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Spectrum of Pheochromocytoma in the ^{131}I-MIBG Era

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^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy allows for both functional diagnosis and anatomical localization of pheochromocytoma. The spectrum of pheochromocytoma since the routine use of preoperative ^{131}I-MIBG scan was studied.

From 1980 to 1986, a total of 34 patients were primarily diagnosed and treated at the University of Michigan Medical Center, Ann Arbor, Michigan, U.S.A. There were 16 males and 18 females. The mean age was 38 years and 4 patients (11.8%) were under 18 years of age. Six patients (17.6%) had family history of pheochromocytoma or multiple endocrine neoplasia (MEN) II syndrome. The presenting symptoms were hypertension in 29 patients (85.3%); attacks of headache, palpitation, sweating, and flushing in 4 (11.8%), and 1 patient presented with a neck mass.

Plasma catecholamines were elevated in 97% of patients while urinary catecholamines and metabolites were elevated in 93.5%. ^{131}I-MIBG was accurate in 82.3%, partly positive in 11.8%, and false-negative in 5.9% of patients. CT scan was accurate in 80%, partly positive in 10%, but failed to show the tumor in another 10% of patients.

At operation, extraadrenal lesions were found in 38.2% of the patients and among these, one-third were extraabdominal. Multiple tumors occurred in 5 (14.7%), and bilateral adrenal lesions occurred in 4 patients (11.8%). Malignancy was diagnosed in 3 patients (8.8%) after an average follow-up period of 2 years.

We conclude that the use of routine preoperative ^{131}I-MIBG scanning improves localization of pheochromocytoma and earlier diagnosis is possible in patients with MEN II syndrome. Multiple tumors, extraadrenal and extraabdominal lesions occur more often than commonly believed. The low rate of confirmed malignancy is probably related to the short period of follow-up.

With the development of ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy, functional diagnosis and anatomical localization of pheochromocytoma is improved. As a result, patients with equivocal biochemical findings from urine or plasma studies are detected to harbor pheochromocytoma. Multiple or extraadrenal tumors can be detected before operation. Early diagnosis of pheochromocytoma in patients with familial disease or MEN II syndrome is possible. The pattern of this disease may, thus, change with the routine use of ^{131}I-MIBG as a preoperative diagnostic procedure. The conventional 10% rule quoted for the rate of extraadrenal, multiple, bilateral, familial, and malignant pheochromocytomas needs to be reviewed.

Since August, 1980, ^{131}I-MIBG scintiscan has been employed at the University of Michigan Medical Center, Ann Arbor, Michigan, U.S.A., as the first localization procedure in all patients suspected to have pheochromocytoma either clinically or biochemically. This report describes our experience with pheochromocytoma primarily diagnosed and treated in our hospital.

Material and Methods

During the 5½-year period from August, 1980 to February, 1986, patients referred to the University of Michigan Medical Center for diagnosis and treatment of suspected pheochromocytoma were studied. Patients who received primary operation elsewhere for pheochromocytoma were excluded. Those with proven pheochromocytoma referred for treatment of persistent or recurrent disease, or for screening of metastasis were also excluded.

Of the 34 patients, 16 were males and 18 were females. Their age ranged from 10 to 67 years with a mean age of 38 years. Four were 14 years old or younger (11.8%) and the remaining patients were 18 years or older (88.2%). Six patients (17.6%) were familial, 3 had a positive family history of pheochromocytoma, 1 had MEN IIa and 2 had MEN IIb syndrome.

Hypertension was the presenting symptom in 29 patients (85.3%). It was paroxysmal in 20 and sustained in 9 patients. Four patients (11.8%) were normotensive but had attacks of headache, palpitation associated with sweating, and flushing. One patient presented with an asymptomatic neck mass. The duration of symptoms ranged from one month to 23 years with a mean period of 4 years.

Urinary excretion of catecholamines and catecholamine metabolites were determined on 12-hour overnight urine samples [1]. Plasma catecholamines were measured by radioenzymatic assay on samples obtained in the fasting, rested, and supine state via an indwelling venous catheter [2].

