Iodine-123-Metaiodobenzylguanidine Scintigraphy in Patients with Chemodectomas of the Head and Neck Region

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While studying the uptake of iodine-123-metaiodobenzylguanidine ([^{123}I]MIBG) in chemodectomas, we coincidentally detected catecholamine secreting tumors in 5 out of 14 patients. In three of these cases, a norepinephrine secreting abdominal paraganglioma was subsequently removed. One patient had a norepinephrine secreting chemodectoma and one had a dopamine secreting chemodectoma. Prior to [^{123}I]MIBG imaging and urinary catecholamine measurements, endocrine activity was suspected in only one of these five patients. Apart from these five cases, two other patients showed elevated catecholamine secretion and abnormal abdominal [^{123}I] MIBG concentrations. However, these two patients were not surgically explored, because of normal computed tomography (CT) and magnetic resonance (MRI) studies. We suspect that catecholamine-secreting tumors are more common in patients with chemodectomas than is assumed in the literature, and we therefore recommend urinary catecholamine screening for all patients with chemodectomas. In case of elevated catecholamine secretion, MIBG scintigraphy is indicated.

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Chemodectomas, also known as glomus tumors, arise from paraganglionic tissue in the carotid body, the jugular fossa, the middle ear, and superior mediastinum. Chemodectomas are extremely rare and of unknown incidence (*1*). About 30% of the cases are familial in origin. The hereditary pattern of familial chemodectomas appears to be autosomal dominant (*1*). Multiple chemodectomas occur in ~25% to 35% of the patients with familial chemodectoma but in <5% of those with the non-familial type (*2*). Malignancy occurs in ~10% (*3*). Together with the aortico-sympathetic, visceral autonomic and intravagal paragangliomas and pheochromocytomas they form a class of tumors known as paragangliomas (*4–6*). Paraganglion cells are derived from the neural crest and migrate in close association with the autonomic ganglion cells. The common feature of these cells is the presence of numerous neurosecretory granules containing catecholamine in their cytoplasm. The highest concentration of these paraganglion cells is in the adrenal medulla, however they are also found in abundance along the aorta and great vessels (*7,8*).

Functioning paragangliomas may arise wherever paraganglion tissue exists but are called pheochromocytomas when they develop in the adrenal gland (*4*). The proportion of hormonally active paragangliomas is thought to be high for adrenal pheochromocytomas, intermediate for aortico-sympathetic and visceral-autonomic paragangliomas and low for chemodectomas (*9*). The percentage of hormonally active chemodectomas has been estimated to be ~1% (*10*). The association of head and neck chemodectomas with other paragangliomas (usually pheochromocytomas) as well as several other tumors (carcinoid, pituitary adenoma, thyroid carcinoma) derived from the neural crest has been reported (*2,9,11–18*), but these combinations are considered to be very rare (*16*).

The uptake of radioactive labeled metaiodobenzylguanidine (MIBG) has been demonstrated in pheochromocytomas (*19*) and neuroblastomas (*20*) as well as carcinoids (*21*), medullary carcinomas of the thyroid, and chemodectomas (*22–24*). The largest study on chemodectomas so far comprised five patients, imaged with [^{131}I]MIBG (*22*). We performed a [^{123}I]MIBG study in 15 patients with a total of 24 chemodectomas. Urinary catecholamines and vanillylmandelic acid (VMA) levels were measured for correlation with the findings of [^{123}I]MIBG imaging. Patients with elevated urinary catecholamine secretion and/or unexpected [^{123}I]MIBG concentrations outside the head and neck region underwent further investigations to detect the source of catecholamine production.

