Hypothyroidism and Iodine Deficiency in Children on Chronic Parenteral Nutrition

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abstract

BACKGROUND AND OBJECTIVES: Iodine is an essential trace element for maintenance of normal thyroid function. Normal thyroid function is a prerequisite for neurocognitive development and growth in children. In the United States, iodine is not routinely added as a trace element in parenteral nutrition (PN). Our objective was to determine the prevalence of iodine deficiency and hypothyroidism in children on chronic PN.

METHODS: This was a cross-sectional study of children <17 years of age and using PN for >6 months at a tertiary children's hospital. Primary outcomes were spot urine iodine concentration (UIC), serum thyrotropin, and free thyroxine levels.

RESULTS: Twenty-seven patients were identified (74% male). The median age at screening was 48 months (range: 7–213 months). The median duration on PN was 27 months (range: 11–77 months). Seventeen out of 20 patients (85%) were iodine deficient (spot UIC <100 μg/L), whereas 11 out of 20 patients (55%) were severely iodine deficient (spot UIC <20 μg/L). The prevalence of acquired hypothyroidism (elevated thyrotropin, low free thyroxine, and UIC <100 μg/L) was 33% (n = 8). None of the children with hypothyroidism screened for autoimmune thyroiditis had positive test results. There was no statistically significant association between duration of PN use and development of iodine deficiency (P = .08) or hypothyroidism (P = .96).

CONCLUSIONS: Children on chronic PN are at risk for developing iodine deficiency and resultant hypothyroidism; hence, these children should be screened for these outcomes. Further studies are needed to define the temporal onset of iodine deficiency and timing to thyroid dysfunction related to PN.

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Dr Ikomi conceptualized and designed the study and drafted the initial manuscript; Drs Cole and Golekoh conceptualized and designed the study and reviewed and revised the manuscript; Ms Vale coordinated the data collection of patients on chronic parenteral nutrition and reviewed the final manuscript; Dr Khoury conducted the analyses and reviewed and revised the manuscript; Dr Jones contributed to all stages of the study design and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Iodine is an essential component for the production of thyroid hormones, and iodine deficiency results in hypothyroidism.

WHAT THIS STUDY ADDS: Defining the frequency of iodine deficiency and hypothyroidism in pediatric patients receiving chronic parenteral nutrition, which the authors of this study address, is the initial step in preventing significant morbidity and mortality associated with a preventable micronutrient deficit.

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Iodine is an essential trace element, with its only known biological function being the synthesis of thyroid hormones. Iodine makes up 65% and 59% of the molecular weights of thyroxine and tri-iodothyronine respectively. Normal intracellular stores of thyroid hormones are important for growth, the progression of puberty, musculoskeletal function, gastrointestinal (GI) metabolism, and neurocognitive development in children.[1] Children maintain adequate stores of iodine primarily through diet.[2] As a result of the iodization of salt and fortification of foods, hypothyroidism in children secondary to iodine deficiency has been mostly eradicated in the United States. However, this remains a leading cause of preventable mental retardation globally.[3]

Children unable to tolerate enteral nutriment, including those with intestinal failure, remain at risk for iodine deficiency because iodine is not routinely supplemented in the trace element mixture used in the United States. Intestinal failure may result from obstruction, dysmotility, surgical resection, congenital defect, or disease-associated loss of absorption, leading to the inability to maintain protein-energy, fluid, electrolyte, and micronutrient balance.[4] Children so affected require intravenous supplementation of both macro- and micronutrients for sustenance of life and are often supplemented with parenteral nutrition (PN). The European Society of Pediatric Gastroenterology, Hepatology and Nutrition recommends that infants and children on PN receive a daily iodide supply of 1 μg/kg per day.[5] In recommendations by the American Society for Parenteral and Enteral Nutrition, it is stated that routine supplementation of PN with iodide could be beneficial, but more research is needed.[6] Recent data have revealed conflicting results with the recommendation of 1 μg/kg per day being inadequate to meet the needs of children on PN,[7,8] whereas other studies have revealed adequate iodine status.[9,10]

In the United States, there have been few case reports of hypothyroidism due to iodine deficiency in children on PN.[11–13] Our team previously published the case report of a sentinel case of severe hypothyroidism (thyrotropin [TSH] level: 82.6 μIU/mL [reference range: 0.64–4.0 μIU/mL] and free thyroxine [fT4] level: 0.1 ng/dL [reference range: 1.0–2.8 ng/dL]), which was noted after a GI motility workup in a boy 2 years and 7 months old who presented to our institution for intestinal rehabilitation after exclusive PN for 7 months.[11] The child was also found to have a low spot urine iodine concentration (UIC) and thus prompted the authors of this study to determine the prevalence of iodine deficiency and hypothyroidism in this at-risk population.

