Original Article

Prevalence of Thyroid Uptake in Diagnostic I-131 MIBG Scintigraphy in Children

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Background: I-123 or I-131 labeled metaiodobenzylguanidine (MIBG) scintigraphy is an important imaging modality for evaluating childhood neural crest tumors such as neuroblastoma. Protection of the thyroid from radiation from free radioactive iodine by premedication with stable iodine is essential but thyroid uptake has still been reported in a considerable proportion of patients undergoing diagnostic I-123 MIBG and post-therapeutic I-131 MIBG scintigraphy. Reports in diagnostic I-131 MIBG scintigraphy are few.

Objective: To determine prevalence of thyroid dysfunction and factors associated with thyroid uptake in patients who underwent diagnostic I-131 MIBG scintigraphy.

Materials and Methods: Diagnostic I-131 MIBG scintigrams were reviewed for presence or absence of thyroid uptake. Factors potentially affecting thyroid uptake including age, weight, height, and history of prior thyroid uptake were investigated.

Results: Thyroid uptake was found in 23.6% of 161 I-131 MIBG scintigrams from 55 patients and was associated with older age (uptake 8.5±7.0 years, no uptake 5.4±3.3 years, p=0.007), and greater body weight (uptake 23.5±12.6 kg, no uptake 18.4±9.0 kg, p=0.014). Prior thyroid uptake increased odds of having thyroid uptake (OR 5.37, 95% CI 2.11 to 13.69, p<0.001). Five of nine patients who received thyroid function testing had subclinical hypothyroidism, which did not seem to relate to thyroid uptake. Overt hypothyroidism was not found.

Conclusion: Thyroid uptake was found in 23.6% of diagnostic I-131 MIBG scintigrams. Scintigrams with thyroid uptake are of patients who were older and had greater body weight. Odds of having thyroid uptake were increased if prior thyroid uptake was present. Subclinical hypothyroidism was found but did not seem to relate to thyroid uptake.

Keywords: Diagnostic I-131 MIBG scintigraphy, Hypothyroidism, Metaiodobenzylguanidine scintigraphy, MIBG scintigraphy, Thyroid diseases

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Metaiodobenzylguanidine (MIBG) is an analogue of norepinephrine (NE) and can be taken up into cells via the NE transporter. MIBG labeled with radioactive isotopes of iodine has long been used in diagnostic and therapeutic nuclear medicine[1]. I-123 MIBG, due to the favorable gamma energy of 159 keV from I-123, results in good quality scintigraphic images and is used for diagnostic purposes mostly in patients with neuroendocrine tumors of neural crest origin, which are important pediatric cancers, as well as applications in cardiology and neurology. I-131 MIBG can be used as a systemic treatment of neural crest tumors due to emission of beta particles from I-131. However, I-131 also emits 364 keV gamma photons that can be used for imaging, but the quality of the scintigraphic image is poorer. Although I-123 MIBG is the preferred radiopharmaceutical for imaging, I-123 is a cyclotron produced radioisotope, is costly, and may not be available in some regions. Approximately 5% of radioactive iodine is unbound from MIBG and an additional 3% is dissociated after administration[2]. This free radioactive iodine is taken up by and imparts radiation to the thyroid gland. For this reason, protection of the thyroid gland from unnecessary radiation exposure is a routine part of patient preparation before administration of

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both I-123 and I-131 MIBG. Thyroid uptake of free radioiodine can be prevented by premedication with stable iodine such as potassium iodide or Lugol's solution before MIBG administration[3]. However, despite premedication with thyroid blocking agents, thyroid uptake has been reported in 21%[4] to 28%[5] of patients receiving I-131 MIBG therapy. A study in patients who underwent diagnostic I-123 MIBG scintigraphy also reported thyroid uptake in patients who did and did not receive thyroid blockade, although uptake was more pronounced in those who did not[6]. Regarding effect on thyroid function, previous studies have determined that thyroid dysfunction occurs in approximately 30%[7] to 80%[5] of patients who received I-131 MIBG therapy. However, studies of I-131 MIBG scintigraphy in these regards are few. Therefore, the primary objective of the present study was to determine the prevalence of thyroid uptake in patients who underwent diagnostic I-131 MIBG scintigraphy. The secondary objectives were to determine factors related with thyroid uptake, and to determine the prevalence of thyroid dysfunction in patients who underwent diagnostic I-131 MIBG scintigraphy.