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METHODS

Between January and November 1988, 15 patients, ranging in age from 22 to 65 yr (mean age 45 yr) were referred for endocrinologic analysis and [^{123}I]MIBG scintigraphy by the Department of Otolaryngology. All patients gave informed consent. In the head and neck region of these patients, 24 chemodectomas were present: 11 jugular glomus tumors, 7 carotid body tumors, and 6 vagal body tumors. In this series, no tympanic glomus tumors were seen. Nine patients were followed because of incomplete tumor removal, attributable mainly to the technical limitations encountered in the safe excision of these tumors from the cranial base. Four patients were analyzed preoperatively and in two cases surgery was either not performed or not planned, for technical reasons. The patients exhibited the common presenting symptoms of the carotid and vagal body tumors, with a painless pulsating lateral cervical mass near the angle of the mandible. The glomus jugulare tumors gave rise to aural symptoms, such as conductive hearing loss, pulsating tinnitus, a discolored eardrum and sometimes cranial nerve palsy. In all 15 patients, the diagnosis of chemodectoma was based on these clinical symptoms and characteristic findings on angiograms, as described elsewhere (*3*). Except for Patient 10, histologic confirmation of the chemodectoma(s) was present in all patients. Twelve cases were familial, involving nine kindreds. Ten patients showed multiple chemodectomas on angiography. In two of these patients, one or more chemodectomas had already been removed prior to scintigraphy. A list of all drugs recently used was obtained to rule out interference with [^{123}I]MIBG uptake; special attention was paid to drugs as reserpine, tricyclic antidepressants, phenylpropanolamine, labetolol, and sympatholytic agents (*25*).

Scintigraphy

Each patient was injected intravenously with 10 mCi [^{123}I] MIBG while in the supine position. Iodine-123-MIBG was obtained from "Cygen" B.V. (Eindhoven, The Netherlands). The synthesis of [^{123}I]MIBG was performed by the method of Wieland et al. (*26*). Iodine-123 was produced by the ^{124}Xe (p,2n) reaction with specification of a maximum ^{125}I impurity of 0.01% at the time of calibration. Iodine-123-MIBG (specific activity at least 25 mCi/mg) was diluted in bacteriostatic phosphate buffer (pH 6.0–6.5) to a specific concentration of at least 2.0 mCi/ml. The free iodine concentration was <0.2%. Thyroidal uptake was blocked by the administration of Lugol's solution, ten drops three times daily (50 mg of iodine) for five days, starting the day before the injection.

A large field-of-view gamma camera (Toshiba GCA 90B®, Toshiba, Tokyo, Japan) equipped with a low-energy general-purpose collimator and interfaced to a dedicated computer (Toshiba GMS-55®, Toshiba, Tokyo, Japan) was used. A 20% window was centered at 159 keV. In all cases, anterior and posterior digitized images of the total body and four images of the head and neck were obtained 24 hr and, in most cases, 48 hr postinjection. Additional single-photon emission computer tomography (SPECT) of the head and neck of all patients was performed 24 hr after the injection. From the SPECT study transaxial, sagittal, and coronal slices, 5.3 mm thick, were reconstructed.

Computer Tomography

Seven patients with elevated catecholamine levels (Patients 1,3,6,7,10,12, and 14) of whom five had abnormal [^{123}I]MIBG concentrations outside the head and neck region were subsequently examined with a Tomoscan 350® (Philips, Best, The Netherlands) scanner. Initial screening of the abdomen was performed using 10-mm thick adjacent slices. If this routine scan was equivocal or negative, a more meticulous examination of the region with abnormal [^{123}I]MIBG uptake was conducted. Such a procedure included narrow collimation in combination with geometric enlargement and back projection magnification. Care was taken that the entire region was visualized and that no major anatomical gaps were introduced by inconsistent expiration between individual slices. In three cases, the CT examination was repeated after i.v. injection of 50 cc meglumine ioxitolamate (Telebrix 350®, Guerbet, Aulnay-sous-bois, France).

Magnetic Resonance Imaging

Patients 1,3,6,7,10,12, and 14 were examined at 0.5 T using a Gyroscan-S5® (Philips, Best, The Netherlands) scanner. In all cases, a body coil was used. Imaging techniques included multisectional acquisition of the adrenal area with 1-cm thick transverse slices, intersection gaps of ~1 mm, an acquisition matrix of 179 × 256 and a display matrix of 256 × 256. The field of view was 400 mm. Patients were examined with a spin echo sequence TR300/TE 20 and a spin echo sequence TR2000/TE 50-100. After imaging of the adrenal area, T2-weighted coronal images of the lower abdomen and mediastinum were taken in two series using a field of view of 500 mm. If this routine scan was equivocal, a more meticulous examination of the area of interest was carried out using transverse T1- and T2-weighted images. In all cases plane resolution was <3 mm. The number of measurements per data line was two (T2-weighted sequences) or six (T1-weighted sequences). Software for motion compensation was not used. Total procedure time varied from 1.5 to 2 hr.