METHODS

We performed a cross-sectional study of children who were <17 years of age at the start of PN, who were on PN for >6 months, and who received <50% of their nutrition enterally, with visits to the intestinal rehabilitation clinic and/or comprehensive nutrition clinic at Cincinnati Children's Hospital Medical Center. This program maintains a database of all patients on chronic PN (duration >4 weeks). Baseline demographic and clinical data were collected and included age, sex, primary diagnosis, duration of PN, and type of enteral supplement, as well as the quantity and description of remaining bowel segments if the patient had undergone bowel resection. The iodine content of any enteral formula was also collected. UICs were obtained in addition to venous blood draws to measure TSH, fT4, and thyroglobulin levels. Children with a known diagnosis of hypothyroidism, a recent blood culture with positive results, or a severe illness in the 4 weeks preceding enrollment were excluded.

For patients identified as having hypothyroidism, thyroid antibodies (thyroid peroxidase and thyroglobulin antibodies) were obtained to exclude autoimmune thyroid disease, which is the most common cause of acquired hypothyroidism in the pediatric population. The children with hypothyroidism were referred to endocrinology for treatment.

We used a high-sensitivity, 2-step, chemiluminescent microparticle immunoassay to determine the presence of TSH in human serum and plasma. We assessed fT4 using equilibrium dialysis followed by tandem mass spectrometry. Thyroglobulin was measured by using a quantitative chemiluminescent immunoassay and/or high-performance, chromatography-tandem mass spectrometry.

The Children's Hospital Medical Center Institutional Review Board approved the study, and written informed consent and assent were obtained from parents and the patients as indicated. Data collected were maintained in a secure electronic database.

Demographic variables are reported as the median and 25th and 75th percentiles (interquartile range [IQR]), the maximum and minimum (range), or the frequency and percentage. Rates of iodine deficiency and hypothyroidism and associated 95% confidence intervals (CIs) were calculated. The time to iodine deficiency and hypothyroidism from the start of PN between those with and without iodine deficiency and those with and without hypothyroidism, respectively, was

examined by using the Wilcoxon rank test. Logistic regression was used to examine risk factors for the development of iodine deficiency and hypothyroidism. $P < .05$ was considered statistically significant. SAS version 9.4 (SAS Institute, Inc, Cary, NC) was used for statistical analysis.

RESULTS

Twenty-seven patients (74% male) were eligible and screened for iodine deficiency and hypothyroidism at least once between July 2015 and November 2016 (Table 1). Age at the time of screening ranged from 7 to 213 months, with a median age of 48 months (IQR: 30–129). The median age at diagnosis of primary GI disease was 5 months (IQR: 1–27 months). Forty-eight percent of patients ($n = 13$) had short bowel syndrome. Other GI disorders leading to PN dependency included pseudo-obstruction syndrome, eosinophilic GI disease, and "food protein"–induced enterocolitis syndrome. The median duration on PN was 30 months (IQR: 17–40; range: 11–77 months). Eight patients were exclusively PN dependent. The median age at the start of PN for those exclusively on PN was 30.2 months (IQR: 19.4–88.3) versus 1.4 months (IQR: 0.8–14.7; $P = .02$) for those also receiving supplements (PediaSure, Glucerna, or Elecare Jr). For those not exclusively PN dependent, the iodine content of supplements ranged from 0 to 156 μg/day. Iodine deficiency (spot UIC <100 μg/L) was identified in 17 of 20 patients (85%). The degree of deficiency is shown in Table 2. One child had an elevated UIC level (>200 μg/L) at baseline.

Among the 24 patients with thyroid function tests, hypothyroidism (TSH level >4 μIU/L) was identified in 8 patients (33%; 95% CI: 15.6%–55.3%). Six children (25%; 95% CI: 9.8%–46.7%) had a TSH level >10 μIU/mL, 4 of whom had severe hypothyroidism with concurrent low fT4 (see Table 3). There was no patient identified with clinical goiter and none of the children screened for autoimmune thyroiditis had positive test results. There was no significant association between length of time on PN and the development of severe iodine deficiency (UIC <20 vs >20; 35.4 months [IQR: 20.1–48.1] vs 61.5 months [IQR: 36.2–76.6]; $P = .08$) or hypothyroidism (TSH level >10 vs <10; 33.6 months [IQR: 19.8–77.2] vs 36.3 months [IQR: 24.6–64.9]; $P = .96$).

