Specificity of Radioiodinated MIBG for Neural Crest Tumors in Childhood

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The high sensitivity of metaiodobenzylguanidine (MIBG) scintigraphy for sympathomedullary tumors such as neuroblastoma and pheochromocytoma is well documented. The specificity of MIBG scintigraphy for these tumors is also high but has been incompletely characterized for other neural crest tumors and non-neural crest tumors of childhood. **Methods:** The medical records and MIBG scans of all children who had undergone MIBG scintigraphy for known or suspected neuroblastoma or pheochromocytoma were retrospectively reviewed at five major referral centers. Those patients found to have pathologies other than neuroblastoma or pheochromocytoma form the basis of this study. **Results:** One hundred children with a total of 110 lesions met the inclusion criteria. All had negative MIBG scans except 1 of 2 children with infantile myofibromatosis, 1 of 2 with neuroendocrine carcinomas, 1 of 2 with pancreaticoblastomas and 1 of 10 with primitive neuroectodermal tumors. **Conclusion:** MIBG scintigraphy is highly specific for neuroblastoma and pheochromocytoma. Only 4% (4/100) of nonsympathomedullary tumors (non-pheochromocytoma and non-neuroblastoma) in childhood showed MIBG uptake, of which only 2% (2/100) were of non-neural crest origin.

Key Words: metaiodobenzylguanidine; childhood tumors; neural crest tumors; specificity

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The diagnostic and therapeutic value of metaiodobenzylguanidine (MIBG) scintigraphy in neuroblastoma and pheochromocytoma is based on its high sensitivity and specificity (*1–7*). Neuroblastoma is the most common extracranial childhood solid tumor, whereas childhood pheochromocytoma is rare (*3,5,6*). The clinical context of suspected neuroblastoma and pheochromocytoma are seldom confused. MIBG scintigraphy has a reported specificity of approximately 95% for neuroblastoma (*1–10*). Most of these data, however, were derived from patients with an established neuroblastoma diagnosis (i.e., the specificity reflects whether or not the MIBG scan truly reflects the presence of disease in an individual with known neuroblastoma either at diagnosis or after therapy). Furthermore, there are very few studies of MIBG scintigraphy performed on non-neuroendocrine childhood tumors and even fewer reports of these tumors demonstrating MIBG accumulation. It is thus important to examine this other aspect of specificity, as to whether childhood tumors other than neuroblastoma and pheochromocytoma concentrate MIBG. Thus, whereas it is well documented that MIBG may accumulate in neuroendocrine (neural crest) tumors, other than neuroblastoma and pheochromocytoma, the frequency with which this occurs is much less well defined (*2,4,5,8,11–13*). The purpose of this study was to retrospectively review a large multicenter experience with MIBG scintigraphy in the investigation of childhood mass lesions and to determine whether non-neuroblastoma and non-pheochromocytoma neural crest tumors and non-neural crest tumors concentrate MIBG, to better characterize the specificity of MIBG scintigraphy for these lesions in the pediatric population.

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MATERIALS AND METHODS

The medical records and MIBG scans of pediatric patients who underwent MIBG scanning for proven or suspected neuroblastoma or pheochromocytoma at the five participating institutions were retrospectively reviewed for demographic data, anatomic site of the presenting lesion, result of MIBG scintigraphy and final diagnosis. Diagnosis was confirmed by either surgical resection or biopsy with histological confirmation (including electron microscopy and immunohistochemistry in selected cases) in almost every case (>95%). The patients who were eventually found to have tumors or non-neoplastic pathologies other than neuroblastoma or pheochromocytoma form the basis of this study. Some of their demographic data is presented in Tables 1 and 2.