Catecholamine Measurements

The urinary excretion of free norepinephrine, epinephrine, dopamine, and vanillylmandelic acid was assessed in 24-hr urine samples collected on three consecutive days. Free norepinephrine, epinephrine and dopamine levels were assayed by high-performance liquid chromatography (HPLC) and electrochemical detection (Coulochem 5100 A ESAR). VMA levels were measured by colorimetry after paperchromatography. For four patients (3,6,7, and 14) the levels of norepinephrine, epinephrine and dopamine in the tumor tissue were determined by the HPLC method and expressed as mmol/g tumor tissue.

RESULTS

Fourteen of the 15 patients completed the study. One patient (No. 5) underwent the clinical examination and scintigraphy but failed to supply the 24-hr urine samples (lack of cooperation). The clinical examinations in the fifteen patients rendered the following additional information. Only one of the 15 patients (No. 14) had a history that was indicative of a functioning paraganglioma, i.e., hypertension, episodic headaches, palpitations, and heavy perspiration. This had not been rec-

TABLE 1
Demographic, Scintigraphic, and Hormone Data on Patients with Chemodectoma

Patient no.	Age, sex	Kindred*	Multiple chemodectomas	MIBG uptake in chemodectoma	Abnormal MIBG uptake elsewhere	Urinary excretion: Vanillylmandelic acid μmole/24 hr range, mean	Urinary excretion: Norepinephrine μmole/24 hr range, mean	Urinary excretion: Dopamine μmole/24 hr range, mean	Number of measurements
1	41, F	—	—	+	—	22–35, 28.5	0.72–1.42, 1.02	0.76–1.78, 1.40	5
2	36, M	A	+	+	—	15–22, 18.0	0.13–0.34, 0.25	1.58–1.90, 1.72	3
3	24, M	B	—	—	Left adrenal	36–102, 73.0	4.35–6.50, 5.27	1.69–7.42, 3.22	7
4	31, M	A	+	—	—	14–28, 20.7	0.18–0.42, 0.32	0.91–1.73, 1.54	3
5	22, F	C	+	—	—				
6	49, F	D	+	—	Left adrenal	21–27, 25.0	1.04–1.82, 1.53	1.70–2.50, 1.98	3
7	39, F	E	—	—	—	19–27, 23.0	0.24–0.34, 0.30	2.52–5.88, 4.66	3
8	65, F	F	+	+	—	20–26, 23.0	0.20–0.21, 0.21	0.69–0.76, 0.72	3
9	50, F	F	—	+	—	25–37, 29.0	0.20–0.26, 0.23	0.21–0.90, 0.59	3
10	62, F	—	+	+	Right adrenal	10–24, 18.3	0.31–0.82, 0.56	1.08–1.44, 1.30	3
11	48, F	G	+	—	—	17–18, 17.3	0.26–0.32, 0.28	1.89–2.09, 2.01	3
12	41, F	H	+	—	Left adrenal	10–17, 13.3	0.41–0.75, 0.53	2.31–3.34, 2.68	3
13	58, F	—	+	+	—	15–18, 16.7	0.11–0.20, 0.16	0.21–0.90, 0.59	3
14	64, M	I	+	+	Left paramedian mid-abdominal	20–28, 25.0	0.35–0.88, 0.56	0.35–3.57, 2.14	4
15	26, M	B	—	+	—	21–27, 23.3	0.22–0.38, 0.28	1.94–2.44, 2.13	3
Normal values						<30	0.06–0.47	0.46–3.40	

* Letters A–I denote separate kindreds.

ognized for more than 20 yr. On physical examination, five patients (1,8,9,10, and 14) had hypertension, according to the definition of the World Health Organization (WHO) (*27*); only one patient (No. 14) received medication (verapamil chloride) for it. The other patients had no signs or symptoms suggesting a hormonal active tumor. None of the patients experienced any side effects of the [^{123}I]MIBG injection. Table 1 lists the patient data, the scintigraphic findings and the urinary levels of free norepinephrine, free epinephrine, dopamine and VMA. [^{123}I]MIBG uptake in one or more chemodectomas in seven patients (1,2,8,10,13,14, and 15) was visualized on planar views and SPECT images. In one patient (No. 9) [^{123}I]MIBG uptake by a chemodectoma was detected only by SPECT (Fig. 1). In total, 13 of the 24 chemodectomas were visualized. Neither the planar views nor the SPECT images revealed any uptake in the chemodectomas of the other seven patients. For each patient showing [^{123}I]MIBG uptake, all known chemodectomas were visualized. Most chemodectomas showed low-to-moderate uptake of [^{123}I] MIBG. Only Patient 1 showed a high uptake in a sporadic chemodectoma which proved to be a norepinephrine-secreting chemodectoma.