^{131}I-MIBG was administered intravenously over 20–30 sec-

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Table 1. Biochemical findings in 34 patients with pheochromocytoma.

	Normal value	Values					% of patients with elevated values
		Mean	Median	Minimum	Maximum	Range	
Plasma							
Epinephrine	<100 pg/ml	515	203	44	3,420	3,376	69.7
Norepinephrine	<500 pg/ml	7,460	2,434	146	90,000	89,854	93.9
Urine							
Epinephrine	<30 μg/24 hr	86	41	5	570	565	66.7
Norepinephrine	<110 μg/24 hr	518	316	17	2,496	2,479	78.8
Metanephrine	<85 μg/24 hr	353	75	3	2,883	2,880	51.5
Normetanephrine	<165 μg/24 hr	851	314	31	6,018	5,987	78.8
VMA	<7 mg/24 hr	28	14	0.1	123	122.9	81.8

onds. The dose was 0.5 mCi/1.7 m^2 increasing to a maximum of 0.5 mCi. Thyroidal uptake of free ^{131}I was blocked by administration of iodide 24 hours before the injection of ^{131}I-MIBG and continued for 5 days. Scanning was performed at 24, 48, and 72 hours after injection. Images of the head, neck, chest, abdomen, and pelvis were obtained using the large field-of-view gamma camera with a high-energy, parallel-hole collimator interfaced with a minicomputer. Anatomical orientation was delineated by surface markers, and, in selected cases, by simultaneous scintigraphic depiction of other organs: kidney by ^{99m}Tc-DTPA, liver and spleen by ^{99m}Tc-sulfur colloid; myocardium by ^{201}T1; blood pool by ^{99m}Tc-labeled red blood cells. The ^{131}I-MIBG scans were interpreted using the criteria previously described [3, 4].

Computed tomography (CT) scan was performed in 30 patients on regions guided by the results of the scintigraphy. Venous samplings and angiography were performed on selected cases when further localization was deemed necessary.

The patients underwent abdominal exploration or thoracotomy (with or without cardiopulmonary bypass) according to the results of localization.

Results

Biochemical Findings

Elevated urinary excretion of vanillylmandelic acid (VMA) was present in 81.8% (27/33), norepinephrine and normetanephrine in 78.8% (26/33), epinephrine in 66.7% (22/33), and metanephrine in 51.5% (17/33) of patients. Plasma norepinephrine was elevated in 93.9% (31/33), and plasma epinephrine in 69.7% (23/33) of patients (Table 1).

Ninety-seven percent (32/33) of patients tested showed elevations in either or both plasma epinephrine and norepinephrine. One patient had normal plasma catecholamine levels but urine showed increased excretion of normetanephrine and epinephrine. Subsequent ^{131}I-MIBG scan and operation confirmed the presence of a left adrenal pheochromocytoma.

Ninety percent (30/33) of patients tested showed elevated urinary excretion of 2 or more compounds, catecholamines, or their metabolites. Of the remaining 3 patients, 1 patient showed elevation only in urinary normetanephrine and plasma norepinephrine. She was a 14-year-old girl suffering from MEN IIb syndrome, had medullary thyroid cancer diagnosed 2 years before, developed flushing attacks for a year, and ^{131}I-MIBG scan showed uptake in both adrenals, which were normal on CT scan. Subsequent operation and pathology confirmed bilateral medullary hyperplasia in grossly normal adrenals (Fig. 1). Another patient had normal urinary catecholamines and metabolites, but both plasma epinephrine and norepinephrine were elevated. She was a 10-year-old girl with no family history of MEN II syndrome or pheochromocytoma, developed hypertension, headache, and sweating for 2 years. ^{131}I-MIBG scan showed pararenal uptake and CT scan delineated a 4-cm mass at the lower pole of the left kidney. Operation confirmed the presence of an extraadrenal pheochromocytoma. The third patient was a 66-year-old woman who accidentally discovered a right neck mass, presumed to be a thyroid swelling. Aspiration cytology of the mass was unrevealing. Plasma calcitonin level was normal. Urinary epinephrine was mildly elevated (118 pg/ml), but norepinephrine was normal. ^{131}I-MIBG scan showed positive uptake. Subsequent operation confirmed the mass to be a paraganglioma.