MIBG scintigraphy was performed as previously described (*1–5*). A variety of large field-of-view single- or double-headed gamma cameras were used with high energy, parallel hole collimators and a 20% energy window centered at 364 keV for ^{131}I-MIBG imaging and low energy, high resolution or general purpose collimators and 20% energy window centered at 159 keV for ^{123}I-MIBG imaging. Dosing schemes were as follows: University of Michigan dose was adjusted to body surface area, 0.5 mCi/1.73 m^2 for ^{131}I-MIBG and 10 mCi/1.73 m^2 for ^{123}I-MIBG; Institute Gustave Roussy dose was adjusted for body weight, 0.1 mCi/kg ^{123}I-MIBG; Netherlands Cancer Institute fixed doses of 0.5 mCi ^{131}I-MIBG or 5 mCi ^{123}I-MIBG; Universitá Cattolica Rome dose was adjusted by body weight, 0.14 mCi/kg (maximum 5 mCi) ^{123}I-MIBG and 0.037 mCi/kg (maximum 1 mCi)^{131}I-MIGB; University of California, San Francisco dose of ^{131}I-MIBG was 0.14 mCi/kg. Acquisition parameters were as follows: University of Michigan ^{123}I-MIBG imaging, multiple overlapping spot views of 10 min (or 250 K counts) ^{131}I-MIBG imaging, multiple overlapping spot views of 20 min (or 100 K counts); Institute Gustave Roussy ^{123}I-MIBG imaging, multiple overlapping spot views of 20 min/image (150–500 K counts); Netherlands Cancer Institute ^{131}I-MIBG imaging, multiple overlapping spot views of 10 min, ^{123}I-MIBG imaging, multiple overlapping views of 5 min or whole body images scanned at 6 cm/min in a 512 × 512 matrix; University of California, San Francisco multiple overlapping spot views of 12 min each (250–500 K counts) or whole body scans at

TABLE 1
Patient Data

	University of Michigan, Ann Arbor	Institut Gustave Roussy, Villejuif	Universita' Cattolica, Rome	Netherlands Cancer Institute, Amsterdam	University of California, San Francisco	Totals
Age						
Mean	5.7 yr	5.0 yr	8.4 yr	5.2 yr	8.7 yr	6.1 yr
Range	10 d–17 yr	1 mo–16 yr	2.5 yr–17 yr	8 mo–16 yr	8 mo–18 yr	10 d–18 yr
Sex ratio (male/female)	9/13	19/20	7/4	9/10	8/1	52/48
No. of patients	22	39	11	19	9	100
No. of ^{131}I-MIBG studies	13	0	7	18	9	47
No. of ^{123}I-MIBG studies	9	39	4	1	0	53
Total of pediatric MIBG studies	484	2000	134	178	139	2935

24 cm/min (500–1000 K counts); Universitá Cattolica Rome ^{123}I-MIBG imaging, multiple overlapping spot views of 10 min (128 × 128 matrix), whole body acquisitions scanned at 15 cm/min (512 × 128 matrix), ^{131}I-MIBG imaging, multiple overlapping spot views of 10 min (128 × 128 matrix).

RESULTS

There were a total of 100 patients (48 girls, 52 boys) with an age range of 10 days to 18 yr (mean 6.1 yr). The sites of the lesions that prompted MIBG scintigraphy were head and neck in 31 patients, thoracic in 27, abdominal in 41, pelvic in 7 and limbs in 4 (the total exceeds the number of patients because some patients had more than one lesion).

The final pathological diagnoses and results of MIBG scintigraphy are presented in Table 3. Only 4 of the 100 patients demonstrated lesions that accumulated MIBG, including a case of infantile myofibromatosis, which has been previously reported (*14*). The MIBG study in the patient with infantile myofibromatosis demonstrated activity in the tumor in the early 24 hr images, but this became less apparent on the 48 hr images. Figures 1–3 show examples of negative MIBG scans in patients with primitive neuroectodermal tumors (PNET), an inflammatory lesion, and bilateral Wilms' tumors. One of two cases of neuroendocrine carcinomas, 1 of 2 pancreaticoblastomas (Fig. 4) and 1 of 10 with PNET showed MIBG uptake. In two patients previously cured of neuroblastomas, second malignancies occurred that were negative for MIBG uptake (one undifferentiated sarcoma and bilateral Wilms' tumors).

