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Thyroid Dysfunction in Children Exposed to Iodinated Contrast Media

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Context: Iodinated contrast media (ICM) is routinely used in imaging studies and contains several 100-fold the recommended daily allowance of iodine.

Objective: To determine whether children exposed to ICM have a higher risk of iodine-induced thyroid dysfunction.

Design: This was a single-institution case-control study, examining patients with incident thyroid dysfunction aged less than 18 years from 2001 to 2015. Cases were matched 1:1 to euthyroid controls by age, sex, and race.

Setting: This was a single-institution case-control study occurring at tertiary care center.

Participants: Cases were defined as those with thyroid dysfunction (by International Classification of Diseases, Ninth Revision diagnosis codes and/or 2 consecutive abnormal serum TSH values $<$6 mo apart). We analyzed 870 cases matched to 870 controls (64% female, 51% White).

Main Outcomes Measures: Using conditional logistic regression, the association between ICM exposure and the primary outcome, thyroid dysfunction, occurring within 2 years of exposure was assessed.

Results: Sixty-nine patients received ICM, including 53 (6%) among cases and 16 (2%) among controls. The risk of incident hypothyroidism was significantly higher after ICM exposure (odds ratio 2.60; 95% confidence interval, 1.43–4.72; $P < .01$). The median interval between exposure and onset of hypothyroidism was 10.8 months (interquartile range, 6.6–17.9). In hypothyroid cases, the median serum TSH concentration was 6.5 mIU/L (interquartile range, 5.8–9.6).

Conclusions: ICM exposure increases the risk of incident hypothyroidism in pediatric patients. Children receiving ICM should be monitored for iodine-induced thyroid dysfunction, particularly during the first year after exposure. **(*J Clin Endocrinol Metab* 101: 2366–2370, 2016)**

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Abbreviations: CI, confidence interval; ICD-9, International Classification of Diseases, Ninth Revision; ICM, iodinated contrast media; OR, odds ratio; UCLA, University of California Los Angeles.

Iodinated contrast media (ICM) agents are routinely used in diagnostic imaging studies. By one estimate, 75 million doses of ICM are administered yearly (1). A single dose of ICM contains approximately 13 500 μg of free iodine (to convert to nmol, multiply by 7.88) (2), which far exceeds the recommended daily intake of iodine for both adults and children. In adults, the recommended daily intake of iodine to maintain proper thyroid function is 150 μg; in children ages 1–8 years old, iodine intake should be 90 μg of iodine per day (3).

The adverse effects of excess iodine have been well established and include iodine-induced thyroid dysfunction (2, 4, 5). These outcomes are potentially significant in infants and children, because the developing brain requires normal thyroid function during the critical window of myelination. Thus, even transient or slight thyroid dysfunction can have long-term implications for neurocognitive development as well as skeletal maturation (6, 7). A number of studies have demonstrated that exposure to ICM, as a common source of excess iodine, increases the risk of thyroid dysfunction (2, 8–11). However, many of these studies have been restricted to adults and neonates, leaving an important gap in the literature concerning the impact of iodine excess upon thyroid function in pediatric patients. We aim to address this knowledge gap by examining the hypothesis that pediatric patients (<18 y old) exposed to ICM are at higher risk for the development of iodine-induced thyroid dysfunction.

Materials and Methods

Medical records of pediatric patients within the University of California Los Angeles (UCLA) healthcare system were accessed after study approval from the UCLA Institutional Review Board. Inclusion criteria for the study were pediatric patients less than age 18 years at the time of either 1) a diagnosis of hyperthyroidism or hypothyroidism by International Classification of Diseases, Ninth Revision (ICD-9) codes; and/or 2) laboratory serum thyroid function testing, regardless of result. The following ICD-9 codes were used to determine a diagnosis of hyperthyroidism: 775.3, 242.41, 242.40, 242.4, 242.81, 242.80, 242.8, 242, 242.0, 242.01, 242.00, 242.2, 242.21, 242.20, 242.3, 242.31, 242.30, 242.1, 242.11, 242.10, 242.9, 242.90, 242.91, and 245. The following ICD-9 codes were used for a diagnosis of hypothyroidism: 244, 243, 244.2, 244.3, 244.1, 244.8, 244.0, and 244.9. For patients with available laboratory serum thyroid function testing results, standard UCLA laboratory values for TSH were used to classify the patients as biochemically hyperthyroid (TSH below reference range), hypothyroid (TSH above reference range), or euthyroid (TSH within the reference range of 0.3–4.7 mIU/L). Classification of patients as hyperthyroid or hypothyroid by biochemical criteria rested on demonstration of 2 consecutive abnormal serum TSH values within a 6-month time period. The onset of thyroid dysfunction was established by either acquisition of one of the above ICD-9 codes or the first abnormal serum TSH value. Finally, iodinated contrast exposure was defined as the earliest date of ICM administration within 2 years preceding the diagnosis date of hyperthyroidism or hypothyroidism.