In five patients (3,6,10,12, and 14), abnormal locations of [^{123}I]MIBG were noted in the abdomen. Only one of them (No. 14) showed simultaneous moderate [^{123}I]MIBG uptake in a chemodectoma (Fig. 2).

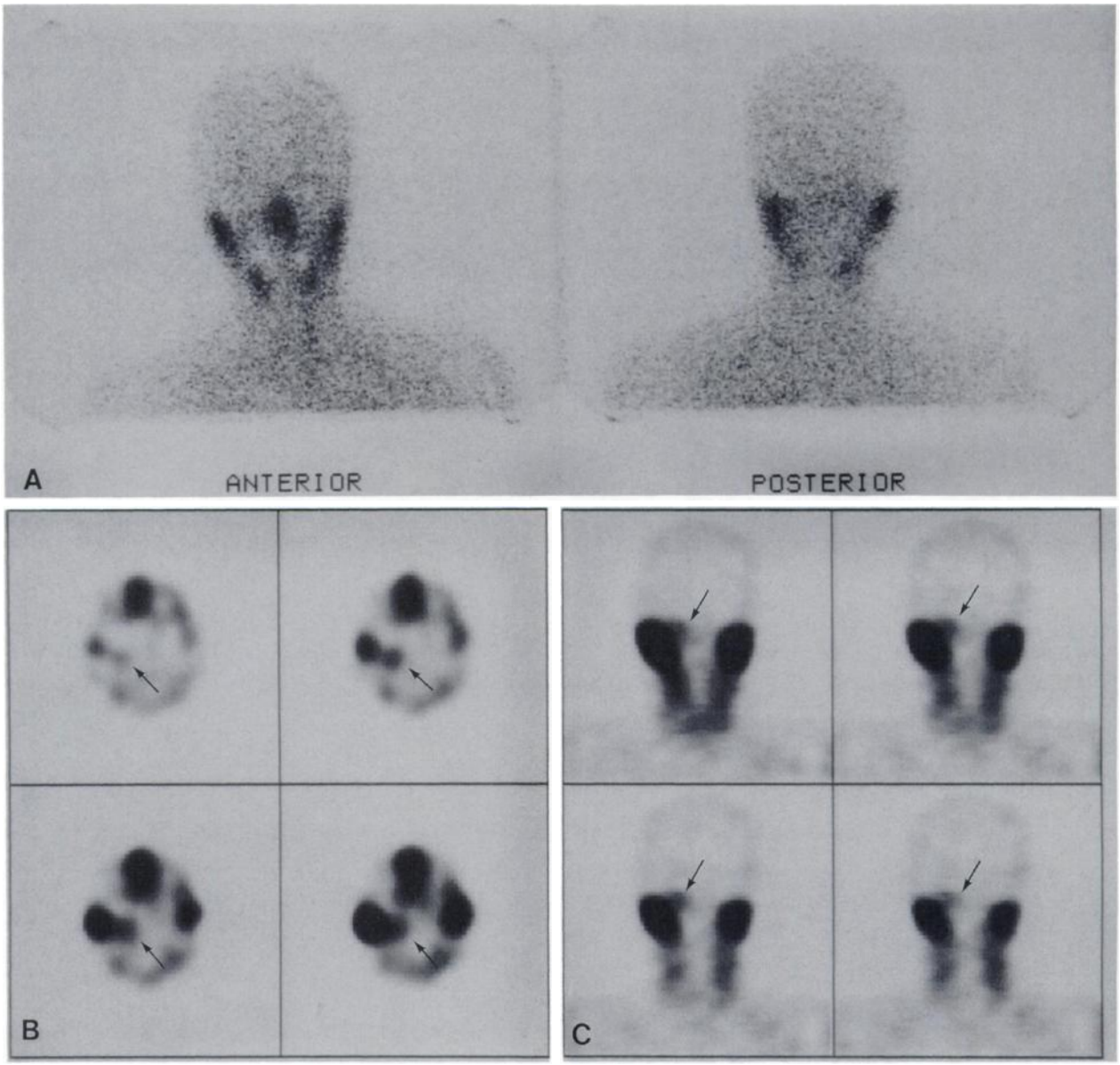

FIGURE 1
(Patient 9) Anterior and posterior [^{123}I]MIBG images of the head do not reveal any uptake in a chemodectoma (A). Transaxial (B) and coronal SPECT images (C) show distinct uptake of [^{123}I]MIBG in right jugular chemodectoma (arrows).