DISCUSSION

MIBG is concentrated across the cell membrane of normal and neoplastic cells of neural crest origin by the so-called uptake-1 amine transport mechanism and then transported into and stored within intracytoplasmic hormone storage vesicles, if these are present (*15–21*). Therefore, it is not surprising that non-neuroendocrine tumors that lack these concentration mechanisms typically do not accumulate MIBG. The mechanism of localization in non-neuroendocrine tumors is not clear. Postulated mechanisms include accumulation as a result of high tumor dependent blood flow and nonspecific diffusional uptake (*13,17,22*). The latter appears to be a major contributor to the nonspecific background observed on MIBG scintigraphy, and that tends to clear more rapidly than specific uptake (*2,3*).

The utility of radioiodine-labeled MIBG in the management of neuroblastoma is established. Its importance in staging and follow-up, to determine treatment response and recurrence detection, is well documented (*1–7,9*). More recently, the therapeutic potential of this radiopharmaceutical has been emphasized (*2,23–26*). The diagnostic and therapeutic value of MIBG in neuroblastoma is due to the combination of its high sensitivity and specificity for this tumor.

The reported specificity of MIBG scintigraphy for neuroblastoma and pheochromocytoma is more than 95% (*1–7,8–10,27*). The vast majority of the literature, however, concerns patients with an established diagnosis, i.e., whether or not the MIBG scan truly reflects the disease status in an individual known to have neuroblastoma or pheochromocytoma either currently or previously. This aspect of the specificity of MIBG has been relatively well explored (*2–7,9*). In these circumstances, specificity for neuroblastoma (or pheochromocytoma) is defined in the traditional way as (true negatives)/(true negatives + false positives) or as predictive value = (true positives)/(true positives + false positives) for the suspect diagnosis in question. The other facet of specificity relates to whether tumors other than neuroblastoma or pheochromocytoma and of different histological origins will concentrate MIBG, thereby reducing the specificity for neuroblastoma or pheochromocytoma. These cases would be classified as "false positives" but might better be termed as "wrong positives" in that the MIBG scintigraphy

TABLE 2
Regional Sites of Lesions Leading to MIBG Scintigraphy

	University of Michigan, Ann Arbor	Institut Gustave Roussy, Villejuif	Universita' Cattolica, Rome	Netherlands Cancer Institute, Amsterdam	University of California, San Francisco	Totals
Head and neck	8	10	4	8	1	31
Thorax	4	8	6	3	6	27
Abdomen	9	18	1	9	4	41
Pelvis	2	3	1	1	0	7
Limbs	1	1	1	0	1	4
Total lesion sites	24	40	13	21	12	110

Number of sites exceeds number of cases due to some having multiple lesions.

TABLE 3
Results of Metaiodobenzylguanidine Scintigraphy in Nonsympathomedullary Childhood Tumors

