The role of 6-[18F]fluorodopamine positron emission tomography in the localization of adrenal pheochromocytoma associated with von Hippel–Lindau syndrome

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Abstract

Objective: [123I/131I]metaiodobenzylguanidine (MIBG) scintigraphy is considered as the gold standard in the localization of pheochromocytoma. However, this method has less optimal sensitivity for the detection of pheochromocytoma associated with von Hippel–Lindau (VHL). Our preliminary results suggest that this is partially due to the low expression of cell membrane norepinephrine transporter system in VHL-related pheochromocytoma cells. Another probable cause may be the low affinity that [123I/131I]MIBG has for these cells. Recently, 6-[18F]fluorodopamine ([18F]DA) positron emission tomography (PET) has been introduced as a novel functional imaging modality with high sensitivity for pheochromocytoma. Therefore, we investigated whether [18F]DA PET is more effective than [123I/131I]MIBG scintigraphy in the diagnostic localization of VHL-related adrenal pheochromocytoma.

Materials and methods: In this study, we evaluated seven VHL patients in whom adrenal pheochromocytomas were confirmed by histopathology results. Adrenal pheochromocytomas were localized using computed tomography (CT), magnetic resonance imaging (MRI), [123I/131I]MIBG scintigraphy and [18F]DA PET.

Results: [18F]DA PET localized pheochromocytoma in all the seven patients, as did in CT. In contrast, three out of the seven had negative results utilizing [123I/131I]MIBG scintigraphy and one out of the six patients had negative MRI results.

Conclusions: [18F]DA PET was found to show more promising results when compared with [123I/131I]MIBG scintigraphy in the diagnostic localization of VHL-related adrenal pheochromocytoma, with a 100% rate of localization. Thus, [18F]DA PET in conjunction with CT/MRI should be considered as an effective method for the proper localization of VHL-related adrenal pheochromocytoma.

European Journal of Endocrinology 156 483–487

Introduction

Pheochromocytoma is a catecholamine-producing tumor of chromaffin cells with dramatic and broad-ranging clinical manifestations spanning hypertension, tachyarrhythmia, sweating, pallor, fever, headaches and weight loss (1). The management of pheochromocytoma follows an algorithm including biochemical testing, conventional imaging modalities, functional imaging modalities and surgery (1–4). The treatment for pheochromocytoma is surgical removal based on accurate localization of the tumor coupled with positive biochemistry.

Conventional imaging modalities, including computed tomography (CT) and magnetic resonance imaging (MRI), are widely used in the initial diagnostic work-up of pheochromocytoma (5–7). In the case of adrenal gland and other ‘incidentalomas’, the widespread use of high-resolution anatomical imaging techniques such as CT and MRI increased the detection of these masses (8). In many cases, functional imaging modalities for localization of pheochromocytomas follow anatomical imaging (3, 9, 10). For example, [123I]metaiodobenzylguanidine (MIBG) is used in the localization of this tumor because of its excellent specificity (3, 9, 11, 12). Suboptimal sensitivity may be caused by the low affinity of MIBG for the cell membrane norepinephrine transporter system, its loss by tumor cell dedifferentiation, the lack of storage granules, altered vesicle transporter, or drug interferences (13, 14).

Von Hippel–Lindau (VHL) syndrome is an autosomal dominantly inherited cancer syndrome in which the
affected individuals develop a variety of tumors including pheochromocytomas (15). Several evaluations have shown that about 25% of VHL syndrome patients will have pheochromocytoma, of whom about half will develop bilateral adrenal tumors (1).

A few important considerations should be taken into account when VHL-related pheochromocytoma is localized. First, as most patients with VHL undergo regular (usually annual) biochemical follow-up, generally smaller rather than larger tumors are found. Secondly, although less common in the younger population, older patients commonly harbor benign adrenal tumors and therefore, a specific imaging method is needed to confirm that an adrenal tumor is indeed pheochromocytoma. Thirdly, because extra-adrenal pheochromocytomas almost always secrete norepinephrine, similar to VHL-related pheochromocytomas, elevated plasma or urine norepinephrine or normetanephrine levels do not necessarily prove the presence of an adrenal pheochromocytoma. Fourthly, it has been previously described that amongst familial pheochromocytomas, [123/131I]MIBG scintigraphy performs with lower sensitivity than with other adrenal pheochromocytomas (16, 17). This is most likely due to the low expression of cell membrane norepinephrine transporter by VHL-related pheochromocytoma cells (13, 16). Moreover, the occurrence of false-negative biochemical testing in VHL patients for pheochromocytoma makes proper localization crucial (18).