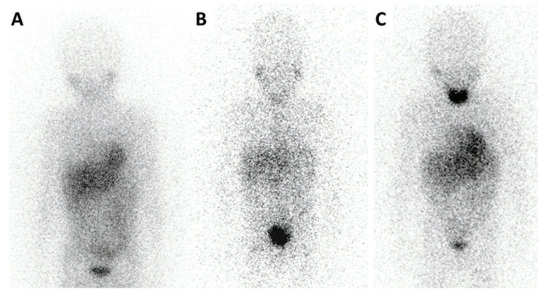

Figure 1. Grading of degree thyroid uptake in I-131 MIBG scintigraphy. (A) No uptake in the thyroid beyond soft tissue background; (B) Faint thyroid uptake beyond soft tissue background but not more intense than liver activity; (C) Intense thyroid uptake more intense than liver activity.

Materials and Methods

Patients

The present retrospective cross-sectional study was approved by the Khon Kaen University Ethics Committee for Human Research (Reference number: HE611086) and requirement for informed consent was waived. Using Cochran's sample size calculation method, and expected prevalence of thyroid uptake of 28% as previously reported[5], the sample size needed to yield an estimate within 95% confidence and 10% precision is 78 cases. However, since this is a retrospective medical record review, the authors decided to include all available cases in order to maximize the precision of the estimate. Patients who underwent I-131 MIBG scintigraphy at the Division of Nuclear Medicine, Department of Radiology, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University between June 1, 2013 and December 31, 2017 were included. Clinical data including age, sex, body weight, height, type of neuroendocrine tumor, and serum thyroid function test were obtained from the patient database of the study center.

I-131 MIBG scintigraphy

At the study center, all patients received thyroid blockade before I-131 MIBG scintigraphy. Patients were instructed to take one drop of 5% Lugol's solution per 5 kilograms of body weight per day with a maximum dose of three drops per day, mixed with water or juice, starting three days prior to I-131 MIBG administration and continued for seven days after. Medications that could interfere with MIBG uptake were discontinued as per recommendation[3]. The dose of I-131 MIBG was calculated based on the patient's body weight with a range of 20 to 80 MBq. I-131 MIBG was intravenously injected slowly over five minutes. Anterior and posterior whole body planar scintigraphic images were acquired using Discovery NM/CT 670 (GE Healthcare, IL, USA) equipped with high energy parallel hole collimator, with an energy peak set at 364 keV ±10%, 256×256 imaging matrix, using continuous acquisition mode with detector speed of 4 centimeters per minute. Images were acquired at 24, 48, and optionally, 72 hours after radiotracer administration.

Interpretation of thyroid uptake in I-131 MIBG images

Planar images were displayed on a standard radiographic display monitor. Thyroid uptake was qualitatively assessed by an experienced nuclear medicine physician and classified as "no uptake" i.e., images with no discernible thyroid radiotracer activity beyond neck soft tissue background activity, "faint uptake" i.e., images with radiotracer activity in the thyroid gland more intense than the neck soft tissue background but not more than liver activity, or "intense uptake" i.e., images with radiotracer activity in the thyroid gland more intense than that of the liver, as shown in Figure 1.