Type of neoplasm	Participating institutions: University of Michigan, Ann Arbor	Institut Gustave Roussy, Villejuif	Universita' Cattolica, Rome	Netherlands Cancer Institute, Amsterdam	University of California, San Francisco	Totals
I. Carcinomas						(1/24)
Wilms' tumor (nephroblastoma)	0/1	0/7	0/1	0/4	0/1	0/14
Pancreaticoblastoma	—	0/1	—	—	1/1	1/2
Germ cell tumor	—	—	0/1	—	—	0/1
Teratoma	0/1	0/1	—	—	—	0/2
Squamous carcinoma	0/1	—	—	—	—	0/1
Adenocarcinoma (unknown primary)	0/1	—	—	—	—	0/1
Adrenocortical carcinoma	—	0/3	—	—	—	0/3
II. Sarcomas						(0/15)
Ewing's sarcoma	—	—	0/3	—	—	0/3
Rhabdomyosarcoma	0/1	0/5	—	0/1	—	0/7
Undifferentiated sarcomas	0/1	0/3	—	—	0/1	0/5
III. Neural crest tumors						(2/38)
Astrogliosis	—	—	—	—	0/1	0/1
Glioma	—	0/2	0/1	0/1	—	0/4
Retinoblastoma	—	—	—	0/1	—	0/1
Medulloblastoma	—	—	0/1	—	—	0/1
Medulloepithelioma	0/1	—	—	—	—	0/1
Neurofibroma	0/1	0/2	—	—	—	0/3
Neurofibromatosis	—	0/1	—	0/3	—	0/4
Neuroepithelioma	—	0/2	—	—	—	0/2
Ependymoma	—	0/1	—	—	—	0/1
Esthesioneuroblastoma	—	0/1	—	0/1	—	0/2
Primitive neuroectodermal tumor (PNET)	0/5	—	0/3	—	1/2	1/10
Neuroendocrine carcinoma	—	0/1	—	1/1	—	1/2
Bronchial carcinoid	—	0/1	—	—	—	0/1
Medullary thyroid cancer	—	0/1	—	—	0/3	0/4
Neuroectodermal melanotic tumors	—	0/1	—	—	—	0/1
IV. Lymphomas						(0/8)
Burkitt's lymphoma	0/1	—	—	—	—	0/1
Hodgkin's disease	0/1	0/1	—	—	—	0/2
Large cell lymphoma	0/1	—	—	—	—	0/1
Lymphoblastic lymphoma	0/2	—	—	—	—	0/2
Non-Hodgkin's lymphoma	0/1	—	—	—	—	0/1
Poorly differentiated lymphomas	—	0/1	—	—	—	0/1
V. Other tumors						(1/7)
Melanoma	—	0/1	—	0/1	—	0/2
Angiomyelo proliferative tumor	—	—	—	0/1	—	0/1
Eosinophilic granuloma	—	—	—	0/1	—	0/1
Infantile myofibromatosis	1/1	0/1	—	—	—	1/2
Benign hemangioendothelioma	—	0/1	—	—	—	0/1
VI. Non-neoplastic lesions						(0/8)
Adrenal abscess (beta hemolytic streptococcus Group B)	0/1	—	—	—	—	0/1
Chronic inflammatory focus	—	—	0/1	—	—	0/1
Hemorrhagic cyst	—	—	—	0/2	—	0/2
Diaphragmatic herniation of liver	—	0/1	—	—	—	0/1
Foregut duplication cyst	0/1	—	—	—	—	0/1
Ovarian tortion	—	—	—	0/1	—	0/1
Vascular abnormality	—	—	—	0/1	—	0/1
TOTALS	1/22	0/39	0/11	1/19	2/9	4/100

does indeed locate a lesion but it is of nonsympathomedullary origin. The term "specificity," as used in this publication, thus relates to the degree to which nonsympathomedullary lesions do not take up MIBG. It is well documented that MIBG can accumulate in other neuroendocrine tumors (e.g., carcinoids, medullary thyroid cancer, Merkel cell tumors, islet cell tumors, carotid body tumors and nonsecreting paragangliomas) (*5,8,11,12,28,29*). The clinical context in which the scan is performed, however, rarely leads to a diagnostic dilemma between neuroblastoma and pheochromocytoma (*6,7,30*). Thus, all the childhood pheochromocytomas studied at the University of Michigan during this time period presented with obvious symptoms and signs of pheochromocytoma, and all were confirmed by measurement of catecholamines and their metabolites and by MIBG scintigraphy (*30*). Other neuroendocrine tumors such as carcinoid and medullary thyroid carcinoma may be MIBG avid, although less frequently than neuroblastoma and pheochromocytoma (*5,8,11,12*). Bomanji et al. (*28,31*) reported uptake of ^{123}I-MIBG in a case of ectopic intracranial retinoblastoma. However, none of the three patients with this tumor,