Positron emission tomography (PET) is an imaging modality that uses short-lived positron-emitting agents that offer the advantages of low radiation exposure, higher sensitivity and high spatial resolution when compared with other scintigraphic modalities. 6-[18F]Fluorodopa- mine ([18F]DA) utilizes a dopamine analog. Dopamine is a better substrate for the cell membrane norepinephrine transporter system when compared with most amines including norepinephrine and [123/131I]MIBG (13). The [18F]DA PET results in a lower radiation dose than [123/131I]MIBG scintigraphy and does not require the blocking of thyroid uptake of radioactive iodine. Moreover, PET scanning can be carried out immediately after the administration of [18F]DA, as opposed to the 24- to 48-h delay necessary for [123/131I]MIBG. One disadvantage is that [18F]DA is currently available only at the National Institute of Health as a Food and Drug Administration investigational drug.

In the present study, we investigate whether [18F]DA PET is superior to [123/131I]MIBG scintigraphy in the localization of VHL-related adrenal pheochromocytomas.

Materials and methods

Subjects

Our patients were selected from a group being evaluated under the National Institute of Child Health and Development, and the National Institute of Neurological Disorders and Stroke Review Boards approved the prospective studies for those patients with known or suspected pheochromocytoma. Our study included patients with confirmed VHL syndrome and who had both the [18F]DA PET scanning and the [123/131I]MIBG scintigraphy as well as CT or MRI. Of the 11 VHL patients evaluated, the seven patients who had histopathological confirmation of pheochromocytoma were included. All patients gave written informed consent. Patients included four males and three females with ages ranging from 22 to 51 (mean age 37 ± 11.48). At the NIH, all patients underwent extensive biochemical testing measured with in-house assays as described previously (19). Imaging studies including CT, MRI, [18F]DA PET scanning, and [123/131I]MIBG scintigraphy were also performed. All patients who underwent [18F]DA PET scanning and [123/131I]MIBG scintigraphy, CT scanning and MRI were done with a period of 6 months from each other. Surgery was performed as appropriate.

CT

CT from the neck to the pelvis was performed with a HiSpeed Advantage scanner (General Electric Medical Systems, Milwaukee, WI, USA). Section thickness was 5 mm through the chest and the upper abdomen to the adrenals and 10 mm through the lower abdomen. All sections were contiguous. A contrast agent was administered orally. Most studies were performed during a bolus of nonionic water-soluble contrast (130 ml injected intravenously at 2 ml/s).

MRI

MRI from the neck to the pelvis was obtained with a 0.5-T scanner (Picker, Highland Heights, OH, USA). T1-weighted spin-echo imaging was performed with a repetition time (TR) of 300 ms, echo time (TE) of 10 ms (TR/TE = 300/10) and eight excitations. T2-weighted spin-echo imaging was performed with TR/TE of 2000/80 and two excitations. Short inversion time inversion-recovery imaging was performed with a TR of 1600 ms, TE of 30 ms, inversion time of 100 ms and four excitations. Images were obtained in the coronal and axial planes.

[123/131I]MIBG

For MIBG scanning, patients were imaged following i.v. administration of 0.5 mCi (18.5 MBq) [131I]MIBG or 10 mCi (32.0 MBq) [123I]MIBG. To protect the thyroid from the accumulation of free radioactive iodine, patients were instructed to take 100 mg saturated solution of potassium iodide by mouth, twice a day for 4 and 8 days for [123I] and [131I]MIBG respectively, starting the night before MIBG administration.
$[^{131}I]$MIBG scans were acquired at 24 and 48 h on a dual-headed gamma camera (ADAC Laboratories, Milpitas, CA, USA) equipped with high-energy general-purpose collimators. Whole body planar scans and 20-min spot planar images of the skull to the mid-femurs were obtained, with additional views of the lower extremities included as needed. On occasion, 72 h images were also obtained. $[^{123}/^{131}I]$MIBG scans were obtained at 24 h and repeated at 48 h as needed. Planar whole body scans were obtained at 24 h using a dual-headed gamma camera (ADAC Laboratories) equipped with low-energy collimators and single photon emission tomography studies extending from the skull to the pelvis were performed by a Triad XLT triple-headed gamma camera (Trionix, Twinsburg, OH, USA).