Localization

^{131}I-MIBG scintigraphy localized the tumor accurately in 82.3% (28/34) of patients. In 4 other patients (11.8%), the scan was partly accurate. Three were interpreted as adrenal gland uptake, but operation revealed extraadrenal tumors in paraaortic, pararenal, and retrocaval locations. One showed uptake in the left adrenal gland and at the celiac axis, but missed the medullary hyperplasia in the right adrenal. Two other patients (5.9%) had a false-negative result. One actually had uptake in the right pelvis, which was interpreted as normal. Venous samplings and angiography localized the tumor in the infrarenal paracaval location and was confirmed at operation. The other did not show uptake in a 7-cm cystic adrenal tumor, which was localized by the CT scan.

In the 30 patients with CT scans performed, 24 showed positive results giving an accuracy of 80%. Dynamic thoracic CT scanning was required in 4 patients with cardiac pheochromocytoma for better anatomical delineation. Apart from these 4 patients, CT scan provided additional information in only 1 patient who had a cystic adrenal pheochromocytoma not shown up in ^{131}I-MIBG. In all the other instances when ^{131}I-MIBG was negative or partly positive, CT scan provided no further information. In fact, a patient with bilateral adrenal medullary hyperplasia, positive on ^{131}I-MIBG, was not shown on CT scan.

Only one instance was encountered when both ^{131}I-MIBG and CT scan were negative and further localization by venous

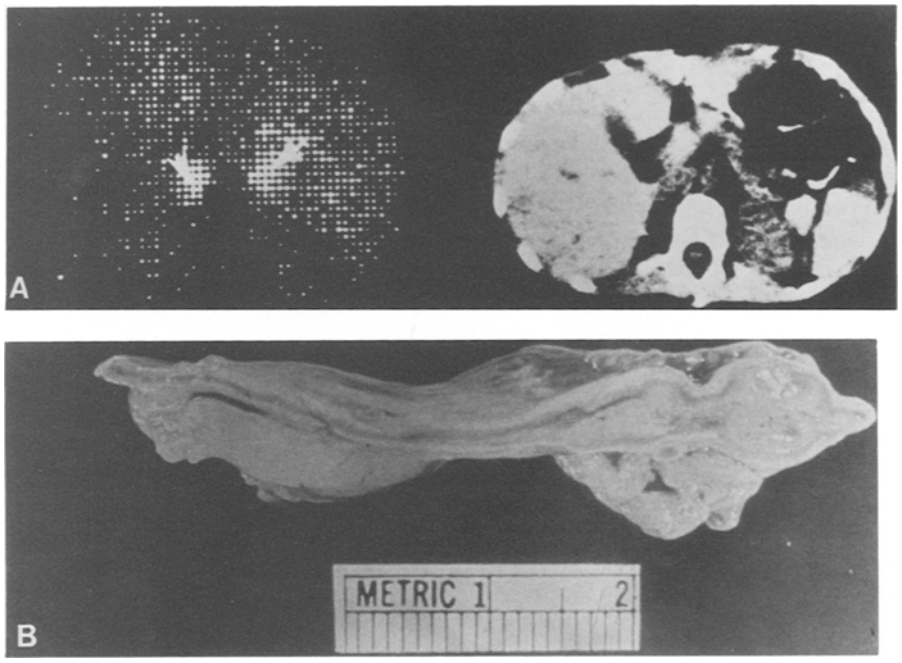

Fig. 1A. Bilateral imaging of the 2 adrenals in the patient with bilateral adrenal medullary hyperplasia. **B.** Cut section of the adrenal specimen showing medullary thickening.

samplings and/or angiography was required. The tumor was found at operation to be at the infrarenal paracaval location.

