Reports, 10(6)

### Authors

Seetharaman, Sujatha

Sasidharan Pillai, Sabitha

Ganta, Avani

et al.

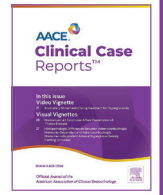
### Publication Date

2024

### DOI

10.1016/j.aace.2024.08.003

Peer reviewed



Case Report

## Iodine Deficiency Hypothyroidism Among Children in the United States - 21st Century Resurgence?



Sujatha Seetharaman, MD, MPH <sup>1</sup>, Sabitha Sasidharan Pillai, MD <sup>2,3</sup>, Avani Ganta, MD <sup>4</sup>, Kate Millington, MD <sup>5,6</sup>, Jose Bernardo Quintos, MD <sup>5,6</sup>, Lisa Swartz Topor, MD, MMSc <sup>5,6</sup>, Monica Serrano-Gonzalez, MD <sup>5,6,\*</sup>

<sup>1</sup> Division of Pediatric Endocrinology and Diabetes, University of California San Francisco, San Francisco, California

<sup>2</sup> Center for Endocrinology, Diabetes and Metabolism, Children's Hospital Los Angeles, Los Angeles, California

<sup>3</sup> Keck School of Medicine, University of Southern California, Los Angeles, California

<sup>4</sup> Division of Pediatric Endocrinology, Southern Illinois University School of Medicine, Springfield, Illinois

<sup>5</sup> Warren Alpert Medical School of Brown University, Providence, Rhode Island

<sup>6</sup> Division of Pediatric Endocrinology, Hasbro Children's Hospital, Providence, Rhode Island

### ARTICLE INFO

**Article history:**

Received 10 April 2024

Received in revised form

6 August 2024

Accepted 12 August 2024

Available online 14 August 2024

**Key words:**

iodine deficiency

hypothyroidism

thyroid hormone resistance alpha

goiter in children

### ABSTRACT

**Background/Objective:** Iodine deficiency hypothyroidism is an important cause of neurocognitive and motor impairment in children globally. In the United States, universal salt iodization, which began in the 1920s, led to a dramatic decline in iodine deficiency hypothyroidism. However, iodine deficiency may be reemerging due to increased consumption of noniodized salts, decreased dairy iodine concentrations, and decreased intake of iodine containing foods due to food allergies, dietary preferences such as vegan diets, or restrictive food intake disorders.

**Case Report:** We present a case series that challenges the existing clinical paradigm for hypothyroidism and describe 3 patients without underlying thyroid dysfunction who were diagnosed with iodine deficiency hypothyroidism over an 18-month period beginning in February 2021 in Northeastern United States. Prior studies reported 2 additional cases diagnosed in that same time frame at our clinical center.

**Discussion:** We report significant heterogeneity in clinical presentation: 3 patients had large goiters, 1 had a mild goiter, and 1 patient had no goiter. Biochemical tests were also variable and included a wide range of thyroid stimulating hormone elevations.

**Conclusion:** We suggest that a spot urine iodine concentration, combined with an elevated serum thyroglobulin level, can be an alternative to a 24-hour urinary iodine excretion for the diagnosis of iodine deficiency hypothyroidism given the clinical challenges of obtaining the latter. Thyroid function normalized in all patients with iodine supplementation.

© 2024 AACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

### Introduction

Iodine is a trace element that is essential for synthesis of the thyroid hormones triiodothyronine (T<sub>3</sub>) and thyroxine (T<sub>4</sub>).<sup>1</sup>

**Abbreviations:** 24-hour UIE, 24-hour urine iodine excretion; Free T4, free thyroxine; spot UIC, spot urine iodine concentration; T3, triiodothyronine; T4, thyroxine; TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone; WHO, World Health Organization.

Informed consent: Parental/patient consent was obtained.

\* Address correspondence to Monica Serrano-Gonzalez, Division of Pediatric Endocrinology & Diabetes, Hasbro Children's Hospital, Warren Alpert Medical School of Brown University, 593 Eddy St, Providence, RI 02903.

E-mail address: [monica\\_serrano@brown.edu](mailto:monica_serrano@brown.edu) (M. Serrano-Gonzalez).

