The Diagnostic Role of I-131 MIBG Imaging in Evaluation of Patients with Accidentally Discovered Asymptomatic Adrenal Masses

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Abstract

The aim of this study was to evaluate the role of I-131 MIBG imaging in the characterization of adrenal masses.

Methods: A total of 23 patients (8 men, 15 women; mean age, 46±17 y) with accidentally discovered unilateral adrenal mass that had been originally detected on CT or MRI underwent I-131 MIBG adrenal scintigraphy. None of the patients showed specific symptoms of adrenal hypersecretion. Screening tests for excess cortical and medullary products showed normal adrenal hormone levels.

Results: Histology after surgery was obtained. Adrenal lesions were represented: 13 had adenomas, 7 had nonadenoma benign lesions (4 pheochromocytomas, 1 cyst, 1 pseudotumor and 1 ganglioneuroma), and 3 had malignant tumors (2 carcinomas, and 1 metastases). Size range, 1.5- to 5-cm diameter; mean, 4.9±3.1 cm. For MIBG imaging, diagnostic sensitivity, specificity, and accuracy were 100%, 94%, and 96%, respectively; the PPV of the MIBG scan to characterize an adrenal mass as a medullary chromaffin tissue tumor was 83%, whereas the corresponding NPV to rule out this type of tumor was 100%.

Conclusion: In patients with accidentally discovered adrenal masses, I-131 MIBG imaging, may provide significant functional information for tissue characterization. MIBG scans is able to detect benign tumors such as pheochromocytoma, particularly when CT or MRI findings are inconclusive for lesion characterization.

Key Words: Adrenals – Tumors – MIBG.

Introduction

THE high resolution of anatomic imaging techniques such as CT and MRI, used in patients with suspected abdominal disease, frequently results in detection of unexpected adrenal masses [1-3]. In this setting, the main clinical concern consists of noninvasive characterization of benign and malignant adrenal lesions to determine the appropriate treatment [1-3]. As an initial diagnostic approach, clinical and laboratory assessment of cortical and medullary adrenal function can identify hyperse-
None of the patients showed other symptoms of adrenal hypersecretion.

**Laboratory analysis:**

Evaluation of adrenal function consisted of screening tests for excess mineralocorticoid, glucocorticoid, androgen, and catecholamine secretion. In particular, plasma aldosterone levels and rennin activity were measured for patients in clinostatic and orthonystatic posture. Plasma cortisol and corticotropin levels were measured at 8:00 AM and 11:00 PM and a 24-h urine assay for free cortisol was performed. Measurements of serum dehydroepiandrostosterone sulfate, 17a-hydroxyprogesterone, androstenedione, testosterone, and electrolyte levels were included. An overnight low-dose dexamethasone suppression test was also performed (1 mg orally at 11:00 PM; measurement of serum cortisol level at 8:00 AM the following morning). Plasma catecholamine levels were measured in 24-h urinary excretion of catecholamines and their metabolites, vanillylmandelic acid and metanephrine, to evaluate medullary adrenal function. Hormonal values were determined by radioimmunoassay or immunoradiometric assay methods using commercially available kits Urinary catecholamine, vanillylmandelic acid, and metanephrine levels were measured using high-performance liquid chromatography. Sodium and potassium levels were assessed using flame photometry with lithium as an internal standard.

**MIBG imaging:**

Before MIBG injection, thyroid iodine uptake was blocked with a saturated solution of potassium iodide (200 mg/d orally, starting before tracer administration and continuing for 8 d). I-131 MIBG (37 MBq; was administered intravenously. Anterior and posterior whole-body as well as abdominal spot views were obtained at 24, 48, and 72 h after tracer injection with additional Tc-99m DTPA subtracted image for better localization of the adrenal region was performed in indicated cases using a large-field-of-view gamma camera (Siemens) with a high energy collimator and a 20% window centered at 364 keV.

**Data analysis:**

Adrenal function, either cortical or medullary, was considered to be healthy when corresponding hormone values were in the normal range. Conversely, cortical or medullary adrenal hypersecretion was determined in cases of clearly increased levels of the corresponding hormones. The anatomic characteristics of adrenal tumors were assessed on CT and MR images. The presence of abnormally increased uptake of MIBG was analyzed in adrenal regions where tumor lesions had been detected by CT or MRI. The intensity of tumor uptake was qualitatively evaluated on a high-resolution display by 2 independent and experienced nuclear medicine physicians. In case of disagreement, final interpretation was determined by consensus reading. Radionuclide studies were assessed independently without knowledge of clinical and pathologic findings. Adrenal activity was considered abnormal when tracer uptake was greater than initial blood-pool and surrounding background activity and when no similar uptake was observed on the contralateral side. Scintigraphic images were categorized as positive or negative. The results were classified as true-positive, true-negative, false-positive, and false-negative compared with final pathological findings. On the basis of the data reported in the literature [8], the criteria to establish true-positive radionuclide scans include the following: MIBG scans were considered true positive in the presence of medullary chromaffin tissue tumors such as pheochromocytoma or ganglion-euroma; Diagnostic sensitivity, specificity, and accuracy, positive predictive values (PPVs), and negative predictive values (NPVs) were calculated. The results of histology after surgery (were considered the standards of reference. Whole-body scintigraphic images of MIBG was also qualitatively analyzed. Abnormal tracer uptake in extra-adrenal locations was assessed by CT or MRI to confirm or rule out the presence of tumor lesions.