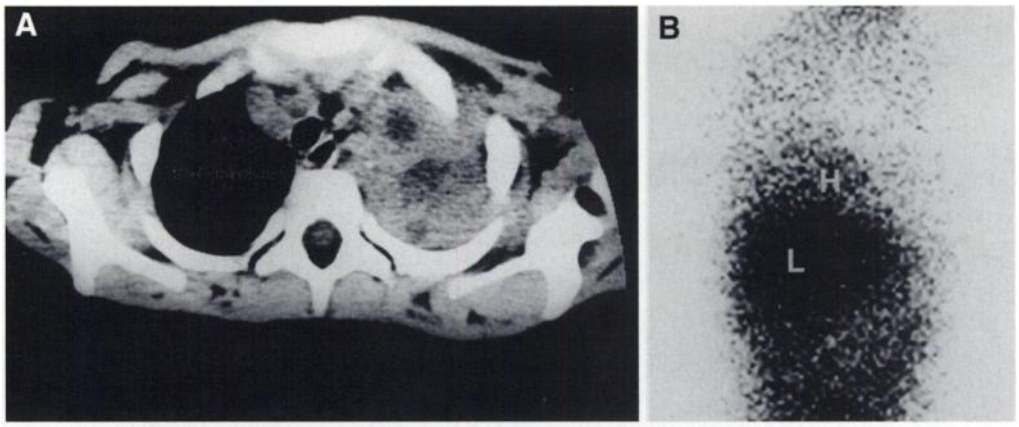

FIGURE 1. (A) Chest computed tomograph of a 5-yr-old boy with a large upper thoracic PNET lesion. (B) Anterior chest and abdomen ^{131}I-MIBG scintigram (10 min acquisition time; 128 × 128 matrix) at 24 hr after injection of 600 μCi shows no uptake in the PNET lesion depicted by computed tomography in A. L = liver uptake; H = heart uptake.

studied by Jacobs et al. (*10*), demonstrated concentration of MIBG. Whereas retinoblastomas are nonsecreting neuroendocrine tumors, the ability of some of these lesions to concentrate MIBG suggests they may manifest biogenic amine uptake and storage capacity. Indeed, two of four patients with MIBG-avid lesions, of the 100 patients studied in this series, were of neuroendocrine origin. An additional two of three ganglioneuromas and ganglioneuroblastomas (data not tabulated in Table 3), which are closely related to the neuroblastoma and pheochromocytoma family of sympathomedullary tumors also demonstrated MIBG uptake.

There are, however, very few studies of MIBG scintigraphy performed on non-neuroendocrine tumors and even fewer reports of such tumors demonstrating MIBG accumulation and causing a false-positive (or wrong positive) MIBG scan (Table 4). Hadley and Rabe first described MIBG scintigraphy in non-neuroendocrine tumors of children (*9*). They investigated two adrenocortical carcinomas and one each of rhabdomyosarcoma, lymphoma and an undifferentiated leukemia, none of which concentrated MIBG.

Schmiegelow et al. then studied 93 children, 25 of whom did not have neuroblastoma (*27*). Eighteen of these 25 children had various tumors, including 6 Wilms' tumors and one case each of malignant glioma, anaplastic brain tumor, Schwannoma, a nonclassified spinal tumor (possibly a chordoma), ovarian dysgerminoma, rhabdomyosarcoma, neurofibrosarcoma, carcinoid tumor, PNET, acute lymphoblastic leukemia, histiocytosis and hepatoblastoma. The only tumors that demonstrated focal MIBG accumulation were one of the Wilms' tumors and the spinal tumor. Of note is that none of the 14 Wilms' tumors in our series showed MIBG uptake. In a review of their experience with MIBG, Troncone et al. reported on eight tumors not originating from the neural crest (*4*). These included one each of anaplastic thyroid carcinoma, Ewing's sarcoma, nephroblastoma, rhinopharyngeal epithelioma, cervical sarcoma, pulmonary adenocarcinoma and two retroperitoneal sarcomas. None of these tumors demonstrated MIBG accumulation. Oberlin et al. examined 15 children with Ewing's sarcoma using ^{123}I-MIBG, and none demonstrated MIBG concentration either by the primary tumor or in metastases (*32*). Hoefnagel reported 34 patients with non-neural crest tumors, including nonsmall cell lung carcinoma, breast carcinoma, glioma, lymphoma, Wilms' tumor, rhabdomyosarcoma, soft tissue sarcoma, pancreatic carcinoma, adenocystic carcinoma, adrenocortical carcinoma and an undifferentiated carcinoma (*5*). The MIBG scans were all negative.