<https://doi.org/10.1016/j.aace.2024.08.003>

2376-0605/© 2024 AACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Thyroid hormone is critical for normal brain development in utero and during the first years of life.<sup>2</sup> Iodine deficiency hypothyroidism is estimated to affect 2.2 billion people worldwide and is an important cause of neurocognitive and motor impairment in children globally.<sup>3</sup> Universal salt iodization was implemented in the United States beginning in the 1920s leading to a dramatic decline in iodine deficiency hypothyroidism.<sup>4</sup> Despite these continued efforts, iodine deficiency has been recently re-recognized as a cause of primary hypothyroidism in youth.<sup>5-7</sup> Potential causes include increased consumption of noniodized salts, decreased dairy iodine concentrations, especially in organic dairy products, decreased intake of iodine containing foods due to food allergies, dietary preferences such as vegan diets, or restrictive food intake disorders.<sup>7</sup>

## Case Report

We present 3 patients between 2 and 10 years of age who were diagnosed with iodine deficiency at a single institution in the Northeastern United States between February 2021 and August 2022. Prior studies reported 2 additional cases of iodine deficiency hypothyroidism diagnosed in that same time frame by the same group (Table).<sup>6</sup> All patients had a normal newborn screen for primary hypothyroidism, were negative for thyroid autoantibodies and had no family history of autoimmune thyroid disease.

### Case 1

A 2-year-old ex-32-week female with severely restricted eating was admitted for growth failure [weight <first percentile (z-score -3.11), height < first percentile (z-score -2.51)]. Labs showed thyroid stimulating hormone (TSH) of 470  $\mu$ U/mL (0.3-5.5), free T4 (FT4) of 0.34 ng/dL (0.8-1.8), a thyroglobulin of 1766 ng/L (1.0-35.0) and a urine iodine concentration (UIC) of 10.5  $\mu$ g/L (>100). She had no goiter. A pediatric nutritional supplement was initiated via nasogastric tube providing about 90  $\mu$ g of iodine daily and her thyroid function normalized within a week. She was treated with levothyroxine, which was discontinued 7 weeks later, as her thyroid function remained normal. Continuing the nutritional supplement, her 3 years 4 month visit showed height at the 9.seventh percentile, weight at the 29th percentile and body mass index at the 74th percentile.

### Case 2

A 10-year-old male with history of pachygyria (congenital malformation of the cerebral cortex characterized by a thickened cortex, large gyri), seizures and developmental delay was referred for weight gain, constipation, cold intolerance, height deceleration and goiter (each lobe 5 cm). He had a restricted diet and avoided dairy, fruits, vegetables, and meat. Initial laboratory evaluation showed FT4 of 0.31 ng/dL (0.8-1.8) and a TSH of 239  $\mu$ U/mL (0.66-4.14). He was treated with levothyroxine and 6 weeks later, he had a thyroglobulin level of 1746 ng/L (1.0-35.0), TSH 5.48  $\mu$ U/mL (0.35-5.5) and FT4 of 1.01 ng/dL (0.8-1.8 ng/L). Due to the high thyroglobulin level, a spot UIC was ordered but not completed by family until 7 months later when he was admitted for severe iron deficiency anemia (hemoglobin 5.2 g/dL) during which time his UIC was 18  $\mu$ g/L (>100). He was initiated on an iodine tablet, 150  $\mu$ g daily. At a follow-up visit 1.5 years later, his goiter size remained unchanged, but his repeat UIC improved to 464.7  $\mu$ g/L (>100) allowing discontinuation of levothyroxine. Thyroid tests remained in target range, 2 and 4 months later.

### Case 3

A 3.5-year-old male with multiple food allergies (dairy, tree nuts, and peanuts) was referred for goiter of 5 months duration. His diet was limited to fig bars, potato chips, graham crackers, a specific brand of vegetable chips and he used only a small amount of table salt. Initial labs showed a total T3 of 2.3 ng/mL (0.4-1.9), free T3 of 4.2 pg/mL (1.6-3.9) and a UIC of 11  $\mu$ g/dL (>100) but family did not follow-up. Two months later, at an outside institution, he was started on levothyroxine for a FT4 was 0.49 ng/dL, TSH of 6.37  $\mu$ U/mL, and total T3 of 240 mg/dL (94-241). Thyroid ultrasound showed an enlarged, hyperemic gland suggestive of thyroiditis. One-month post-levothyroxine, thyroid labs normalized (TSH of 2.03  $\mu$ U/mL and FT4 of 1.57 ng/dL). Four months later, the goiter resolved, and thyroid function remained normal, and the family returned to our

## Highlights

- Iodine deficiency hypothyroidism can occur in children with food restrictions.
- Iodine deficiency hypothyroidism displays clinical and biochemical heterogeneity.
- Spot urine iodine and serum thyroglobulin levels can facilitate the diagnosis.