Site and Distribution

Intraadrenal tumors were found in 21 patients (61.8%) (Table 2). Of these, 3 patients with MEN II syndrome had bilateral adrenal medullary hyperplasia. One further patient who was not familial or MEN II, had nodular medullary hyperplasia in both adrenals plus an extraadrenal site around the celiac axis. Bilateral adrenal involvement thus occurred in 4 patients (11.8%) in this series.

Extraadrenal tumors were found in 13 patients (38.2%). Of these, 4 were thoracic, being located in the middle mediastinum, and 1 was in the neck, giving an extraabdominal location rate of 14.7%. Of the 8 intraabdominal extraadrenal tumors, 2 were paraaortic, at the levels of the celiac axis and renal hilum; 3 were paracaval, at the level of right renal hilum, above the left renal vein and medial to the lower pole of left kidney; and 3 were retrocaval, at the level of the renal hilum. Two of these 8 patients harbored multiple tumors giving a multiple tumor rate of 14.7% (5/34). All 3 familial patients harbored extraadrenal abdominal pheochromocytomas.

Two (50%) of the 4 children in our series harbored extraadrenal abdominal tumors. In the other 2 who had intraadrenal tumors, 1 had MEN II syndrome and medullary hyperplasia in both adrenals.

All patients were followed up at a mean period of 20 months with a maximum period of 53 months. All are alive except for 1 patient. She had a cardiac tumor and died of disseminated intravascular coagulation on the first postoperative day.

Malignancy was confirmed in 3 patients (8.8%), 2 by lymph node involvement at the time of operation and 1 by subsequent distant metastasis. All 3 patients had a family history of pheochromocytoma. One of them was only 14 years old.

Table 2. Location of pheochromocytoma in 34 patients.

	n
Intraadrenal	21 (61.8%)
Unilateral	18
Bilateral	3
Extraadrenal	13 (38.2%)
Abdominal	8[a]
Thoracic	4
Neck	1

[a]One patient has 3 tumors: bilateral, adrenal, and an extraadrenal focus.

Four patients had microinvasion in their tumors, 1 showed capsular and 3 showed vascular invasions. They were suspicious of malignancy. However, on follow-up, from 6 to 16 months, there were no signs of recurrence or metastasis.

Discussion

Reports on pheochromocytoma before the discovery of ^{131}I-MIBG mainly concentrate their discussions on proven tumors [5–9]. Negative laparotomies for pheochromocytoma, persistent, or recurrent diseases, are seldom topics of discussion [10]. There is also a high rate of autopsy diagnosis of the disease in the past [11].

Since the discovery of ^{131}I-MIBG scintigraphy, and its exclusive use in our institution in the initial period, many multiple, extraadrenal, extraabdominal, and metastatic lesions were unexpectedly diagnosed. Patients with multiple unsuccessful operations for pheochromocytoma had, for the first time, a solution to their problem [12]. Patients with MEN II or familial disease can undergo screening by ^{131}I-MIBG even when clinical and biochemical evidences are equivocal [13].

With the use of ^{131}I-MIBG as an initial localization procedure

Table 3. Prevalence of extraadrenal, multiple, familial, and malignant tumors in pheochromocytoma.

Author	Year	n	Extra-adrenal (%)	Multiple (%)	Familial (%)	Malignant (%)
Melicow [5]	1977	100	17	3	–	7
Modlin [6]	1979	72	18	8	–	10
van Heerden [7]	1982	106	20	–	11.3	14
Scott [8]	1982	64	25	9.4	–	12.5
Hartley [9]	1985	46	11	11	9	7
Stenstrom [21]	1986	439	22	–	–	–
Present series		34	38.2	14.7	17.6	8.8

in suspected pheochromocytomas, the striking difference between our series and previous reports is the high rate of extraadrenal lesions (Table 3). This is largely contributed by the finding of middle mediastinal tumors and the scintigraphic uptake by small extraadrenal lesions which may escape detection in a surgeon's laparotomy without prior localization. However, the high rates of extraadrenal lesions (50%) and malignancy (25%) in children are compatible with other reported experiences [14].

