Nuclear medicine imaging in the evaluation of endocrine hypertension

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ABSTRACT
Endocrine hypertension forms a small (< 5%) but curable subset of patients with hypertension. Common endocrine causes of hypertension include pheochromocytoma, Cushing’s syndrome, primary hyperaldosteronism, and thyroid disorders. Nuclear medicine imaging plays an important role in evaluation of patients with endocrine hypertension. It has established role in patients of pheochromocytoma/paraganglioma, Cushing’s syndrome, aldosteronism, and thyroid disorders. We present a brief overview of role of nuclear medicine imaging in endocrine hypertension. Development of newer radiotracers might further broaden the role of nuclear medicine in these patients.

Key words: Endocrine hypertension, imaging, nuclear medicine, pheochromocytoma

INTRODUCTION
Hypertension is the commonest cardiovascular disorder affecting about 20% adult populations worldwide. The prevalence of hypertension in India is reported as ranging from 10 to 30.9%. It is important because it markedly increases the risk of stroke, heart failure, myocardial infarction (heart attack), and renal failure. In more than 95% of patients, no underlying cause can be determined, known as essential hypertension. Essential hypertension is currently considered an incurable disorder that requires life-long medical management. A small fraction (< 5%) of patients with hypertension have diagnosable causes known as secondary hypertension. The clinical importance of identifying cases of secondary hypertension is obvious, however. Unlike essential hypertension successful treatment of the underlying cause may provide a cure for patients with secondary hypertension. Secondary forms of hypertension that are endocrine in origin differ most notably from essential hypertension in that an etiology can be identified, onset is often abrupt, severity may be greater, a positive family history of hypertension is frequently missing, and there is no specific age criterion for occurrence. Specific symptoms may help guide the diagnostic evaluation. Secondary forms of endocrine hypertension can emerge in connection with such diverse endocrine disorders as primary hyperaldosteronism, Cushing’s disease, or pheochromocytoma, among others.

PHEOCHROMOCYTOMA
A pheochromocytoma is a tumor of neuroectodermal origin that produces excess quantities of catecholamines as well as numerous other physiologically active peptides. This overabundance of catecholamines causes blood pressure to increase, accompanied by a constellation of signs and symptoms that can imitate those seen with a diverse grouping of medical and surgical disorders. A pheochromocytoma is a rare cause of secondary hypertension, responsible for less than 1% of all cases of hypertension. Early recognition, precise localization, and attentive management of a benign pheochromocytoma in most instances lead to a complete cure. These tumors can prove life-threatening, particularly during surgical and obstetric procedures.[1] These points highlight the need for accurate preoperative localisation.
Conventional imaging
Computed tomography (CT) is usually first test done for evaluation of adrenal glands. Unenhanced CT is important to provide density measurements of lesions; it is usually followed by a, preferably delayed, contrast-enhanced study that can quantify the percentage of absolute or relative contrast enhancement washout and shows the vessels in the region of the adrenal glands. This can assist in characterisation and distinguishing adenomas from other adrenal tumours with 98% sensitivity and 92% specificity. However, it cannot differentiate between cortical and medullary tumors. Most sporadic adrenal pheochromocytoma are at least 2-3 cm in diameter and can be readily visualised with CT. Smaller (1-2 cm in diameter) pheochromocytoma are usually homogeneous in appearance, with a density of 40-50 HU on unenhanced CT. Larger pheochromocytoma, however, can be inhomogeneous with areas of hemorrhage, and low attenuation necrosis may be present. After contrast administration, pheochromocytomas enhance avidly and have a prolonged contrast washout phase. Pheochromocytomas have higher signal intensity than that of fat on T2-weighted sequences. This characteristic finding is due to the hypervasularity of the tumors. However, the specificities of both CT and MRI scans are disappointingly low (as low as 60%) in localizing pheochromocytoma particularly metastatic variants. Patients that harbour adrenal masses, which are not adequately characterised with CT or MRI, can be further evaluated with functional nuclear medicine modalities. In many patients with pheochromocytoma, especially in those with extra-adrenal pheochromocytoma, adrenal pheochromocytoma larger than 5 cm, or mutations of genes encoding mainly subunits B and D of the mitochondrial enzyme succinate dehydrogenase (SDHB and SDHD), the possibility of metastatic disease or multiple tumors should be considered. For this, functional imaging modalities are most useful. These modalities are based on physiological and pathophysiological processes (cellular metabolism, tissue perfusion and local synthesis, uptake and storage of hormones and their receptors) and assist the preoperative staging of tumors. Furthermore, they can be of use in the evaluation of suspicious lesions and the identification of metastatic or recurrent tumors. Lesions detected by anatomical imaging can be specifically identified as pheochromocytoma by functional imaging agents that target the catecholamine synthesis, storage, and secretion pathways of chromaffin tumor cells.