Seven patients (1,3,6,7,10,12, and 14) with elevated catecholamine levels of whom five had abnormal [^{123}I] MIBG concentrations in the abdomen underwent further examination. The results of the computed tomography (CT) and magnetic resonance imaging (MRI) investigations in these seven patients and the histopathologic data are shown in Table 2. Patients 3 and 6 had a pheochromocytoma of the left adrenal gland that was excised under labetolol prophylaxis without adverse effects. In Patient 14, an aortico-sympathetic paraganglioma was removed. Histologically, these tumors resembled the paraganglionic tissue found in pheochromocytomas. The tumors contained only norepinephrine. In all three cases (3, 6, 14), catecholamine secretion normalized postoperatively. Patient 14 became free of symptoms.

Patient 1 had a left-sided glomus jugulare tumor that was partially removed. During and after the operation, periods of severe hypertension developed but could be managed with 400 mg labetolol three times a day. Postoperatively, norepinephrine excretion normalized, but VMA excretion was elevated on one follow-up visit. In two patients (10 and 12), no lesions were revealed by either CT or MRI, although distinct abdominal deposits of [^{123}I]MIBG had been seen on two consecutive days. Patient 7 underwent partial resection of a vagal body tumor that was not revealed by [^{123}I]MIBG imaging. The tumor contained only dopamine. Postoperatively, the average dopamine excretion decreased but did not normalize, probably because a large part of the tumor remained in situ.

DISCUSSION

The standard for diagnosis of chemodectomas is angiography. However, this is an invasive procedure and therefore only performed preoperatively to demonstrate the vascular supply of these lesions (*3*). For screening purposes and postoperative control, contrast-enhanced CT is used (*28*). A scintigraphic method offers several potential advantages such as better detection of recurrent lesions in a scarred field, the absence of artifacts from clips, and the possibility to detect metastases in the entire body. A further advantage is the absence of the small but appreciable risk of contrast reactions. For these reasons, we evaluated the use of [^{123}I]MIBG in patients with chemodectomas.

Because normal [^{123}I]MIBG uptake in parotid glands and submandibular glands interferes with the visualization of chemodectomas, planar views were supplemented by SPECT of the head and neck area. SPECT made the delineation of chemodectomas easier and demonstrated a chemodectoma in one patient that were not visible on planar views. In total, we noticed uptake ranging from low to high intensity in 13 of 24 chemodectomas accounting for 54%. Von Moll et al. using [^{131}I]MIBG found uptake in 2 out of 5 chemodectomas