**Results**

Of the 23 patients on whom these studies were performed, 13 had adenomas, 7 had nonadenoma benign lesions (4 pheochromocytomas, 1 cyst, 1 pseudotumor and 1 ganglioneuroma), and 3 had malignant tumors (2 carcinomas, and 1 metastases). Significantly increased 131I-MIBG uptake by adrenal lesions occurred in patients with a pheochromocytoma or a ganglioneuroma (true-positive results) (Fig. 1). Heterogeneous tracer activity was unexpectedly found in one instance of a large and necrotic cortical carcinoma (false-positive result). The PPV of MIBG imaging to characterize an adrenal mass as a medullary chromaffin tissue tumor was 83%; conversely, the corresponding NPV to rule out this type of tumor was 100% Whole-body MIBG images were normal in all cases. CT and MRI studies showed 13 and 10 well-capsulated tumor lesions of left and right adrenal glands, respectively. In all cases, the margins of adrenal masses were regular including (size range, 1.5 - 5 cm; mean, 4.9 ±3.1 cm), whereas the size...
of adenomas was significantly \( p < 0.001 \) smaller than that of other benign lesions as well as malignant tumors, no statistical difference in tumor size was observed between nonadenoma benign lesions and malignant adrenal masses.

The results for I-131 MIBG in terms of diagnostic sensitivity, specificity, and accuracy, as well as PPVs and NPVs, are illustrated in Table (1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>I-131 MIBG scan</th>
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<tbody>
<tr>
<td>No. of studies</td>
<td>23</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>94%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>96%</td>
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<tr>
<td>PPV</td>
<td>83%</td>
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<tr>
<td>NPV</td>
<td>100%</td>
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Table (1).

Fig. (1): Patient with asymptomatic right adrena pheochromocytoma. (A) CT abdominal scan shows round right adrenal mass. (B) Abdominal posterior view of MIBG image as well as DTPA subtracted image shows round area of intense tracer uptake in right adrenal bed.

Discussion

Image-based evidence of asymptomatic (non-hypersecreting) adrenal masses has recently increased because of the widespread use of highly sensitive diagnostic techniques such as CT and MRI for the evaluation of abdominal complaints. For these patients, the most critical step is to identify the type of tumor to determine the appropriate treatment. Although anatomic criteria indicative of high risk of malignancy may be obtained using CT and MRI, recently proposed a morpho-functional examination by scintiscans using MIBG for patients with incidentally discovered adrenal tumors. In this study, we report our experience regarding the usefulness of I-131 MIBG adrenal scintigraphy to characterize accidentally discovered asymptomatic adrenal tumors originally detected on CT or MRI; for this purpose, we reviewed nuclear MIBG adrenal scans obtained in our department MIBG has been shown to undergo specific uptake and storage by adrenal medulla, the sympathetic autonomic nervous system, and tumors derived from these tissues [9].

A significant portion of tracer uptake into these tissues occurs by means of the specific and high-affinity sodium uptake mechanism as well as the energy-dependent type I amine uptake mechanism. In particular, within the adrenal medullary and pheochromocytoma cells there may be storage granules [10].

Previous studies have clearly shown the usefulness of radioactive MIBG imaging in the diagnostic evaluation of patients with pheochromocytoma and with extra-adrenal paragangliomas [11]. However, in these studies.

MIBG scintigraphy was used to localize and detect tumor sites in patients with hypersecreting lesions; no data regarding asymptomatic pheochromocytoma have been reported. In our study, we investigated the role of MIBG imaging to identify asymptomatic pheochromocytoma with indeterminate adrenal masses. Usually, pheochromocytomas are characterized by an increased level of catecholamines, as well as their metabolites, and by corresponding symptoms so that diagnosis is clear [12].
However, lesions may occur without symptoms [8,13-16]. In our experience, including the 3 y of our study, we found 4 (28%) asymptomatic pheochromocytoma lesions and 10 (72%) classic hypersecreting pheochromocytomas. Furthermore, this finding represented 4 (17%) of our patient population (n=23) with asymptomatic adrenal masses. Therefore, this condition merits specific attention. In such patients, clinical diagnosis of pheochromocytoma using laboratory tests is impossible. Therefore, the integrated imaging results of MIBG and CT or MRI seem to be clinically relevant for this purpose. In fact, the presence of MIBG uptake in an asymptomatic adrenal mass can characterize the lesion as a pheochromocytoma. Whereas this tumor type specifically concentrates MIBG into its catecholamine storage granules, other adrenal space-occupying abnormalities do not accumulate this agent. In particular, this finding was found in our series in 4 cases of asymptomatic tumors histologically proven to be pheochromocytoma. A similar result was also obtained in a case of asymptomatic ganglioneuroma detected in the upper abdomen. A comparable finding was described by Smit et al. [17] in a patient with a paraganglioma of the neck with no clinical or biochemical evidence of catecholamine secretion, but with significant MIBG uptake. Thus, as previously reported by us [18], we believe that MIBG scintigraphy is diagnostically useful to identify or rule out nonfunctional tumors of medullary chromaffin tissue. This observation adds an indicative criterion for the characterization of asymptomatic pheochromocytoma with nondiagnostic biochemical tests. MIBG uptake by this adrenal lesion in the absence of catecholamine hypersecretion suggests that tracer tumor activity reflects storage rather than hormone secretion. This finding is consistent with previous data showing no significant relationship between MIBG lesion uptake and catecholamine secretion [19,20].