Statistical analysis

Patient characteristics, results of I-131 MIBG

Table 1. Characteristics of 55 patients

Characteristics	n (%)
Age at diagnosis (years)	
Mean±SD	4.9±4.5
Median (range)	3.9 (0.2 to 21.7)
Sex	
Male	27 (49.1)
Female	28 (50.9)
Histology	
Neuroblastoma	46 (83.6)
Ganglioneuroblastoma	5 (9.1)
Ganglioneuroma	3 (5.5)
Undifferentiated neural crest tumor	1 (1.8)
INSS staging	
Stage 2	3 (5.5)
Stage 3	5 (9.1)
Stage 4	45 (81.8)
Stage 4s	2 (3.6)
Number of I-131 MIBG studies	
Mean±SD	2.9±2.4
Median (range)	2 (1 to 11)

SD=standard deviation; INSS=International Neuroblastoma Staging System; MIBG=metaiodobenzylguanidine

scintigraphy, and serum thyroid function test were summarized using mean, standard deviation, and percentage. Welch's t-test was used to test the difference of continuous variables. Univariate logistic regression was used to test the difference of categorical variables between I-131 MIBG scintigraphy studies without and with thyroid uptake. Statistical analysis was carried out using Stata version 10 (StataCorp, LLC, TX, USA). A p-value smaller than 0.05 indicated statistical significance. Accompanying 95% confidence intervals (95% CI) were reported where appropriate.

Results

Patients

Between June 1, 2013 and December 31, 2017, 161 diagnostic I-131 MIBG scintigraphy studies were done in 55 patients, 26 patients underwent a single study and 29 patients underwent multiple, ranging from 2 to 11 studies. The cohort consisted of almost equal numbers of males and females and the average age was 4.9±4.5 years. Four patients were older than 15 years of age at the time of diagnosis. All patients had neural crest tumors with neuroblastoma being the most prevalent. Disease stage was mostly advanced with the majority having stage 4 disease. Patient characteristics are described in Table 1.

Thyroid uptake in I-131 MIBG scintigraphy

Among the 161 I-131 MIBG scintigraphy studies, 123 (76.4%) had no thyroid uptake, 30 (18.6%) had faint thyroid uptake, and 8 (5.0%) had intense thyroid uptake. Scintigraphic studies were regrouped into two groups, the first group being studies with no thyroid uptake (n = 123), the second group consisted of studies with either faint or intense thyroid uptake (n = 38). Table 2 provides comparison of age, weight, and height between the two groups. Images with thyroid uptake were from patients who, at the time of imaging, were significantly older (age 8.5±7.0 years versus 5.4±3.3 years, p=0.007), and had greater body weight (weight 23.5±12.6 kg versus 18.4±9.0 kg, p=0.014). To assess whether thyroid uptake on a previous MIBG scintigraphy increased the odds of having a positive thyroid uptake in a present scan, 26 studies from patients who received a single study and 29 studies, which were first studies of patients who received multiple studies, were excluded. The remaining 106 studies were categorized into studies with a history previous thyroid uptake and studies without, as detailed in Table 3. Univariate logistic regression determined that presence of thyroid uptake in a previous I-131 MIBG study increased the odds of uptake in the present I-131 MIBG study with an odds ratio of 5.37 (95% CI 2.11 to 13.69, p<0.001).

Thyroid function testing

Among 55 patients, nine patients received serum thyroid function testing at some point during the course of treatment and follow-up. Details of these patients are described in Table 4. Of the nine patients, four had normal thyroid function, and five had subclinical hypothyroidism with mildly elevated thyroid stimulating hormone (TSH) level. One patient with subclinical hypothyroidism was prescribed low dose of levothyroxine replacement due to elevated TSH levels on multiple occasions. Overt hypothyroidism with markedly elevated TSH and decreased thyroid hormone levels was not identified in the present cohort.