The proportion of familial cases (17.6%) is higher than the commonly believed 10%. This can be explained by the inclusion of pheochromocytomas that are diagnosed at a relatively early stage as exemplified by our patients with MEN II syndrome. In fact, the adrenal glands appeared normal on CT scan and in the gross appearance of the resected specimen. Early diagnosis would not be possible without the use of ^{131}I-MIBG scan. Such early diagnosis is also reflected in the mean age of patients in our series being 10 years younger than in other reports [5–9].

The low rate of confirmed malignancy in this series contrasts with the almost 50% rate of malignancy previously reported by our institution [15]. The latter figure is probably biased by the large number of special referrals and the long intervals after primary operation before the patients are referred. The 8.8% malignant rate is also somewhat low compared to other reported series and this may be related to the short period of follow-up of these patients. Since metastasis can occur as long as 27 years after primary diagnosis [16, 17], a longer follow-up of our patients may show an increased diagnosis of metastatic or recurrent disease. Furthermore, microinvasion in pheochromocytoma, although not a diagnostic criterion for malignancy, needs close surveillance on follow-up for recurrent disease.

Because of the advantage of whole body scanning and its high sensitivity and specificity rate, ^{131}I-MIBG scan is recommended as an initial procedure for localization [18, 19]. Indeed, conventional CT scan gives no additional information when ^{131}I-MIBG localizes a tumor. This explains why, in the last 4 patients, we proceeded directly to operation after a positive ^{131}I-MIBG localization without performing CT scan. However, CT scan, especially dynamic CT scan, and other procedures like venous samplings and angiography may be indicated when ^{131}I-MIBG uptake is negative or when better anatomical delineation is needed [20].

In conclusion, the development of ^{131}I-MIBG scintigraphy has changed our practice in the management of pheochromocytoma as it is now the first localization study performed. Extraadrenal, extraabdominal, and multiple tumors occur more often than commonly believed. Early diagnosis of pheochromocytoma is possible in patients with MEN II syndrome. Longer follow-up of patients is needed to ascertain the true occurrence of malignancy.

Résumé

La scintigraphie à l'^{131}I-MIBG permet de diagnostiquer et de localiser les phéochromocytomes. Toute la gamme de types de phéochromocytomes reconnu depuis l'utilisation préopératoire systématique de la scintigraphie à l'^{131}I-MIBG est présentée.

Entre 1980 et 1986, 34 patients ont été explorés et traités au Centre Médical de l'Université de Michigan, Ann Arbor, Michigan. Il y avait 16 hommes et 18 femmes. L'âge moyen était de 38 ans, et 4 patients (11.8%) avaient moins de 18 ans. Six patients (17.6%) avaient des antécédents familiaux de phéochromocytome ou de néoplasmes endocrines multiples (MEN) du type II. Les symptômes amenant à consulter étaient l'hypertension chez 29 patients (85.3%), des crises de céphalées, des palpitations et un flush chez 4 patients (11.8%); un patient présentait une masse cervicale.

Les catécholamines plasmatiques étaient élevées chez 97% des patients alors que les catécholamines et leurs métabolites étaient en quantité élevée chez 93.5% des patients. La scintigraphie à l'^{131}I-MIBG était positive chez 82.3%, partiellement positive chez 11.8%, et faussement négative chez 5.9% des patients. La tomodensitométrie était positive chez 80%, partiellement positive chez 10%, et faussement négative chez 10% des patients.

A l'intervention, des lésions extra-surrénales étaient présentes dans 38.2% des cas, et parmi celles-ci, un tiers étaient extra-abdominales. Les tumeurs étaient multiples dans 5 cas (14.7%), et bilatérales surrénales dans 4 cas (11.8%). Une tumeur maligne était diagnostiquée chez 3 patients (8.8%), après une période de suivi de 2 ans en moyenne.