In order to accurately classify incident hyperthyroid and hypothyroid cases, exclusions were applied to individuals with ICD-9 codes corresponding to various thyroid treatments and procedures. Patients were excluded if the following ICD-9 codes occurred before ICM exposure: 06.52 (complete substernal thyroidectomy), 06.4 (complete thyroidectomy), 06.3 (other partial thyroidectomy), 06.31 (excision of lesion of thyroid), 06.39 (other partial thyroidectomy), 06.51 (partial substernal thyroidectomy), 06.5 (substernal thyroidectomy), and 06.50 (substernal thyroidectomy, not otherwise specified). For those patients with available serum thyroid function tests, results were cross-referenced against ICD-9 codes to exclude any patients miscoded for the directionality of thyroid dysfunction.

This was a case-control study of patients matched 1:1 on the basis of age, sex, and race (White vs non-White, obtained by self-report as captured in the medical record). A conditional logistic regression model was used to estimate the odds ratio (OR) (and its 95% confidence interval [CI]) of thyroid dysfunction after ICM exposure. All data analysis was performed using SAS version 9.3. Two-tailed *P* values were reported and considered statistically significant if less than 0.05.

Results

The study sample consisted of 870 cases and 870 controls (Table 1). Most patients with incident thyroid dysfunction developed hypothyroidism (84%). Given the rarity of hyperthyroidism in our sample, we were not able to further characterize this subpopulation. There was a significantly higher risk of incident hypothyroidism after ICM exposure (OR 2.60; 95% CI, 1.43–4.72; $P < .01$). The median (interquartile range) time between ICM administration and incident hypothyroidism was 10.8 (6.6–17.9) months. Among hypothyroid cases exposed to ICM with an available serum TSH, the median serum TSH concentration was 6.5 mIU/L (interquartile range, 5.8–9.6; range, 4.8–43.3 mIU/L) (Figure 1).

The most common sources of ICM exposure were computed tomography scans of the abdomen and/or pelvis

Table 1. Patient Demographics

Characteristics	Total Cases (n = 870)	Hypothyroid Cases (n = 728)	Controls (n = 870)
Female, number (%)	556 (63.9)	453 (62.2)	556 (63.9)
Race, number (%) White	439 (50.5)	376 (51.7)	439 (50.5)
Exposure rate, number (%)	53 (6)	39 (5)	16 (2)
Average age at exposure, mean (SD), y	8.4 (6.1)	8.2 (5.8)	7.3 (7.3)

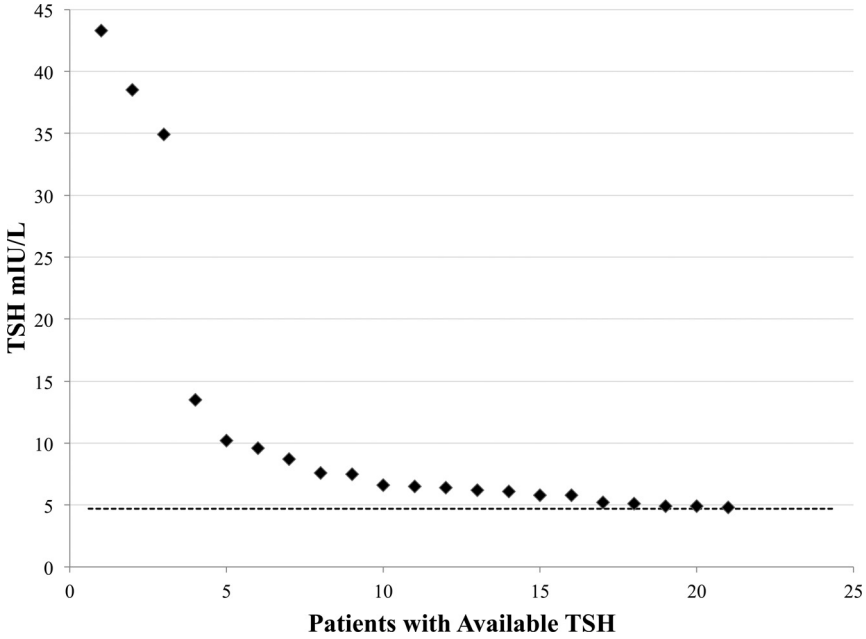

Figure 1. Serum TSH concentrations in hypothyroid cases with available TSH. Each plotted point represents 1 hypothyroid case with available TSH (n = 21). Normal TSH range was defined as 0.3–4.7 mIU/L (upper limit defined by dotted line, y = 4.7).

with iv contrast, followed by computed tomography scans of the chest and urethocystograms (Figure 2).