**6-$[^{18}F]$DA PET**

For PET scanning, the patients were studied under fasting conditions and asked to avoid caffeine, tobacco and alcohol for at least 12 h before the scan. This was to avoid any interference with the imaging process – caffeine is a weak adrenergic stimulant, and tobacco and alcohol are known to stimulate the sympathetic system and norepinephrine. Patients received $[^{18}F]$DA (1.0 mCi; 37 MBq) i.v. Images were obtained using an Advance scanner (General Electric) with a 1.5 cm field of view. The first five patients had images limited to two fields of view that covered the upper abdomen, from above the liver to below the kidneys, each acquired over 20 min and attenuation corrected with 8-min transmission scans. These images were obtained in a three-dimensional mode (with filtered back-projection reconstruction algorithm). The last two patients underwent imaging of the entire torso with 8-min emission and 3-min transmission scans for attenuation correction. These images were acquired in two-dimensional mode (with an iterative reconstruction algorithm).

**Image analysis**

Anatomical imaging studies were interpreted by radiologists who were not blinded to the results of $[^{18}F]$DA PET, $[^{123}/^{131}I]$MIBG scintigraphy, or other patient information. $[^{18}F]$DA PET and $[^{123}/^{131}I]$MIBG scintigraphy studies were each read independently by two nuclear medicine physicians (J A C and C C C), during separate reading sessions with discrepancies reconciled by consensus. $[^{123}/^{131}I]$MIBG and $[^{18}F]$DA PET images were reviewed at separate times to minimize the recall bias. These readers were blinded to the results of all other imaging modalities. Lesions were graded on a scale of 1–5 (1, not pheochromocytoma; 2, probably not pheochromocytoma; 3, equivocal; 4, probable pheochromocytoma and 5, definite pheochromocytoma). Lesions with scores of 4 and 5 were counted as positive findings. For sensitivity calculations, $[^{18}F]$DA PET and $[^{123}/^{131}I]$MIBG scans were considered either positive or negative, regardless of the number of lesions seen.

**Results**

The diagnosis of pheochromocytoma was proven in the seven VHL patients by surgical removal of the tumor followed by histopathological examination. $[^{18}F]$DA PET correctly identified lesions with a score of 5 in all patients, indicating definite pheochromocytoma (Table 1).

Of the seven patients, five underwent $[^{123}I]$MIBG scans and two underwent $[^{131}I]$MIBG scans. Three patients (43%) had negative MIBG scans. Patients 2 and 4, both undergoing $[^{123}I]$MIBG, showed false-negative results. Similarly, patient 6 showed false-negative results using $[^{131}I]$MIBG (Fig. 1).

Of the seven patients, six were imaged by MRI. Pheochromocytomas were localized in five patients. Patient 4 had false-negative MRI results, whereas CT correctly gave positive results for all the seven patients (Table 1).

**Discussion**

The present study demonstrates the ability of $[^{18}F]$DA PET to detect and localize VHL-related adrenal pheochromocytoma. $[^{18}F]$DA PET and CT resulted in correct localization of VHL pheochromocytoma.

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**Table 1** Patient characteristics for the seven evaluated patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor location</th>
<th>Tumor size (cm)</th>
<th>6-$[^{18}F]$Fluorodopamine PET</th>
<th>$[^{123}/^{131}I]$MIBG</th>
<th>CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Left adrenal</td>
<td>1.0×1.0×1.0</td>
<td>+</td>
<td>0/0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>Right adrenal</td>
<td>3.5×3.5×2.5</td>
<td>+</td>
<td>0/0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>Bilateral adrenal</td>
<td>8×6×4 (left)</td>
<td>+</td>
<td>0/0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Right adrenal</td>
<td>8×6×5 (right)</td>
<td>+</td>
<td>0/0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>Bilateral adrenal</td>
<td>1.5×1.0×0.8</td>
<td>+</td>
<td>0/0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>Right adrenal</td>
<td>3.0×1.5×0.6 (left)</td>
<td>+</td>
<td>0/0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Left adrenal</td>
<td>1.6×1.0×1.5</td>
<td>+</td>
<td>0/0</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Medication for patients with negative $[^{123}/^{131}I]$MIBG scintigraphy: patient 2, none; patient 4, Accupril 10 mg/day; patient 6, Paxil 20 mg/day. +, Positive; −, negative; 0, not performed; PET, positron emission tomography; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; CT, computed tomography. Patient 5: right tumor not removed. MRI 5 years prior to surgery.
localization in all the seven patients, whereas $^{[123/131I]}$MIBG scintigraphy localized pheochromocytoma in only four out of the seven patients and MRI scans detected pheochromocytomas in five out of the six patients.

