CASE REPORT

The use of 18-fluoro-dihydroxyphenylalanine and 18-fluorodeoxyglucose positron emission tomography scanning in the assessment of metaiodobenzylguanidine-negative phaeochromocytoma

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Abstract

123I-Metaiodobenzylguanidine (123I-MIBG) scintigraphy scanning is commonly used in the imaging of phaeochromocytoma (and paraganglioma) to confirm the site of disease and whether any spread has occurred. However, 123I-MIBG imaging is negative in 15% of cases of benign phaeochromocytoma and around 50% of cases of malignant phaeochromocytoma. In recent years, positron emission tomography (PET) scanning using various different radiotracers has been shown to be a good alternative or supplementary investigation in phaeochromocytoma. We present the cases of four patients with symptoms and signs suggestive of phaeochromocytoma, but who had negative 123I-MIBG scans, and illustrate the usefulness of 18-fluoro-dihydroxyphenylalanine PET scanning in their assessment. In one of the patients, we illustrate how fluorodeoxyglucose PET scanning can provide useful information about the extent of malignant disease. These illustrative cases lend further support for the use of PET scanning in the assessment of phaeochromocytoma and suggest that it may have a particularly important role in the investigation of patients in whom 123I-MIBG scanning is negative.

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Introduction

Phaeochromocytoma is a rare (~0.5% of all cases) but potentially curable cause of hypertension (1). If left undiagnosed, it can be fatal, reflecting the risks associated with hypertensive crisis, catastrophic haemorrhage and malignancy. No clinician is immune to the presentation of phaeochromocytoma in its myriad of guises, and most average-sized hospitals need to detect a very small number of cases per year from among many times this number of patients exhibiting hypertension and other features of sympathetic nervous system overactivity.

Diagnosis of phaeochromocytoma

Once the presence of a phaeochromocytoma is clinically suspected, biochemical confirmation of the diagnosis is established by demonstrating elevated levels of catecholamines (noradrenaline, adrenaline and dopamine) and/or their metabolites (normetadrenaline, metadrenaline and vanillyl mandelic acid (VMA)) in blood and/or urine (2). Normetadrenaline and metadrenaline levels are probably the most sensitive biochemical tests for phaeochromocytoma, while VMA is highly specific for phaeochromocytoma (or neuroblastoma) but has a lower sensitivity for phaeochromocytoma. In most cases (excepting some familial syndromes) only when the biochemical diagnosis has been secured, should investigation proceed to the second phase, i.e. anatomical localisation of the tumour. Computed tomography (CT) or magnetic resonance imaging (MRI) of the adrenal glands are the investigations of choice in those cases where elevated adrenaline or metadrenaline levels point to the tumour being of likely adrenal origin. In many centres, radionuclide scanning using 123I- or 131I-metaiodobenzylguanidine (MIBG), which is specifically taken up by chromaffin tissue, is used to confirm that the visualised lesion is indeed a phaeochromocytoma rather than an adrenal ‘incidentaloma’ (the latter is found in up to 5% of patients undergoing abdominal imaging), and to assess whether there is any evidence of distant spread to suggest malignancy. The order of scans may be reversed in patients with non-familial phaeochromocytoma and normal plasma or urine adrenaline or metadrenaline levels, in whom an extra-adrenal phaeochromocytoma is more likely, and in whom a positive MIBG scan may avoid the need for whole-body CT or magnetic resonance imaging (MRI).
**MBI G-negative phaeochromocytoma**

However, in some cases, no definite abnormality is seen on CT or MRI, and MIBG scans are negative in around 15% of phaeochromocytomas and in up to 50% of malignant tumours. This can lead to a dilemma in patients with only borderline elevation of catecholamine levels, especially noradrenaline (or normetadrenaline), in whom a negative MIBG scan fails to bring closure to the search for a phaeochromocytoma, causing anxiety in the patient and doctor. In some of these ‘MBI G-negative’ patients, the phaeochromocytoma may be located on whole-body CT or MR imaging. However, these are prone to false-positive or false-negative results. Selective venous sampling may also be used to locate the phaeochromocytoma, but this is a specialist technique (requiring an expert interventional radiologist) which is easy to misinterpret and carries risks including the provocation of a hypertensive crisis and is therefore rarely used. In cases of ‘occult’ phaeochromocytoma, positron emission tomography (PET) scanning may provide a firm diagnosis.