## Clinical Relevance

It's important for providers to consider iodine deficiency when children and adolescents present with antibody negative hypothyroidism, with or without a goiter.

clinic for follow-up. A 24-hour urine iodine excretion (UIE) was 9.9  $\mu$ g/d (26-705). Potassium iodide drops (125  $\mu$ g daily) were started, and 2 months later, UIC improved to 293.2  $\mu$ g/L (>100). Levothyroxine was discontinued after 6 weeks. He continues iodine supplementation, and his thyroid function remains normal.

## Discussion

This case series, with individual characteristics summarized in Table, including Cases 1-3 described above and our previously reported Cases 4<sup>5</sup> and 5<sup>6</sup>, contributes to the literature regarding re-emergence of iodine deficiency hypothyroidism in the United States.<sup>7-12</sup> It highlights significant heterogeneity in pediatric presentations, such as severe, mild or absent goiters (Case 1), varied TSH levels, and thyroid function tests mimicking thyroid hormone resistance alpha (Cases 3, 4).<sup>5</sup> These diverse clinical presentations may result from the thyroid gland's varying adaptation and/or maladaptation to iodine deficient states.

A stable TSH in the circulation is maintained primarily due to the dynamic interplay of thyrotropin-releasing hormone from the hypothalamus and the feedback effects of T3 and T4 on the hypothalamus and pituitary gland.<sup>13</sup> Iodine constitutes 65% of the weight of T4, and 58% of the weight of T3,<sup>14</sup> playing a key role in the negative feedback loop of thyroid hormone on TSH release. Iodine is absorbed from the stomach and the duodenum, then actively transported into the thyrocytes via the sodium-iodide symporter in a TSH dependent manner.<sup>14</sup> Inside the thyrocyte, iodine undergoes oxidation followed by organification before being incorporated into thyroglobulin. Iodinated thyroglobulin is coupled to produce T4 and T3 which are released into the circulation and carried target tissues via binding proteins.<sup>14</sup> Degradation of T4 and T3 in the periphery by deiodinases releases iodine back in to the plasma iodine pool.<sup>14</sup>

More than 90% of ingested iodine is excreted in the urine within 24 to 48 h of ingestion.<sup>2,3</sup> Hence, median UIC measured from spot urine samples can be utilized for diagnosis of iodine deficiency.<sup>2,3</sup> According to the World Health Organization median UIC of 50-99  $\mu$ g/L indicates mild, 20-49  $\mu$ g/L indicates moderate, and <20  $\mu$ g/L indicates severe iodine deficiency in children > 6 years.<sup>3</sup> National Health and Nutrition Examination Survey results showed a significant decrease in UIC from 243  $\mu$ g/L in 2001-2004 to 166  $\mu$ g/L in 2017-2020 among U. S. school age children.<sup>15</sup> Inadequate iodine intake was more likely in children who never or rarely consumed dairy products.<sup>11</sup> However, repeated UIC measurements might be required to accurately assessing iodine deficiency<sup>16</sup> as UIC is indicative of an individual's more recent diet than long term diet.<sup>16</sup> A 24-hour UIE may reflect iodine status more accurately both at the individual and at the population level.<sup>17</sup> In individuals in whom