I-123/131 Metaiodobenzylguanidine
Similar to the sympathetic nervous system, pheochromocytoma and most extra-adrenal paragangliomas express cell membrane norepinephrine transporters (NET) through which catecholamine can enter cells to be stored in vesicle. Metaiodobenzylguanidine (MIBG) has been used for diagnostic imaging in pheochromocytoma because of its resemblance to norepinephrine and its good affinity and uptake by the NET. Until recently the gold standard functional imaging method for pheochromocytoma was scintigraphy with I-131MIBG, with sensitivity of 77%-90% and excellent specificity of 95%-100%. However, it is scintigraphy with another radionuclide, I-123 MIBG, which offers the option of performing single photon emission tomography (SPECT) and is reported to have sensitivity of 83%-100% and specificity of 95%-100% for detecting pheochromocytoma. Scintigraphy imaging with I-123 MIBG, compared with I-131 MIBG, is advantageous because of its optimal β-emissions and lack of β-particles that result in a lower absorbed dose. In addition, the I-123 isotope can be visualized with SPECT imaging, further increasing its diagnostic accuracy. Importantly, the normal adrenal medullary may show physiological uptake of both I-131 and I-123 MIBG. Unfortunately availability of I-123 MIBG, compared to I-131 MIBG, is limited and it is not available in India and many other countries. Suboptimal sensitivity of MIBG scintigraphy might be associated with the relatively low affinity of MIBG to the NET, the lack of storage granules or the loss of transporters by tumor cell de-differentiation. Furthermore, medication use interfering with MIBG uptake in patients could result in false-negative results. SPECT with I-123MIBG improves the identification of lesions in case of lesions with limited uptake or those with central necrosis. Recent use of SPECT-CT in such patients has shown further improved its utility with accurate anatomical localisation. In a recent study by Fukuoka et al. showed that SPECT-CT detected additional lesions in 81% patients for I-123MIBG and 53% patients for I-131MIBG when compared to planar scintigraphy. The experience at our centre is similar, with I-131 MIBG SPECT-CT providing advantage over planar scintigraphy for small lesions, lesions with necrosis and extra-adrenal lesions [Figures 1 and 2].

Somatostatin receptor scintigraphy
Somatostatin receptor imaging might be considered as a supplement for MIBG scintigraphy in pheochromocytoma and paragangliomas patients with suspected metastatic disease. From in vitro and in vivo studies, it has been established that somatostatin receptor subtypes 3 and 4 are expressed in pheochromocytoma, including adrenal and metastatic disease. In-111pentetreotide (Octreoscan; Mallinckrodt Inc.) has only moderate affinity for these subtypes, compared with subtypes 2 and 5. Somatostatin receptor scintigraphy (SRS) has been used with variable results to detect this tumor. It has higher sensitivity for detecting metastatic pheochromocytoma than for detecting benign pheochromocytoma. Newer somatostatin
analogues like 1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid -Tyr3-octreotide (DOTATOC) have shown favourable characteristics in imaging with high affinity for somatostatin receptors and a stable and easy process of labelling.[23] Although most existing somatostatin-based tracers only have affinity for the somatostatin receptor subtype 2, which is not always present on pheochromocytoma and paraganglioma cells, newer compounds, such as 1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid-1-NaI3-Octreotide (DOTANOC), also have affinity for other somatostatin receptor subtypes.[24] Kroiss et al. compared Ga-68 DOTANOC spositron emission tomography (PET)-CT with I-123MIBG scintigraphy in patients with pheochromocytoma.[25] In pheochromocytoma patients, on a per-lesion basis, the sensitivity of Ga-68DOTA-TOC was 91.7% and that of I-123 MIBG was 63.3%. Our experience is similar, with Ga-68 DOTANOC/TOC being better than I-131 MIBG for detecting extra adrenal pheochromocytoma, smaller lesions and lesions with central necrosis [Figure 3].

F-18 Fluorodopa and F-18 Flurodopamine PET-CT
Advantages of PET, compared with other functional imaging modalities, include the means of immediate whole-body imaging, the possibility of quantitative assessment of uptake, and the absence of artifacts from scar tissue or from the presence of metallic clips after surgery.[26] Although PET with F-18 Fluorodeoxyglucose (FDG) has been used with some success for imaging metastatic pheochromocytoma, it is nevertheless a non-specific ligand that shows uptake in various tumors.[27] Moreover, because of low metabolic activity of pheochromocytomas FDG uptake in these tumors is usually low. F-18 labeled dihydroxyphenylalanine (FDOPA) has enabled PET imaging of benign pheochromocytoma.[28] FDOPA enters the cell via the amino acid transporter based on the capability of pheochromocytomas and other neuroendocrine tumors to take up, decarboxylate, and store amino acids and their biogenic amines.[24] Recent studies confirmed the usefulness of this technique in benign and malignant pheochromocytomas.[29] It has been found to be superior to both I-123/131 MIBG and FDG for these tumors.[30,31] In a study by Eisenhofer et al.[32] it was found that in patients with metastatic disease, a per-lesion-based analysis showed a limited overall sensitivity of FDOPA PET: less than half of the metastases detected by CT/MRI were detected by FDOPA PET. On the other hand, in 71% of patients with malignant pheochromocytomas/paragangliomas, one or more metastases were discerned by the technique. Moreover, a subgroup analysis indicated that its sensitivity is excellent for non- SDHB metastases (94%) but poor for SDHB-related metastases (20%). For non-metastatic pheochromocytoma FDOPA performed similar to I-123 MIBG. Another tracer for imaging pheochromocytoma is F-18 Fluoroalominane.[33] Fludoropamine (FDA) PET is clearly superior to I-131 MIBG with sensitivities of 100% and 56%, respectively. In the study by Henri et al.[34] FDA PET showed high sensitivity, for both primary tumors and metastases (76% and 77%, respectively). They concluded that FDA PET was superior to FDOPA PET and I-123 MIBG scintigraphy for localizing metastases. In fact, the
number of lesions detected by FDA PET far exceeded the number of lesions on CT and MRI and other functional imaging modalities. We at our centre have found FDOPA PET-CT to be better than I-131 MIBG for imaging pheochromocytoma and especially extra-adrenal lesions.