Because MIBG scintigraphy is generally performed only in individuals with proven neuroblastoma, when suspicion for neuroblastoma is high or in patients with another suspected neuroendocrine tumor such as pheochromocytoma, it is hardly surprising that there is very little documentation regarding MIBG scintigraphy in non-neuroendocrine tumors. In this retrospective analysis of the pediatric experience with MIBG at five major referral centers for these studies spanning nearly 10 yr, only 100 patients were found to have tumors or other non-neoplastic conditions when those with sympathomedullary tumors (neuroblastomas and pheochromocytomas) were excluded. The series was performed with a wide range of

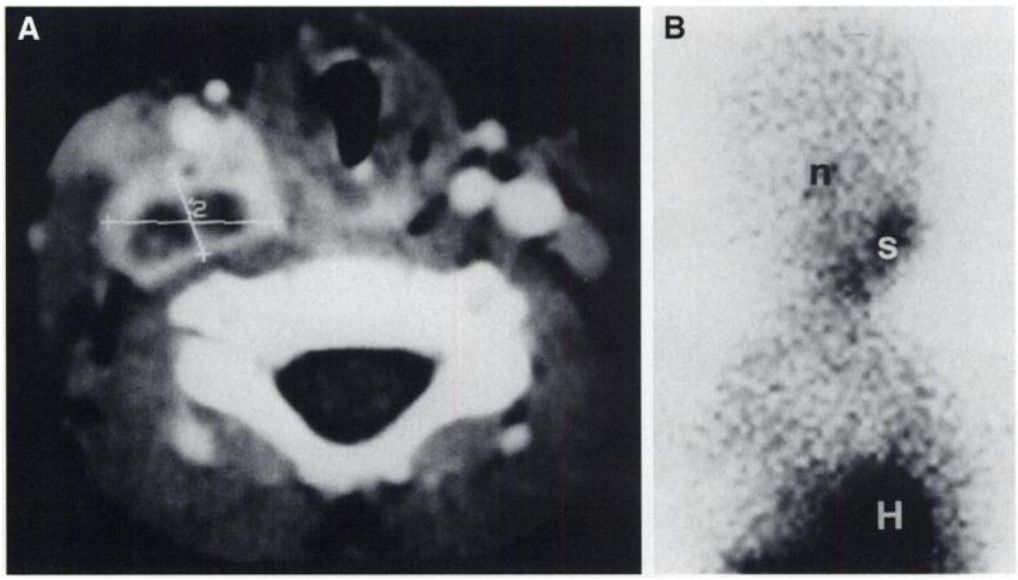

FIGURE 2. (A) Neck computed tomograph of an 8-mo-old boy depicts a centrally necrotic lesion that eventually proved to be an inflammatory focus. (B) Iodine-123-MIBG scintigram (10 min acquisition time; 128 × 128 matrix) of head, neck and chest 24 hr after injection of 1.5 mCi shows no uptake in the inflammatory lesion. Incidental note is made of absent tracer uptake in the right salivary glands, a phenomenon well described in Horner's syndrome. H = heart uptake; S = salivary gland uptake; n = nasopharyngeal uptake.