The presurgical characterization of pheochromocytoma is critical for appropriate patient preparation before tumor resection. In the case of a hypersecreting tumor, this diagnostic information can be obtained using clinical data and laboratory measurement of adrenal medullary hormones. Conversely, this approach cannot be used for asymptomatic pheochromocytomas. Although a high T2-weighted MR signal intensity has been reported as a characteristic of pheochromocytomas, other adrenal lesions such as adenomas, carcinomas, and metastases may give similar images [5,6].

Therefore, the presence of MIBG uptake in asymptomatic pheochromocytomas may represent a new noninvasive imaging criterion to perform tumor characterization and appropriate dibenzyline administration before surgery. Thus, careful observation is warranted for asymptomatic patients with normal catecholamine levels. Anesthesiologists and other physicians must be alerted to manage a hypertensive crisis during the induction of anesthesia, during surgery, and in other stressful circumstances for such patients. MIBG imaging might be proposed to screen nonhypersecreting adrenal masses to confirm or rule out the presence of silent pheochromocytoma. This approach has also been suggested by others in a different patient population [21].

In our study, no MIBG uptake occurred in adrenal masses other than pheochromocytomas or ganglioneuromas, such as adenomas, cysts, pseudotumors, or malignant lesions. However, a false-positive MIBG result was observed in a case of a adrenal carcinoma. Although this finding was the only occurrence of a false-positive result, the PPV of MIBG imaging to characterize an adrenal mass as a chromaffin tissue tumor was not very high (83%); this finding was related to the small number of true-positive cases. The reasons for MIBG uptake in an adrenal carcinoma are unclear. The possible neuroendocrine origin of such lesions might result in MIBG concentration. Miettinen [22] showed neuroendocrine differentiation in a significant number of adrenal carcinomas. Hoefnagel [23] studied a patient with this type of tumor, but no MIBG uptake was found. Additional research is needed in this field. We performed MIBG scintigraphy using 131I because this radiolabel is used in our department. Adrenal glands are frequently associated with malignant tumors, particularly cortical carcinomas, lymphomas, and metastases. The characterization of benign and malignant lesions may be difficult in asymptomatic patients, although several hormonal and histological criteria have been proposed. In the absence of specific endocrine hypersecretion, however, no individual finding can absolutely resolve this issue. Although CT and MRI patterns can suggest the diagnosis of malignancy by such criteria as large tumor size, high contrast, or gadolinium enhancement, as well as by increased signal intensity on T2-weighted MR images or no signal change on chemical-shift MR sequence, these criteria are suggestive but not necessarily diagnostic of malignancy [5,6].

Although fine-needle biopsy has been proposed as part of the algorithm for diagnosing and treating patients with asymptomatic adrenal masses, this method is invasive and can have complications [8,24].
The results of this study and those of others [8] suggest that I-131 MIBG imaging may play a significant role in noninvasively characterizing silent adrenal tumors. Therefore I-131 MIBG imaging should be inserted in the diagnostic protocol of such patients to supplement CT or MRI findings, particularly when these images are inconclusive for lesion characterization.

Conclusion:

I-131 MIBG Adrenal scintigraphy has the potential to play a clinically significant role in the diagnostic evaluation of patients with asymptomatic pheochromocytomas. The main contribution consists of functional information for tumor characterization. Since most of the asymptomatic adrenal masses are adenomas I-131 MIBG should be used if the norchlolesterol scan is negative to confirm or rule out the presence of asymptomatic pheochromocytoma. If MIBG imaging results are also normal, FDG PET may be considered when clinical suspicion of malignancy is high. Conversely, when neoplastic patients are evaluated, FDG PET should be initially performed; if FDG PET results are normal, it should be followed by norcholesterol and, in sequence, MIBG studies. Thus, in patients with radiographically indeterminate adrenal masses, nuclear imaging is recommended for tumor diagnosis and for the selection of appropriate therapy, particularly when the CT or MRI findings are inconclusive for lesion characterization.

References