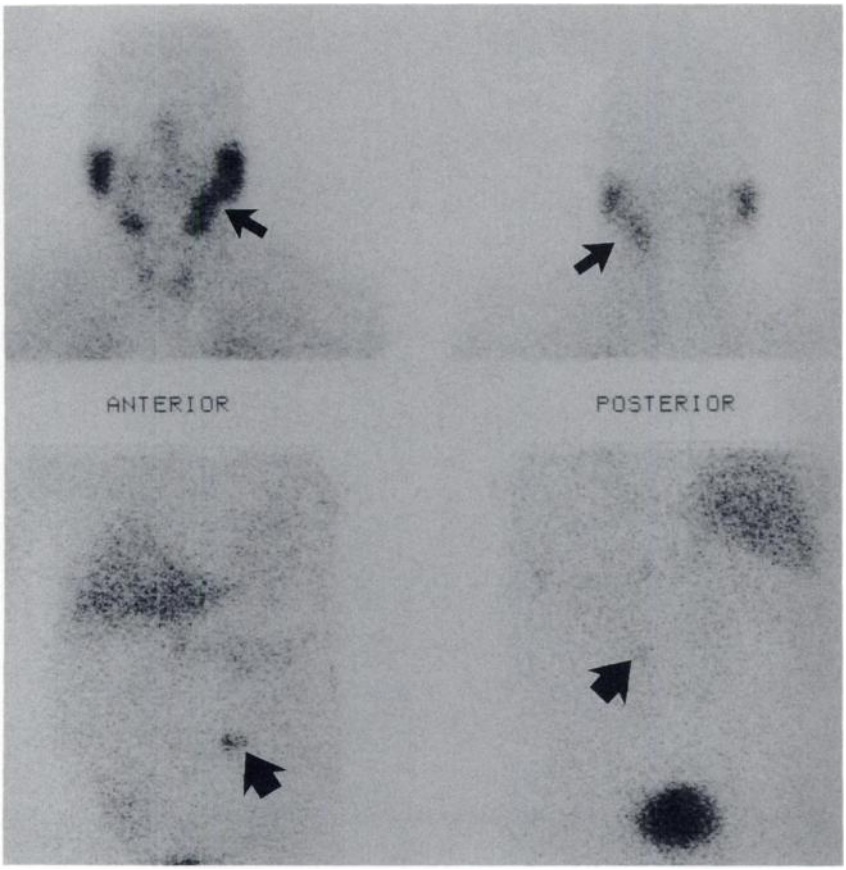

FIGURE 2
(Patient 14) Detail [^{123}I]MIBG images show uptake in left carotid chemodectoma (arrow) and in the associated aortico-sympathetic paraganglioma (large arrow). A right carotid chemodectoma had been removed 20 yr earlier.

TABLE 2
Analysis of Patients with Elevated Catecholamine Excretion

Patient no.	Vanillylmandelic acid elevated/total no. of measurements	Norepinephrine elevated/total no. of measurements	Dopamine elevated/total no. of measurements	CT/MRI abdomen	Histological diagnosis	Tumor content	
						Norepinephrine μmole/g	Dopamine nmole/g
1	2/5	5/5	0/5	Normal	Jugular chemodectoma	(Measurement not performed)	
3	7/7	7/7	1/7	Pheochromocytoma in left adrenal	Pheochromocytoma	2.35	0
6	0/3	3/3	0/3	Pheochromocytoma in left adrenal	Pheochromocytoma	22.10	0
7	0/3	0/3	2/3	Normal	Vagal chemodectoma	0.00	15
10	0/3	2/3	0/3	Normal	—	—	—
12	0/3	1/3	0/3	Normal	—	—	—
14	0/4	2/4	1/4	Paraaortic Paraganglioma	Paraganglioma (ectopic pheochromocytoma)	3.40	0

(40%) (*22*). The number of chemodectomas in the latter study is too small to make a valid comparison between the two isotopes. It is interesting to notice that the norepinephrine-secreting tumor in Patient 1 showed the highest uptake. Shapiro et al. reported two catecholamine secreting chemodectomas showing no [^{131}I] MIBG uptake (*19*). Whether this discrepancy is caused by the lower dose of [^{131}I]MIBG or by differences in norepinephrine kinetics is not clear. As already stated by von Moll et al., the ability of a tumor to take up MIBG can be independent of its ability to secrete catecholamines (*22*). The moderate sensitivity, found in our study, suggests a limited role of [^{123}I]MIBG in patients with chemodectomas.

However, in performing [^{123}I]MIBG scintigraphy and urinary screening for catecholamines, we unexpectedly found a high number of surgically proved catecholamine-secreting tumors of the paraganglia (functioning paragangliomas). Iodine-123-MIBG uptake provided an important clue to the hormonal activity of four of the five functioning paragangliomas. This was particularly the case in Patient 14 who initially showed only marginally elevated urinary catecholamine levels despite his obvious symptoms. Hormonal activity in patients with chemodectomas can be caused by the chemodectoma itself or by an associated catecholamine-secreting tumor in the thorax or the abdomen. The percentage hormonally active chemodectomas has been estimated to be ~1% (*10*). Approximately 2,000 patients with one or more chemodectomas have been described. There are 17 documented cases of associated functioning paragangliomas outside the head and neck region suggesting an overall incidence of <1% (*9,10,29*). The high incidence of functioning paragangliomas (functioning chemodectomas included) in our study may be attributable to several factors. First, we screened all patients for hormonal activity. In the past this was probably only performed in the event of clinical symptoms that suggested a hormonally active tumor. In our group, only one patient (No. 14) had symptoms suggesting a catecholamine secreting tumor. Yet these symptoms had not been appreciated prior to this study. For the four other patients with a functioning paraganglioma, symptoms of a hormonally active tumor were equivocal or absent.