The search for pheochromocytoma in patients with VHL syndrome usually starts very early, since the other tumors which are also associated with VHL syndrome usually occur in the patient prior to the occurrence of pheochromocytoma (20). Thus, typically, only a small adrenal pheochromocytoma is suspected or found either by mildly elevated plasma normetanephrine or nor-epinephrine levels or by positive CT scan results. However, since VHL-related pheochromocytoma secrete norepinephrine and there is a high frequency of benign adrenal adenomas in the general population, with 3% of persons over the age of 50 presenting with adrenal masses upon autopsy (21), functional imaging is frequently necessary to prove that an adrenal lesion is indeed pheochromocytoma. Available nuclear medicine imaging modalities relevant to pheochromocytoma include tumor-specific radiopharmaceuticals, such as $^{[123/131I]}$MIBG, $^{[18F]}$DA, $^{[11C]}$hydroxyephedrine (HED) ($^{[11C]}$HED) and $^{[11C]}$meta-HED ($^{[11C]}$meta-HED), the less specific $^{[18F]}$dihydroxyphenylalanine (DOPA) ($^{[18F]}$DOPA) and nonspecific $^{[18F]}$fluoro-2-deoxy-D-glucose (FDG) ($^{[18F]}$FDG) (11, 22–28). The sensitivity of $^{[11I]}$MIBG was found to be 75% for VHL-related pheochromocytomas (17). We have previously reported on the utility of $^{[18F]}$DA for localizing pheochromocytoma (22). In a recent comparative study in 16 individuals with metastatic pheochromocytoma, $^{[18F]}$DA was compared with $^{[11I]}$MIBG and found to be a superior functional imaging modality (29). Recent studies using $^{[11C]}$HED and $^{[11C]}$meta-HED PET also successfully localized adrenal pheochromocytoma including VHL-related pheochromocytoma (25, 26). Whole body imaging using $^{[11C]}$meta-HED PET was found to be superior to $^{[123]}$MIBG (26). Furthermore, current use of new PET/CT devices is now a promising avenue in more accurate diagnostic localization of various tumors including pheochromocytoma (26, 28).

Our results support the use of $^{[18F]}$DA PET in VHL-related pheochromocytoma. This technique should be particularly useful in symptomatic patients in whom $^{[123/131I]}$MIBG results are negative, in older patients with adrenal masses where the presence of benign adenomas are common and in VHL patients in whom pheochromocytoma is the first manifestation of the disease.

In a retrospective study, Miskulin et al. (11) assessed whether routine preoperative $^{[123]}$MIBG scintigraphy is necessary before adrenalec-toy for pheochromocytoma. They concluded that in nonfamilial cases where there is clear biochemical evidence for pheochromocytoma and a unilateral adrenal mass consistent with pheochromocytoma is detected with CT or MRI, adrenalectomy can be offered without MIBG scintigraphy. This recommendation is valid mainly for epinephrine secreting tumors since these tumors mostly arise in the adrenal gland. For pheochromocytomas that secrete predominately nor-epinephrine, such as those associated with VHL and succinate dehydrogenase mutation, anatomical imaging studies should still be coupled with functional imaging since these tumors are often bilateral, recurrent, or located extra-adrenally. Furthermore, benign adrenal adenomas are common especially in older patients and can be mistakenly considered as pheochromocytoma.

In summary, $^{[18F]}$DA PET was found to be superior when compared with $^{[123/131]}$MIBG scintigraphy in the diagnostic localization of VHL-related adrenal
pheochromocytoma, with a 100% rate of localization. Thus, $^{18}$F-DOPA PET in conjunction with CT should be considered as the most effective method for the proper functional localization of VHL-related adrenal pheochromocytoma.

Acknowledgements

We would like to thank Millie Whatley and Dr McClellan M Walther for their assistance in the preparation of this manuscript. This research was supported (in part) by the Intramural Research Program of the NIH, NICHD.

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Received 29 November 2006
Accepted 25 January 2007

www.eje-online.org