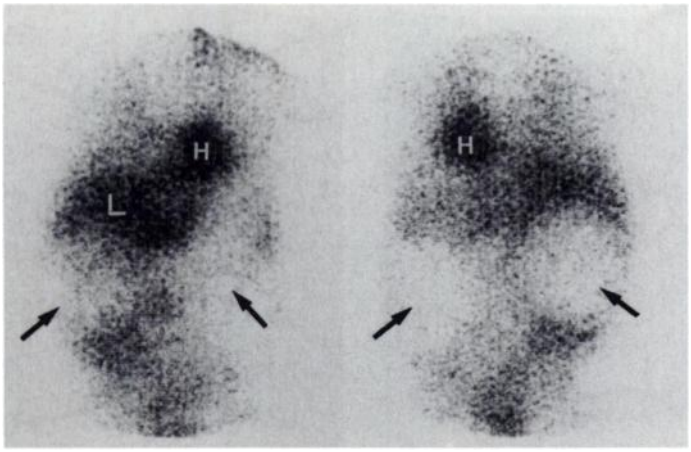

FIGURE 3. Anterior and posterior ^{131}I-MIBG scintigrams (10 min acquisition time) of chest and abdomen 24 hr after injection of 0.5 mCi shows absent tracer uptake in large bilateral Wilms' tumors (arrows). H = heart uptake; L = liver uptake.

TABLE 4
Reports of Positive MIBG Scintigraphy in Non-Neuroendocrine Lesions

Tumor	No. of cases	Authors	Ref.
Wilms' tumor	1	Schmiegelow et al.	27
Nephroblastoma with neural differentiation	1	Saint-Andre et al.	34
Caecal adenomatous polyp	1	Feggi et al.	33
Parathyroid adenoma	1	Hayward et al.	13
Renal artery stenosis	2	Schmiegelow et al.	27
		Horne et al.	22
Focal pyelonephritis	1	Jacobs et al.	36
Dilated renal pelvis	1	Bahar	37
Adrenal adenoma	1	Horne et al.	22
Hepatic hemangioma	1	Horne et al.	22
Infantile myofibromatosis	1	Stewart et al.	14
Choriocarcinoma	1	Von Moll et al.	8
Fibroma	1	Muino Miguez et al.	35

radiopharmaceutical doses and imaging protocols. None of the non-neural crest lesions demonstrated MIBG concentration except a single case of infantile myofibromatosis, which has been previously reported (*14*) and one of two pancreaticoblastomas.

An extensive search of the literature revealed only a few additional cases of MIBG accumulation in non-neural crest tumors (see Table 4). These include an adenomatous polyp of the caecum (*33*), an hepatic hemangioma and an adrenal adenoma (*22*), a nephroblastoma with neuronal differentiation (*34*), a fibroma (*35*) and a parathyroid adenoma (*13*). Many of these cases, however, occurred in adults. Other non-neoplastic conditions that have been reported to give rise to false-positive MIBG studies include renal artery stenosis (*22,27*), focal pyelonephritis (*36*) and a dilated renal pelvis (*37*). The latter is readily explained by the fact that the kidney is the primary route of MIBG excretion (*2,3,5,17*).

The imaging characteristics of ^{123}I-MIBG are superior to those of ^{131}I-MIBG and also permit SPECT. Where logistically and economically feasible ^{123}I-MIBG is probably the radiopharmaceutical of choice. It is possible that ^{123}I-MIBG may demonstrate subtle uptake that might be missed by ^{131}I-MIBG. Although the most strikingly positive lesion was the pancreaticoblastoma (Fig. 4) imaged with ^{123}I-MIBG, the previously described infantile myofibromatosis was documented with ^{131}I-MIBG (*14*).

Our results, together with the literature reviewed, indicate that MIBG is only rarely concentrated by non-neural crest tumors and that MIBG scintigraphy is useful in noninvasively establishing the diagnosis of neuroblastoma, pheochromocytoma and related tumors, in the appropriate clinical setting, with very high specificity. This contrasts with the radiolabeled somatostatin analogs (e.g., ^{111}In-diethylenetriaminepentaacetic acid-octreotide), which show high sensitivity for sympathomedullary and other neuroendocrine tumors but also depict many non-neuroendocrine tumors as well as autoimmune and inflammatory lesions (*5,38*).