Discussion

This case-control study of pediatric subjects aged less than 18 years old from a single tertiary care center demonstrated a significantly higher risk of incident hypothyroidism within a median (interquartile range) of 10.8 (6.6–17.9) months after exposure to ICM. To our knowledge, this is the largest study to date examining the risks of thyroid dysfunction associated with iodinated contrast exposure in an exclusively pediatric patient population.

The physiologic basis for decreased thyroid dysfunction after excess iodine exposure is known as the acute Wolff-Chaikoff effect, in which the thyroid gland responds to excess iodine by a temporary reduction of thyroid hormone production, perhaps through the formation of inhibitory substances that include iodolactones and iodoaldehydes (4, 12). Failure to escape from acute Wolff-Chaikoff effect, which usually occurs within 24–48 hours after the excess iodine load, can result in transient or potentially permanent hypothyroidism (4, 5, 13). Separately, iodine-induced hyperthyroidism can occur after excess iodine exposure through a mechanism known as the Jod-Basedow phenomenon. Both iodine-induced hypothyroidism and iodine-induced hyperthyroidism typically occur in susceptible individuals with underlying thyroid disease, but iodine-induced thyroid dysfunction can also occur in individuals without preexisting thyroid conditions (5, 13).

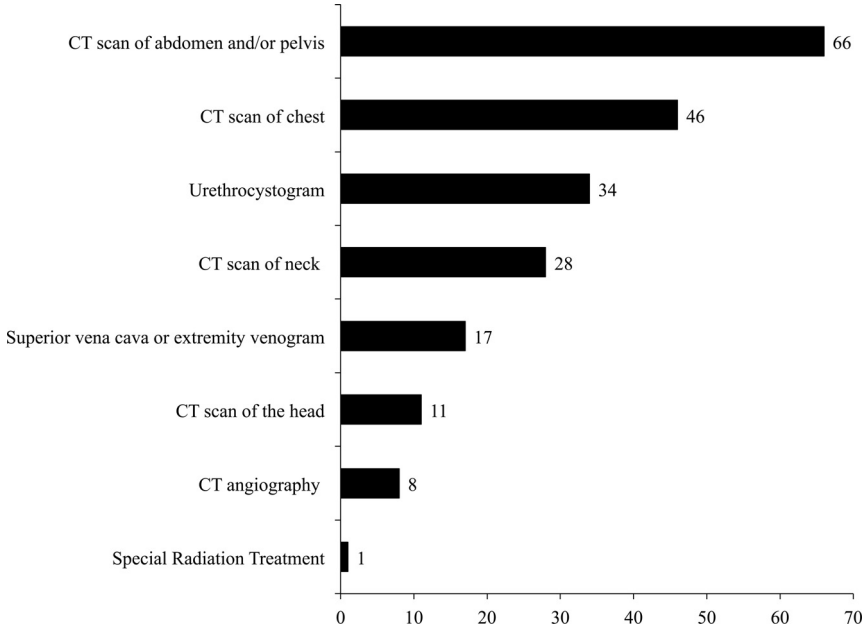

Figure 2. Frequency of cumulative exposures. Plot represents all procedures from the date of ICM exposure to the date of diagnosis. Patient may be in each category once, but may also be in multiple categories.

Previous studies have investigated the potential for the development of thyroid dysfunction after ICM exposure (2, 8, 9, 11, 14). In a large case-control study of Boston-area adult patients, Rhee et al (2) reported that ICM exposure was associated with incident hyperthyroidism (OR 1.98; 95% CI, 1.08–3.60, including overt hyperthyroidism: OR 2.50; 95% CI, 1.06–5.93) and incident overt hypothyroidism (OR 3.05; 95% CI, 1.07–8.72). In Taiwan, Kornelius et al (11) reported a significantly higher risk of thyroid dysfunction after ICM exposure (hazard ratio 1.46; 95% CI, 1.29–1.66) among 1 million patients in the general population over a single year time period. Pediatric pa-

tients (defined as <20 y old) in this cohort were used as the reference group and were thus unable to be assessed for risk of thyroid dysfunction after ICM exposure.