**Table**  
Initial and Follow-up Clinical and Lab Characteristics of Patients With Iodine Deficiency Hypothyroidism

Case number	Case 1	Case 2	Case 3	Case 4 <sup>5</sup>	Case 5 <sup>6</sup>
<b>Initial clinical presentation</b>					
Age at presentation (yrs)	2	10	3.5	6	13
Sex	Female	Male	Male	Female	Male
Clinical features	Ex-32-wk premature infant	Seizure disorder	Multiple food allergies (diary, peanuts, tree nuts)	Vegan diet	Autism
	Speech delay	Developmental delay		Non-iodized salt only	Restricted diet
	Restricted eating				
Symptoms	Growth delay	Weight gain, constipation, cold intolerance, neck swelling, growth delay	None	None	Neck swelling, fatigue
Goiter	None	Firm, each lobe 5 cm	Goiter noted by PCP, details not available	Non-tender, smooth, each lobe 6-7 cm	Firm, symmetric, each lobe 8-8.5 cm
Thyroid ultrasound	Normal thyroid gland	Not done	Enlarged, hyperemic thyroid	Enlarged thyroid, heterogenous echotexture, microcystic changes and fibrous septations	Enlarged thyroid, heterogenous echotexture, diffuse hyperemia
<b>Initial thyroid function tests<sup>a</sup></b>					
TSH (μIU/mL)	470 (0.30-5.50)	239 (0.66-4.14)	6.37 (0.34-5.5)	5.03 (0.34-5.50)	416 (0.35-5.50)
Free T4 (ng/dL)	0.34 (0.80-1.80)	0.31 (0.80-1.80)	0.49 (0.70-1.50)	0.30 (0.58-1.20)	< 0.10 (0.80-1.80)
Total T3 (ng/dL)	Not done	125 (82-213)	240 (40-190)	258 (94-241)	41 (82-213)
Anti-thyroid antibodies	Negative	Negative	Negative	Negative	Negative
Thyroglobulin (ng/L)	1766 (1.0-35)	1746 (1.0-35)	Not done	1098 (<13)	Not done
Spot urine iodine concentration (μg/L)	10.5 (>100)	18 (>100)	11 (>100)	15.8 (>100)	Not done
24-h urine iodine excretion (μg/L)	Not done	Not done	9.9 (26-705)	Not done	<5 (26 - 705)
<b>Treatment</b>					
Levothyroxine (μg/kg/d) (Duration, wks)	50 μg/d (5.4 μg/kg/d) x1 wk and then 25 μg/d (2.7 μg/kg/d) x 7 wk	50 μg/d (1.5 μg/kg/d) x 78 wk	50 μg/d (2.6 μg/kg/d) x 24 wk	None	25 μg/d (0.5 μg kg/d) x 6 wk
Iodine supplement (μg/d)	~90	150	~125	150	150
<b>Follow-up Labs</b>					
Follow-up interval	0.5 mo	0.5 mo	1.5 mo	3 mo	1 mo
TSH (μIU/mL)	3.29 (0.30-5.50)	1.7 (0.30-5.5)	0.82 (0.30-5.5)	2.72 (0.34-5.50)	0.71 (0.35-5.5)
Free T4 (ng/dL)	1.23 (0.80-1.80)	0.98 (0.80-1.80)	1.2 (0.80-1.80)	Not done	1.45 (0.80-1.80)
Total T3 (ng/dL)	182 (105-269)	Not done	Not done	182 (94-241)	Not done

Abbreviation: TSH = thyroid stimulating hormone.

<sup>a</sup> Reference ranges in parentheses.

collection of a 24-hour UIE is challenging, an elevated thyroglobulin along with a spot UIC can be helpful in assessing iodine status.<sup>5,6,9,11</sup>

With mild iodine deficiency, there is increased vascularity and increased iodine uptake in the thyroid gland, preferential synthesis of T3 over T4, and an increase in thyroglobulin levels.<sup>18</sup> T3 has approximately 4 times the potency of T4 but requires 25% less iodine and this may explain why patients with iodine deficiency may have an elevated T3 and biochemically may resemble thyroid hormone resistance alpha (Cases 3 and 4).<sup>18</sup> Because these initial autoregulatory responses are independent of TSH, patients may be clinically and biochemically euthyroid in early stages.<sup>18</sup> With persistent iodine deficiency these intra- and extra-thyroidal autoregulatory mechanisms become insufficient and clinically significant hypothyroidism can result.<sup>18</sup>

In severe iodine deficiency, there may be a diffuse goiter (Cases 2, 3, 4, and 5)<sup>5,8,9,12</sup> or no goiter at all (Case 1).<sup>3,8,18</sup> One possible explanation for the lack of goiter is that the thyroid gland maintains its size by increasing its efficiency of iodide trapping.<sup>3,18</sup> In severe iodine deficiency, a large colloid goiter may occur due to secretion of large amounts of poorly iodinated thyroglobulin into the circulation. This process can result in an iodine leak, causing renal iodide loss and ensuing a vicious cycle.<sup>18</sup> Chronic TSH stimulation of the thyroid gland in iodine deficiency has been shown to be a risk factor for thyroid cancer, particularly follicular thyroid cancer.<sup>19</sup>

The patients presented here received iodine supplementation based upon the recommended daily intake of iodine per the WHO: 90–120 µg daily for children aged 1–13 years, and 150 µg daily for adolescents >13 years age.<sup>3</sup> Management of the patients included reintroduction of iodine by encouraging utilization of iodized table salt and targeted recommendations by registered dietitians. Families were counseled on symptoms of hyperthyroidism that can develop with iodine supplementation.<sup>20</sup>

This case series encourages providers to expand the differential diagnosis for antibody negative hypothyroidism in children.

## Disclosure

The authors have no conflicts of interest to disclose.