Secondly, not only the VMA levels in 24-hr urine samples were measured, as in the past (*10*), but also the free catecholamine levels. According to Duncan et al., this is the most sensitive method for detecting pheochromocytomas (*30*). The VMA levels were elevated in only one patient in our series and marginally elevated in a second. Even when elevated, the possibility of a functioning chemodectoma is sometimes disregarded. Smit et al. described a patient with a chemodectoma showing intense [^{131}I]MIBG uptake and modestly elevated urinary VMA levels, which they attributed to cardiac failure rather than to excessive secretion of the chemodectoma (*24*). Thirdly, we performed whole-body scintigraphy with [^{123}I]MIBG, which is probably more sensitive in detecting pheochromocytomas and provides better image quality than [^{131}I]MIBG (*31*).

Of course some selection may have occurred. A high percentage of the patients studied were known to have a familial history of multiple chemodectomas. Since the aim of our study was to evaluate [^{123}I]MIBG scintigraphy of chemodectomas in the head and neck region, we could only investigate patients who had not been operated upon for technical reasons, i.e., those with multiple chemodectomas or those who had undergone only a partial resection. Patients with multiple chemodectomas may be more prone to develop an associated functioning paraganglioma. We reviewed the case reports collected by Dunn et al. and found that of the 16 patients with a functioning paraganglioma and chemodectomas, at least 10 had multiple chemodectomas and 6 had a familial history (*9*). In our patient population, there was one patient with a solitary chemodectoma associated with a pheochromocytoma, but the chemodectomas occurred in his family history. Retrospective analysis of the data on 20 patients with chemodectoma examined in our hospital in the past five years revealed another patient with a solitary, nonfamilial chemodectoma and a functioning mediastinal paraganglioma.

The familial occurrence of the association of chemodectoma with a paraganglioma has been described (*2,16*). As shown in Table 1 the high incidence of functioning paragangliomas in this study was not due to the enrollment of several members of one family with both types of tumor. Two patients (10 and 12) exhibited an increased uptake of [^{123}I]MIBG in an adrenal gland with elevated levels of norepinephrine; however, these findings were not confirmed by CT or MRI. These two patients will be followed because pheochromocytomas are known to develop gradually in the course of decades and an increase in the uptake of [^{123}I] MIBG may be the earliest evidence of adrenal medullary disease (*32,33*).

The patient with the dopamine-producing chemodectoma is the fourth patient to be reported in the literature (*34*). The tumor was not visualized by [^{123}I] MIBG. Proye et al. have described two cases of dopamine-producing pheochromocytomas that were not revealed either by [^{131}I]MIBG (*35*). Interestingly, neither the chemodectoma nor the two pheochromocytomas, described by Proye et al. contained any norepinephrine. The most likely explanation for the nonvisualization of these dopamine secreting paragangliomas is the absence of a specific norepinephrine uptake mechanism and/or a defective storage mechanism.

Although the number of chemodectomas taking up

[^{123}I]MIBG is limited, this does not imply that [^{131}I]MIBG cannot play an important role in the treatment of irresectable chemodectomas, showing the capacity to store MIBG. Patient 1 is currently considered for treatment with therapeutic doses of [^{131}I]MIBG, because the chemodectoma showed its capability for MIBG uptake and is not susceptible for further surgical treatment. In conclusion, this study suggests that functioning paragangliomas in patients with chemodectomas are more common than is estimated in the literature. Because of the selection the high percentage of functioning paragangliomas cannot directly be applied to solitary, nonfamilial chemodectomas. Nevertheless with long-term follow-up and appropriate screening, functioning paragangliomas will be seen with increasing frequency in patients with chemodectomas. For this reason and because of the minimal symptoms, we feel that patients with chemodectomas should be screened for elevated 24-hr urinary catecholamine levels using MIBG scintigraphy when elevated levels are found.

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FIRST IMPRESSIONS

SUBJECT:
A compound leaf of the Hawaiian Schefflera (Brassaia Arboricola), approximately 10 cm in diameter.

TRACER:
10 mCi of ^{99m}Tc in 0.5 ml of 0.16% saline.

ROUTE OF ADMINISTRATION:
Cutting placed in 0.5 ml of pertechnetate solution. Subject approximately 12 cm from pinhole.

TIME AFTER INJECTION:
12 hours of continuous acquisition.

INSTRUMENTATION:
LFOV gamma camera with a 1-mm pinhole collimator.

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