TABLE 1 Demographics and Laboratory Results

Variable ($N = 27$)	*n* (%) or Median (25th–75th Percentile)	*n*
Boys	20 (74.1%)	27
Age at screening, mo	48 (30–129)	27
Age at GI diagnosis, mo	5 (1–27)	24
Age at start PN, mo	20 (1–59)	25
Months on PN	30 (17–40)	20
Percentage of nutrition from PN	96.2 (76.1–100)	22
Iodine in formula, μg[a]	17.8 (3.3–49.5)	14

[a] Only for those on formula ($n = 14$).

TABLE 2 Spot Urine Iodine Levels and Thyroid Levels

	n (%)
UIC ($N = 20$), μg/L	
<100	17 (85.0)
≥100	3 (15.0)
<20, severe	11 (55.0)
20–50, moderate	4 (20.0)
51–99, mild	2 (10.0)
TSH ($N = 24$), 0.5–4.0 μIU/mL	
>4	8 (33.3)
≤4, normal	16 (66.7)
>10	6 (25.0)
≤10	18 (75.0)
fT4 ($N = 21$), 1.0–2.8 ng/dL	
<1.0	7 (33.3)
≥1.0	14 (66.7)

TABLE 3 Clinical and Biochemical Characteristics of Hypothyroid Children

Patient Data	Boy, 13 y	Boy, 3 y	Boy, 4 y	Boy, 20 mo	Girl, 20 mo	Boy, 11 y
Diagnosis	Intestinal Failure	Short Bowel Syndrome	CMV Enterocolitis	Wiskott-Aldrich Syndrome	Intestinal Failure	Short Bowel Syndrome
Duration on TPN, mo	13	37	12	[a]	17	72
TPN, %	100	97.4	100	100	100	[a]
TSH, 0.4–4.0 μIU/mL	89.2	88.6	120	46.2	21.1	16.6
fT4, 1.0–2.8 ng/dL	<0.4	0.4	<0.4	1.8	0.7	1.6
Thyroglobulin, 0.8–29.4 ng/mL	1890.0	1052.8	345.2	61.1	365.9	36.2
Urine iodine, 100–200 μg/L	<5	7.6	12.1	45.1	12.1	11.1
Thyroid antibodies	Negative	Negative	Negative	Negative	Negative	Negative

CMV, cytomegalovirus; TPN, total parenteral nutrition.
[a] Data unknown at the time of analysis.

DISCUSSION

The Food and Drug Administration–approved pediatric trace element

mixture for PN currently available for manufacture and use in the United States does not contain iodine. This is the mixture routinely used by most pediatric centers. The authors of previous studies have shown adequate iodine status in children on PN, likely secondary to adventitious sources. One study of 18 children receiving long-term PN revealed an iodide contaminant between 0.4 and 1.2 μg/dL in parenteral solutions and 1.4 to 2.3 μg/dL in fat emulsions given to children ages 4 to 18 years.[9] At the time, betadine (povidone iodine) was routinely used as the antiseptic of choice. Betadine, often a 10% povidone-iodine solution, contains 10 mg of iodine in 1 mL; hence, a small application would be adequate to normalize iodine stores. In recent times, chlorhexidine has increasingly gained favor as both the antiseptic and disinfectant of choice to prevent nosocomial infections. After this shift from betadine to chlorhexidine, iodine deficiency may be reoccurring at a higher frequency than previously reported.

Iodine is well absorbed in the duodenum and is cleared from the circulation by the kidneys and thyroid gland. Circulating iodine cleared by the thyroid gland typically varies with the intake of iodine.[14] The majority of our cohort on PN were undergoing nutritional rehabilitation because of surgical short bowel syndrome with minimal oral intake. Interestingly, our study did not reveal a statistically significant association between the primary GI diagnosis, the length of time on PN, or the percentage of nutrition by PN and the development of iodine deficiency or hypothyroidism.