Discussion

In the present study, the authors aimed to determine the prevalence of thyroid uptake in patients that underwent diagnostic I-131 MIBG scintigraphy. To the authors' best knowledge, the present report is one of the first large study to be published to investigate thyroid uptake in diagnostic I-131 MIBG scintigraphy. Although I-123 MIBG is preferred over I-131 MIBG for diagnostic imaging, the cost of production of I-123

Table 2. Comparison of age, weight, and height between diagnostic I-131 MIBG scintigraphy studies without and with thyroid uptake

Characteristic*	Without thyroid uptake (n = 123, 76.4%)			With thyroid uptake (n = 38, 23.6%)			p-value**
	Mean	SD	95% CI	Mean	SD	95% CI	
Age (years)	5.4	3.3	4.8 to 6.0	8.5	7.0	6.1 to 10.8	0.007
Weight (kg)	18.4	9.0	16.8 to 20.0	23.5	12.6	19.2 to 27.8	0.014
Height (cm)	106.8	22.0	102.7 to 110.8	118.3	29.0	108.6 to 128.0	0.057

SD=standard deviation; CI=confidence interval

* Age, weight, and height at the time of diagnostic I-131 MIBG scintigraphy

** Welchs's t-test was used instead of regular two-sample t-test to account for the unequal sample size and variance between the two groups

Table 3. Effect of history of thyroid uptake on previous diagnostic I-131 MIBG scintigraphy

Thyroid uptake	No history or previous uptake	History of previous uptake	Total	OR	95% CI	p-value
Without thyroid uptake	60	19	79	5.37	2.11 to 13.69	<0.001
With thyroid uptake	10	17	27			

OR=odds ratio; CI=confidence interval

Table 4. Details of patients with thyroid function test results

Patient	Age* (years)	Sex	Thyroid function status	TSH level# (mIU/dL)	Number of prior scans	Number of prior scans with thyroid uptake	Intensity of thyroid uptake
1	4.3	F	Euthyroid	4.09	2	0	-
2	7.0	M	Euthyroid	3.56	7	0	-
3	15.8	M	Euthyroid	2.44	4	2	1 faint, 1 intense
4	22.1	F	Euthyroid	1.21	6	6	5 faints, 1 intense
5	3.0	F	Subclinical hypothyroidism	7.39	2	1	1 faint
6	6.3	M	Subclinical hypothyroidism	5.89	5	0	-
7	7.4	M	Subclinical hypothyroidism	6.9	4	2	2 faints
8	8.8	F	Subclinical hypothyroidism	4.57	5	0	-
9†	5.2	M	Subclinical hypothyroidism	9.56	3	1	1 faint

TSH=thyroid stimulating hormone; F=female; M=male

* Age at time of thyroid function test

In case of multiple blood tests, the highest value was selected. Only TSH levels are presented here; accompanying thyroid hormone levels were within normal range for all patients

† The 9th patient had subclinical hypothyroidism but received low dose oral levothyroxine replacement due to elevated TSH levels on multiple occasions