## Author contributions

M.S.G. and J.B.Q. conceptualized and designed the case series. S.S. collected and organized data, drafted the initial manuscript, critically reviewed, and revised the manuscript. M.S.G., S.S.P., A.G., K.M., and L.S.T. helped with patient's data collection, critically reviewed, and revised the manuscript's intellectual content. All authors approved the final manuscript. And agree to be accountable for all aspects of the work.

## Acknowledgment

We thank the patients and their caregivers.

## References

1. Accessed September 20, 2023. <https://ods.od.nih.gov/factsheets/Iodine-HealthProfessional/>
2. Zimmermann MB. Iodine deficiency. *Endocr Rev.* 2009;30(4):376–408.
3. Council I, UNICEF, World Health Organization. *Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination.* 2001.
4. Leung AM, Braverman LE, Pearce EN. History of U.S. Iodine fortification and supplementation. *Nutrients.* 2012;4(11):1740–1746.
5. Sasidharan PS, Quintos JB. Thyroid function tests of iodine deficiency goiter can mimic thyroid hormone resistance alpha. *J Pediatr Endocrinol Metab.* 2022;35:1433–1436.
6. Moore CE, Sasidharan Pillai S, Austin J, Fredette ME, Serrano-Gonzalez M. Severe hypothyroidism and large goiter due to iodine deficiency in an adolescent male in the United States: a case report and review of the literature. *Case Rep Endocrinol.* 2022;2022:7235102.
7. Hatch-McChesney A, Lieberman HR. Iodine and iodine deficiency: a comprehensive review of a Re-emerging issue. *Nutrients.* 2022;14(17):3474.
8. Booms S, Hill E, Kulhanek L, Vredevelde J, Gregg B. Iodine deficiency and hypothyroidism from voluntary diet restrictions in the US: case reports. *Pediatrics.* 2016;137(6):e20154003.
9. Caprio AM, Umamo GR, Luongo C, Aiello F, Dello Iacono I, Palumbo S, et al. Case report: goiter and overt hypothyroidism in an iodine-deficient toddler on soy milk and hypoallergenic diet. *Front Endocrinol.* 2022;13:927726.
10. Leung AM, Lamar A, He X, Braverman LE, Pearce EN. Iodine status and thyroid function of Boston-area vegetarians and vegans. *J Clin Endocrinol Metab.* 2011;96(8):E1303–E1307.
11. Yeliosof O, Silverman LA. Veganism as a cause of iodine deficient hypothyroidism. *J Pediatr Endocrinol Metab.* 2018;31(1):91–94.
12. Pacaud D, Van Vliet G, Delvin E, Garel L, Chad Z, Delange F, et al. A Third World endocrine disease in a 6-year-old North American boy. *J Clin Endocrinol Metab.* 1995;80(9):2574–2576.
13. Mariotti S, Beck-Peccoz P. Physiology of the Hypothalamic-Pituitary-Thyroid Axis. [Updated 2021 Apr 20]. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. *Endotext [Internet].* South Dartmouth, MA: MDText.com, Inc; 2000.
14. Rousset BDC, Miot F, et al. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. *Chapter 2 thyroid hormone synthesis and secretion.* *Endotext.* MDText.com, Inc; 2000.
15. Zhang K, Cheng J, Yu J, Chen Y, Shi X, Zhu C, et al. Trends in iodine status among U.S. Children and adults: a cross-sectional analysis of national Health and nutrition examination Survey data from 2001–2004 to 2017–2020. *Thyroid.* 2022;32(8):962–971.
16. König F, Andersson M, Hotz K, Aeberli I, Zimmermann MB. Ten repeat collections for urinary iodine from spot samples or 24-hour samples are needed to reliably estimate individual iodine status in women. *J Nutr.* 2011;141(11):2049–2054.
17. Chen W, Wu Y, Lin L, Tan L, Shen J, Pearce EN, et al. 24-Hour urine samples are more reproducible than spot urine samples for evaluation of iodine status in school-age children. *J Nutr.* 2016;146(1):142–146.
18. Eastman CJ, Zimmermann MB. In: Feingold K.R., Anawalt B., Blackman M.R., eds, et al. *The Iodine Deficiency Disorders.* South Dartmouth, MA.
19. Zimmermann MB, Galetti V. Iodine intake as a risk factor for thyroid cancer: a comprehensive review of animal and human studies. *Thyroid Res.* 2015;8:8.
20. Goyal I, Pandey MR, Sharma R. Hypothyroidism and goiter in a young male with suspected dietary iodine deficiency followed by thyrotoxicosis after iodine supplementation. *AACE Clin Case Rep.* 2020;6(1):e19–e22.