Our study revealed that 85% of patients had low iodine stores, whereas 33% developed hypothyroidism. This is in contrast with a recent retrospective analysis of children on PN for 6 months or longer that revealed no evidence of iodine deficiency or hypothyroidism in children on PN not supplemented with iodine.[10] The methodology used for evaluating iodine sufficiency in that study featured the use of serum iodine, whereas we measured spot UIC. Four methods are recommended for the assessment of iodine status in a population: (1) measuring UIC to assess iodine status over days to weeks; (2) measuring serum thyroglobulin to assess iodine status over weeks to months; (3) assessing the goiter rate, which is a measure of long-term iodine status over months to years; and (4) measuring TSH, which is sensitive mainly in the newborn period (as a marker of maternal iodine status).[15] We used UIC, thyroglobulin, and TSH values for our evaluation. We showed that children who developed hypothyroidism also had elevated thyroglobulin levels. Serum thyroglobulin has been shown to be well correlated with the severity of iodine deficiency as measured by UIC.[16] Thyroglobulin, a glycoprotein synthesized in the thyrocyte, plays an important role in thyroid hormone production. After its synthesis, thyroglobulin is transported and stored in the follicular colloid of the thyrocyte, where tyrosine residues undergo iodination (catalyzed by thyroid peroxidase and hydrogen peroxide) to produce mono-iodotyrosine and di-iodotyrosinase. Thyroglobulin then undergoes proteolysis by lysosomes to release thyroid hormones, which are secreted into the bloodstream. When iodine intake is insufficient, low circulating levels of thyroid hormones stimulate the release of thyroid-releasing hormone, which in turn increases TSH. A high TSH level leads to an increase in the synthesis and proteolysis of thyroglobulin to increase thyroid hormones.[17] Therefore, in iodine deficiency, an increased amount of thyroglobulin is released into the blood.

There are currently no standard recommendations for monitoring iodine status in children on chronic PN. Because intrathyroidal iodine stores are adequate to sustain thyroid hormone production for 3 months,[18] we suggest that children on long-term PN (>6 months) not supplemented with iodine should have a determination of their iodine status. This is especially important for the prevention of acquired hypothyroidism, which, if untreated, can lead to abnormal cognition, growth, and metabolism. The timing of the development of iodine deficiency or hypothyroidism in children on PN is not known. Although all the children in our study who developed hypothyroidism had low spot UIC, not all children with low iodine levels developed hypothyroidism. Perhaps more time on PN was needed before the onset of hypothyroidism.

Because of the significant consequences of acquired hypothyroidism in childhood, patients identified as having hypothyroidism were referred to endocrinology and thyroid hormone (levothyroxine) treatment was initiated by the endocrinologist. In addition, our patients were also supplemented with 100 μg (1 mL) daily of ultradilute potassium iodide via gastro-jejunal tube or by mouth. This was compounded at our pharmacy by using the commercial potassium iodide 1-g/mL solution and is stable for 60 days at room temperature. Subsequently, urine iodine levels were monitored monthly for dose adjustments. An alternative is the use of iodized salt if the child is able to tolerate small amounts by mouth. The goals of therapy are to correct mild, moderate, or severe iodine deficiency to optimize iodine level and prevent iodine deficiency disorders.

Our study has limitations, which include the use of single spot urine iodine to determine iodine status. Although urine iodine expressed in micrograms per liter or micrograms

of iodine per gram of creatinine is an excellent indicator of iodine intake (90% of dietary iodine is cleared by kidney and excreted in urine), 24-hour urine collection or an average of 3 specimens are recommended because of the variable intake of iodine from day to day. In our population, the logistics of obtaining multiple urine specimens was difficult. However, most of the patients in this study had minimal oral intake when on PN, making the iodine levels from day to day less variable. The constellation of results of patients with hypothyroidism who showed elevated TSH, low fT4, and elevated thyroglobulin levels, in the presence of low spot UIC and negative thyroid antibodies, makes this more convincing for true iodine deficiency as the cause of acquired hypothyroidism. Our study size was also small, and larger studies are needed to further evaluate this trend.

The frequency and temporal onset of iodine deficiency related to PN is not defined. Our data are the first to reveal a higher prevalence of iodine deficiency and hypothyroidism in children on chronic PN.

CONCLUSIONS

Children on PN are at increased risk for iodine deficiency and acquired hypothyroidism. Because iodine is essential for thyroid hormone production, children on chronic PN not supplemented with iodine should be screened for thyroid dysfunction.

ABBREVIATIONS

CI: confidence interval
fT4: free thyroxine
GI: gastrointestinal
IQR: interquartile range
PN: parenteral nutrition
TSH: thyrotropin
UIC: urine iodine concentration

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