is high and may not be available in some centers, thus diagnostic I-131 MIBG scintigraphy is still a relevant imaging modality. The 55 patients in the present group were cancer patients with the majority being children with neuroblastoma, which is one of the most common childhood solid malignancies. The group, however, was not exclusively young children i.e., four patients were older than 15 years of age. The authors did not exclude these four patients by considering that these few cases would not confound the primary objective of the study. Thyroid uptakes were seen in 23.6% of 161 diagnostic I-131 MIBG scintigrams, which was similar to the reported rate of 28% in post-therapeutic I-131 MIBG scintigrams[5]. Previous studies have suggested that uptake in the thyroid may be due to a combination of uptake of free radioactive iodine by the thyroid follicular cells, and uptake of radioiodine labeled MIBG itself due to sympathetic innervation of the thyroid[6,8]. The present study found that patients with thyroid uptake in this cohort tended to be older and had greater body weight, which might indicate that the present study current regimen of thyroid blockade was not adequate in larger patients i.e., the maximum dose of three drops of 5% Lugol's solution per day may not be enough to saturate the thyroid gland of larger children, thus resulting in uptake of free radioiodine. However, some patients with thyroid uptake were small children and had uptake on multiple scans, which could indicate that uptake in the thyroid of these patients may be due to uptake of the I-131 MIBG molecule itself or could simply be due to poor compliance in taking the thyroid blocking agent. Interestingly, the current results suggest that a strong predictor of thyroid uptake on an I-131 MIBG scintigraphy is the presence of thyroid uptake in a previous study. Therefore, patients who show thyroid uptake in an I-131 MIBG scintigraphy should be carefully prepared when planning future studies. Dosage of thyroid blocking medication may need to be increased if the previous dose was suboptimal, especially in older children. Compliance to the thyroid blocking agent should always be advised to the patient and caregiver. Regarding effect on thyroid function in patients who underwent diagnostic I-131 MIBG imaging, unfortunately, only a small proportion of the current cohort underwent serum thyroid function testing. Even so, subclinical hypothyroidism was found in five out of nine patients tested. Thyroid dysfunction does not seem to correlate with thyroid uptake on I-131 MIBG scintigraphy since subclinical hypothyroidism was found both in patients who did and did not have thyroid uptake. Conversely, one patient with thyroid uptake in all six I-131 MIBG studies had normal thyroid function. This finding concurred with a previous study in patients who received I-131 MIBG therapy and found no relation between thyroid dysfunction and the presence of thyroid uptake seen in post-therapeutic I-131 MIBG scintigraphy[7]. However, another study found the contrary where thyroid dysfunction in patients who received repeated I-131 MIBG therapy did indeed correlate with thyroid uptake[9]. However, the current study was done in patients who underwent diagnostic I-131 MIBG scintigraphy with much lower radiation dose than what is used in therapeutic I-131 MIBG, so correlating the present findings to previous studies done in therapeutic I-131 MIBG may not be appropriate. A previous study compared biodistribution of I-131 MIBG between diagnostic and post-therapeutic scans and found that thyroid uptake was more frequently found in post-therapeutic images than in diagnostic images[10].

A limitation of the present study was that only nine out of 55 patients had their thyroid function tested and results showed that thyroid dysfunction developed without any pattern. Due to the descriptive and retrospective nature of the present study, no conclusion can be drawn regarding the effect of diagnostic I-131 MIBG imaging and resulting thyroid uptake on thyroid dysfunction. Despite this, the observation that more than half of the patients tested had some degree of thyroid dysfunction should raise awareness of the importance of thyroid function screening in patients who underwent diagnostic I-131 MIBG scintigraphy. Care should also be taken to ensure proper and adequate thyroid blockade prior to diagnostic I-131 MIBG scintigraphy to prevent any unnecessary radiation burden on the thyroid gland with focus on older children and those who have a history of thyroid uptake on prior diagnostic I-131 MIBG scintigraphy. Regarding implications on future clinical practice of how to further prevent the thyroid uptake of the radioisotope, as discussed, attention should be paid on patients who has history of thyroid uptake and larger patients. In these patients, increase of stable iodine dose should be considered as well as ensuring patient compliance.

Conclusion

Thyroid uptake was found in 23.6% of diagnostic I-131 MIBG scintigraphy studies. Scintigrams with thyroid uptake are of patients who were older and had greater body weight which could indicate suboptimal dosing or poor compliance of thyroid blocking agent. Odds of having thyroid uptake in a present I-131 MIBG scintigraphy study increased if history of thyroid uptake in a prior study was present. Subclinical hypothyroidism was found in five out of nine patients who had thyroid function testing, a finding that should raise awareness of the need for thyroid function screening in patients underwent diagnostic I-131 MIBG scintigraphy.

What is already known on this topic?

Thyroid uptake activity has been reported in pediatric patients that underwent diagnostic I-123 MIBG scintigraphy and post-therapeutic I-131 MIBG scintigraphy. However, there are no reports regarding the prevalence of thyroid uptake in diagnostic I-131 MIBG scintigraphy.

What this study adds?

Thyroid uptake was found in 23.6% of diagnostic I-131 MIBG scintigraphy studies, a proportion similar to that reported in diagnostic I-123 MIBG scintigraphy and post-therapeutic I-131 MIBG scintigraphy.

Thyroid uptake was found more likely in larger children and in those who had uptake in prior studies.

Conflicts of interest

The authors declare no conflict of interest.

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