In children presenting with a suspected neoplastic mass, the characterization of the tissue type may be critical to further management and prognosis (*5–7*). This may be especially problematic when histology reveals the tumor to be composed of small, round, blue cells. The differential diagnosis of such a histological picture is broad and includes neuroblastoma, Wilms' tumor, rhabdomyosarcoma, lymphoma, leukemia and PNET. Since neuroblastoma is the commonest extracranial solid childhood malignancy, it is often the initial diagnosis entertained (*2,5–7*). A related problem is that of the mass identified by anatomical imaging in a location where neuroblastoma is possible or probable but in which biopsy would be excessively invasive or in which knowledge of whether or not the tissue was of neural crest origin would alter further management (e.g., a fine needle biopsy versus an excisional biopsy at open surgery). MIBG scintigraphy with its high tissue specificity for neuroblastoma and pheochromocytoma can be

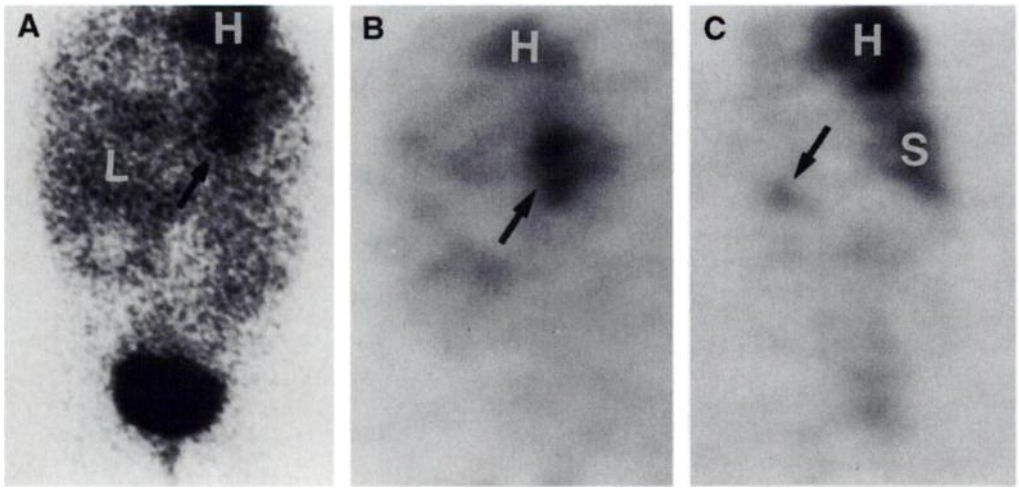

FIGURE 4. (A) Iodine-123-MIBG scintigram of thorax, abdomen and pelvis (12 min spot view of 200 K counts) 22 hr after injection of 5 mCi showing tracer uptake in a pancreaticoblastoma (arrow) in a 6-yr-old boy. L = liver uptake; H = heart uptake; B = bladder. SPECT images (360° acquisition over 30 min) in the same patient with pancreaticoblastoma (arrow) (B) coronal section, (C) sagittal section. H = heart uptake; S = spleen; tumor = arrow.

used as a diagnostic tool in this setting to provide noninvasive confirmation of the suspected diagnosis and exclude alternative diagnoses (e.g., lesions of non-neural crest origin) in a child presenting with a lesion of obscure histological origin. The procedure also appeared useful in two cases in which patients previously treated and cured of neuroblastoma presented with new mass lesions that subsequently proved to be new neoplasms of non-neural crest origin.

CONCLUSION

In a multicenter retrospective study of 100 nonsympathomedullary lesions in children, only four showed MIBG uptake, just two of which were of non-neural crest origin. This observation confirms that in children MIBG-avid lesions are almost certainly of sympathomedullary origin.

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