**PET scanning in phaeochromocytoma**

PET radiotracers that have been successfully used in the investigation of phaeochromocytoma include 18-fluoro-dihydroxyphenylalanine (18F-DOPA) (3), 18-fluoro-dopamine (18F-dopamine) (4, 5) and 18-fluoro-deoxyglucose (18F-FDG). Both 18F-DOPA and 18F-dopamine PET have been reported to be highly sensitive and specific for phaeochromocytoma, while 18F-FDG PET, although less sensitive and specific for benign phaeochromocytoma, may be particularly useful in imaging malignant phaeochromocytoma where tumour cells exhibit higher metabolic activity (6). 123I-MIBG and 18F-dopamine uptake is dependent on the expression of catecholamine uptake and storage mechanisms (including the noradrenaline transporter (SLC6A2 NET1) and the vesicular monoamine transporters (VMAT1 and VMAT2); (7)) in tumour cells; 18F-DOPA uptake is governed by the expression of neutral amine precursor uptake and decarboxylation mechanisms; 18FDG uptake is related to glucose uptake by tumour cells. Thus, the more specific cellular uptake mechanisms are mainly confined to cells of neuroendocrine origin, while those for glucose uptake are more globally expressed. This explains the differences in sensitivity and specificity of the various radiotracers in phaeochromocytoma tissue.

Recently, we have encountered four patients with biochemical findings suggestive of phaeochromocytoma, but with negative 123I-MIBG scans. Three of the patients were ultimately diagnosed with benign phaeochromocytoma and one with malignant disease. The diagnosis in each case was confirmed by histology. In this report, we describe and illustrate how the results of 18F-DOPA, and in one case both 18F-DOPA and 18F-FDG, PET scans proved central to their effective management.

**Case 1**

A 56-year-old man with a history of hypertension and epilepsy presented after a fall from a ladder. He had signs of accelerated hypertension including papilloedema. Urinary noradrenaline and dopamine levels were markedly elevated. A CT scan showed a suspicious left paranephric mass although this failed to take up 123I-MIBG; normal bilateral adrenal uptake was noted (Fig. 1a). In contrast, 18F-DOPA PET scanning revealed abnormal uptake in the left paranephric region (Fig. 1b), confirming the diagnosis of extra-adrenal phaeochromocytoma (paraganglioma). The patient was treated with phenoxybenzamine prior to successful surgical removal. Histology showed nests of polygonal cells with eosinophilic cytoplasm, patchy vascular invasion and positive immunocytochemistry for chromogranin A, consistent with extramural phaeochromocytoma (paraganglioma).

Initially he made a good recovery, however a few months later, he complained of neck, back and chest pain. An 18FDG-PET scan showed spinal, pelvic and rib metastases (Fig. 1c). He was managed palliatively according to his wishes and died a few months later. As the 18F-DOPA PET and 18FDG-PET scans were separated by several months, it is not possible to say whether one or more of the metastatic lesions might have been visible on 18FDG-PET imaging if this had been undertaken at the time of preparation for surgery. Accordingly, it could be argued that there is a case for the combined use of 18F-DOPA PET and 18FDG-PET scanning in the initial assessment of those patients in whom malignancy is suspected at the outset.

**Case 2**

A 51-year-old man with a history of hypertension developed sweating, headache and palpitations, which occurred almost exclusively on defecation. On clinical examination, he was noted to have multiple café-au-lait patches, and a clinical diagnosis of neurofibromatosis was made. His mother and daughter were reported to have phaeochromocytoma tissue. Somewhat unexpectedly, however, this failed to identify any abnormalities within the pelvis. In view of the strong temporal correlation between the patient’s symptoms and defecation, a 123I-MIBG scan was performed to look for extra-adrenal phaeochromocytoma tissue. Somewhat unexpectedly, however, this failed to identify even the primary adrenal lesion (Fig. 2a). Therefore, an 18F-DOPA PET scan was performed, which demonstrated localised uptake confined to the right adrenal gland (Fig. 2b). The patient
was treated with combined α- and β-adrenoceptor blockade and subsequently underwent laparoscopic adrenalectomy, from which he made a good recovery. Histology showed an encapsulated tumour composed of large polygonal cells with eosinophilic granular cytoplasm and pleomorphic nuclei. Immunocytochemistry showed strong positivity for chromogranin and synaptophysin, consistent with phaeochromocytoma. Postoperatively, he remains in remission both clinically and biochemically.