Nous concluons que l'utilisation systématique de la scintigraphie à l'^{131}I-MIBG améliore la localisation des phéochromocytomes, permettant un diagnostic plus précoce chez les patients présentant un syndrome MEN II. La multiplicité tumorale et les localisations extra-médullosurrénales ou extra-abdominales se voient beaucoup plus fréquemment qu'on le pensait auparavant. Le taux de malignité peu élevé était probablement en rapport avec la courte période de suivi.

Resumen

La escintigrafía con ^{131}I-MIBG permite tanto la localización anatómica como el diagnóstico funcional del feocromocitoma. Las características o espectro del feocromocitoma a partir del uso rutinario de ^{131}I-MIBG han sido estudiadas.

Entre 1980 y 1986, un total de 34 pacientes fueron diagnosticados y tratados en el Centro Médico de la Universidad de Michigan, Ann Arbor, Michigan, 16 hombres y 18 mujeres. La edad promedio fue 38 años, con 4 pacientes (11.8%) menores de 18 años. Seis pacientes (17.6%) tenían historia familiar de feocromocitoma o de síndrome de neoplasia endocrina múltiple tipo II. Los síntomas de presentación fueron: hipertensión en 29 casos (85.3%), ataques de cefalea, palpitación, sudoración, y enrojecimiento ("flushing") en 4 (11.8%), y un paciente presentaba masa cervical.

Las catecolaminas plasmáticas aparecieron elevadas en 97% de los pacientes, mientras las catecolaminas urinarias y sus metabolitos aparecieron elevadas en 93.5%. La escintigrafía con ^{131}I-MIBG resultó certera en 82.3%, parcialmente positiva en 11.8%, y falsa-negativa en 5.9% de los casos. La tomografía computadorizada resultó certera en 80%, parcialmente positiva en 10%, pero falló en demostrar el tumor en otro 10% de los pacientes.

En la operación se hallaron lesiones por fuera de las suprarrenales en 38.2% de los pacientes, y entre estos un tercio estaban por fuera del abdomen. Tumores múltiples ocurrieron en 5 pacientes (14.7%), lesiones suprarrenales bilaterales en 4 (11.8%). Se diagnosticó malignidad en 3 casos (8.8%) después de un período promedio de seguimiento de 2 años.

Nuestra conclusión es que el uso preoperatorio rutinario de la escintigrafía con ^{131}I-MIGB representa un avance en la localización preoperatoria del feocromocitoma, con lo cual se puede hacer un diagnóstico más temprano en pacientes con el síndrome de neoplasia endocrina múltiple tipo II. Hay una mayor incidencia, de la que comunmente se conoce, de tumores múltiples, extraadrenales, y extraabdominales. La baja tasa de malignidad confirmada probablemente se relaciona con el corto período de seguimiento.

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Invited Commentary

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Since the initial report of the clinical use of ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) in scintigraphic localization of pheochromocytoma by Sisson et al. [1] at the University of Michigan Medical Center in 1981, there have been multiple studies by Sisson, Beierwaltes, and their co-workers that have demonstrated the value of this radiopharmaceutical in localization of pheochromocytomas of all types [2–5]. This includes sporadic adrenal and extraadrenal tumors, familial types of pheochromocytoma, and the various metastatic deposits of malignant lesions. In a recent study of ^{131}I-MIBG in 600 patients at the University of Michigan Medical Center, results of analysis showed: prevalence, 29%; sensitivity, 88%; specificity, 99%; negative predictive accuracy, 95%; and positive predictive accuracy, 98% [6]. Quite similar results have been reported by others [7–9].

The present retrospective study involves 34 patients with pheochromocytoma who were primarily diagnosed at the University of Michigan Medical Center from 1980 to 1986. The authors state that, at the beginning of this study, ^{131}I-MIBG scintiscan was adopted as the first localization procedure in all patients suspected to have pheochromocytoma either clinically or biochemically. In the 34 patients, plasma catecholamines were elevated in 97%. ^{131}I-MIBG scanning was accurate in