Normal thyroid function is crucial for proper neurodevelopment that begins in early gestation and continues into early childhood (15). Consequences of hypothyroidism during early life may include irreversible impairments in motor, hearing, and cognitive development (16), especially in the first 36–40 months of life during which myelination is still incomplete (17). The impact of subclinical hypothyroidism on neurological development, however, remains poorly understood, especially in children less than 3 years old (18).

Among pediatric patients, much of the current literature reports the risks of thyroid dysfunction after ICM exposure in only preterm and full-term neonates, rather than in the general pediatric population, and uses only small observational cohorts or case reports. Linder et al (10) reported elevated serum TSH concentrations in 6 of 21 (29%) full-term infants who underwent cardiac catheterization or cardiac surgery, procedures which both require the administration of iodinated coronary angiography. Similarly, a case report series regarding 3 neonates (age at diagnosis of hypothyroidism; range, 12–31 d) with congenital heart disease reported the development of hypothyroidism (serum TSH concentrations; range, 13.6–175 mIU/L) 9–13 days after cardiac angiography (9). Bona et al (19) examined the effect of iv iopamidol in 10 full-term infants. Compared with 20 controls, iopamidol use was not associated with serum thyroid dysfunction (19). A study by l'Allemand et al (20) examined the effects of different ICM agents in preterm and term neonates and reported cases of hypothyroidism in both groups, although the preterm neonates more often developed hypothyroidism (75% preterm infants vs 14% term infants receiving Omnipaque; 78% preterm infants vs 30% term infants receiving polyvinylpyrrolidone-iodine; 6% term infants receiving Amipaque). Recently, the United States Food and Drug Administration released an advisory notifying the public of the potential for thyroid dysfunction in infants after ICM administration (21).

Our results shed light on the risks of ICM exposure in a pediatric population during a critical period of growth that is highly dependent on normal thyroid function. Several limitations should be mentioned. As this was an observational study, normal thyroid function before ICM exposure could not be ascertained. However, in California, over 99% of newborns are screened for normal thyroid function within 6 days of birth as a part of the standard of care, in line with newborn screening procedures worldwide, thus excluding patients with congenital hypothyroidism (22, 23). One limitation to this screening is that the TSH cut-off used in screening may allow for capture of false negatives (24). Additionally, ill neonates may undergo ICM administration before congenital hypothyroidism screening, allowing for possible misclassification of baseline thyroid function. However, the routine clinical follow-up of children, obligated by immunization schedules and annual school physical examinations, enables assessment for clinical features suggestive of thyroid dysfunction, such as objective growth deceleration or acceleration, or other more subjective symptoms. In the context of normal thyroid function at birth and subsequent absence of clinical suspicion of thyroid dysfunction through normal development, the presumption is that our cohort of patients had normal thyroid function at baseline. However, it remains possible that our study inadvertently included patients with clinically unnoticed hypothyroidism before ICM exposure.

The present study includes patients who underwent voiding cystourethrography. Although the quantity of iodine delivered systemically during this type of study is less than that delivered in other types of radiographic studies, some degree of absorption does occur (25). Iodine is also absorbed across mucosal membranes (12, 26) and transdermally, particularly in infants (27), who have relatively greater body surface area. Because the indications for subjects' iodinated contrast radiological studies were not assessed, it is possible that the cases may carry a predisposition to thyroid dysfunction unrelated to ICM exposure, such as thyroid dysfunction related from nonthyroidal illness. Furthermore, our study did not examine the duration of thyroid dysfunction (ie, whether transient or persistent) among subjects or assess whether subjects received the rare occurrence of radioactive iodine treatment. An additional constraint on our study was the limited availability of thyroid function tests in hypothyroid cases. Finally, serum thyroid autoantibodies, which if positive heighten the risk of thyroid dysfunction, were available in only very few of the subjects in our study sample and could not be used for analysis.

Conclusions

This study reports the risks of thyroid dysfunction after iodinated contrast exposure in an exclusively pediatric United States patient population. Given the increasingly frequent application of contrast-enhanced radiography, our findings call attention to a potential cause of impaired development during an important period of early life. Future investigational work in this area may include assessment of the duration of thyroid dysfunction in pediatric subjects after ICM exposure, identification of comorbidities that predispose to thyroid dysfunction, and age strat-

ification to identify higher-risk subgroups. Our findings suggest that children receiving ICM should be monitored for iodine-induced thyroid dysfunction, particularly during the first year after exposure.

Acknowledgments

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