Case 3

A 35-year-old man presented with palpitations and sweating, which were worse when lying on his left side. His blood pressure was persistently elevated, and both plasma noradrenaline and adrenaline levels were raised several fold, with further increases demonstrable in response to the patient lying on his left side. An ultrasound scan revealed a right adrenal mass. However, because both the patient and physician were convinced that the tumour must be left sided, he was referred for further investigation. 123I-MIBG scan was negative (Fig. 3a). In order to confirm the localisation of the tumour, an 18F-DOPA PET scan was performed, which showed abnormal uptake confined to the right adrenal gland (Fig. 3b). He was treated with phenoxybenzamine followed by laparoscopic adrenalectomy with complete resolution of his symptoms. Histology showed an encapsulated tumour composed of large polygonal cells with granular amphophilic cytoplasm and pleomorphic nuclei with scattered bizarre cells and occasional mitotic figures, consistent with phaeochromocytoma.

Figure 1 (a)123I-MIBG scan showing bilateral adrenal uptake (arrows), which can be a normal finding. There is also a normal pattern of uptake in the liver and salivary glands. (b) 18F-DOPA PET scan showing abnormal uptake in the left paranephric region (arrow) confirming the diagnosis of extra-adrenal phaeochromocytoma. Normal uptake is seen in the gallbladder area. (c) 18FDG PET scan showing spinal, pelvic and rib metastases (arrows). Normal pattern of uptake is seen in the heart, brain, gall bladder and bladder regions (excretion).

Figure 2 (a)123I-MIBG scan showing normal pattern of uptake, failing to identify the primary adrenal lesion. (b) 18F-DOPA PET scan showing abnormal uptake in the right adrenal gland (arrow). A normal pattern of uptake is also seen in the kidneys; DOPA is converted to dopamine in the kidneys, then excretion occurs via the urinary tract and bladder.
Case 4

A 48-year-old man presented with palpitations and high blood pressure. He had a history of left adrenal phaeochromocytoma removed surgically 20 years earlier and had remained well in the intervening period. CT scan revealed a 1.5 cm right adrenal mass (Fig. 4a), but he had no elevation of adrenaline secretion and the mass did not accumulate $^{123}$I-MIBG (Fig. 4b); therefore, it was not clear whether this mass was functional and further investigation by adrenal venous sampling failed to confirm the presence of a right adrenal phaeochromocytoma. He was treated medically for 7 years because of the need to be certain about the localisation of a tumour before performing a second adrenalectomy (and the preference of the patient for medical treatment unless the presence of phaeochromocytoma was irrefutable) (8). However, an $^{18}$F-DOPA PET scan finally confirmed the presence of a phaeochromocytoma in the right adrenal gland (Fig. 4c). The patient was treated with phenoxybenzamine, underwent successful laparoscopic right adrenalectomy and is now maintained on long-term glucocorticoid and mineralocorticoid replacement therapy. Histology showed features consistent with a phaeochromocytoma confined within the adrenal gland with no evident mitotic activity, necrosis or vascular invasion.

Conclusions

In summary, we present four cases of patients with phaeochromocytoma in whom $^{123}$I-MIBG imaging was negative and in whom PET scanning enabled non-invasive diagnosis and determination of the extent of disease. We propose therefore that $^{18}$F-DOPA PET should replace venous sampling as the next step in locating elusive tumours, whilst $^{18}$F-FDG PET may be more useful in patients with malignant phaeochromocytoma in whom de-differentiation of the tumour has occurred. In some circumstances, different metastatic deposits in the same patient may show differential radiotracer uptake if cells in some tumour deposits have de-differentiated to the extent that they no longer express mechanisms for the uptake of noradrenaline or neutral amine precursors (6). Although PET scanning is currently only available in a small number of specialist centres, the incidence of phaeochromocytoma is sufficiently low that all confirmed or suspected cases, or at least all of those with negative $^{123}$I-MIBG scans, could readily be referred to a PET centre for full assessment. At present, many phaeochromocytoma patients are managed in non-tertiary care centres, where there is the dual risk of false-positive diagnosis of a tumour in a normal adrenal gland visualised (as in the first case) by $^{123}$I-MIBG scanning, and false-negative diagnoses preventing surgical cure. Confident localisation permits laparoscopic removal of all but the largest adrenal and extra-adrenal phaeochromocytomas.
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References