**CUSHING’S SYNDROME**

Hypercortisolemia is associated with hypertension in approximately 80% of adult cases and half of children. In patients with Cushing’s disease, night-time blood pressure decline is significantly lower than that in patients with essential hypertension. In adrenocorticotropic hormone (ACTH) dependent states, most typically an ACTH-secreting adenoma (also known as Cushing’s disease), the excess of cortisol originates from direct adrenal stimulation. This represents about 80% of the ACTH-dependent causes of Cushing’s disease. Non pituitary ectopic source of ACTH like small cell lung carcinoma, oat cell carcinoma, and carcinoid of bronchus and thymus is responsible for rest of cases. Most ACTH-independent cases of Cushing’s disease result from an adrenal adenoma, carcinoma, or micronodular or micronodular hyperplasia. Despite the sharp anatomic detail of CT or MRI, evaluation with adrenal scintigraphy in conjunction with hormonal analysis is used not only in defining the function of adrenal lesions but also in the diagnosis and staging of malignant neoplasms of adrenal origin.\(^{35}\)

**NP-59 adrenal scintigraphy**

Cholesterol analog, like I-131 6-iodomethyl-19-norcholesterol (NP-59), are incorporated in low-density lipoproteins and accumulated by adrenocortical cells through a receptor-mediated process.\(^{36}\) The availability of sensitive ACTH assays and the routine use of anatomic imaging techniques for detection of pituitary adenomas and other ACTH-secreting tumors have reduced the use of adrenal scintigraphy for the diagnosis of ACTH dependent Cushing syndrome. ACTH-independent Cushing syndrome can result from an adrenal adenoma, adrenal carcinoma, or bilateral nodular adrenal hyperplasia. The scintographic pattern of adrenal adenoma is unilateral visualization of the gland containing the adenoma; the contralateral gland is not visualized because it is hypofunctional and atrophic as the result of prolonged ACTH suppression by autonomous cortisol secretion from the adrenal adenoma. In adrenal carcinoma, there is nonvisualization of the adrenal glands bilaterally. These tumors do accumulate radiocholesterol but usually have insufficient tracer uptake for visualization on scintigraphy. However, tumoral glucocorticoid secretion is sufficient to cause hypercortisolism, suppress pituitary ACTH production, and radiocholesterol accumulation by the contralateral adrenal gland.\(^{37}\) In the evaluation of patients with persistent cortisol excess after bilateral adrenalectomy for ACTH-dependent Cushing syndrome, NP-59 scintigraphy has been used for identification of adrenal remnants and to guide surgical intervention.

**PET/PET-CT**

The main utility of PET/PET-CT lies in localizing the site of ectopic ACTH production causing Cushing’s syndrome. Conventional imaging modalities cannot localize the source of ACTH in 30-50% of patients with Cushing’s syndrome caused by ectopic ACTH secretion. FDG PET has been evaluated for this purpose.\(^{38,39}\) However, its role remains controversial. Pacak et al.\(^{40}\) in their study, found FDG PET to be inferior to SRS with In-111petriotide for detecting ectopic ACTH producing tumors. Zemskova et al.\(^{41}\) assessed the utility of various functional imaging modalities for detection of ectopic ACTH-producing tumors. Low dose SRS, high dose SRS, FDG-PET, and FDOPA-PET had sensitivities per patient of 57%, 50%, 64%, and 55% and positive predictive values (PPV) per lesion of 79, 89, 53, and 100%, respectively. They concluded that a combination of conventional imaging along with SRS should be used for initial evaluation of such tumors. SRS with Ga-68 DOTATOC/NOC has been employed for detecting ectopic ACTH producing tumors.\(^{42}\) Experience from our centre shows limited value of this modality for this indication. FDG PET-CT has been investigated in patients with adrenal

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**Figure 3:** A 28-year-old male with MEN 2 syndrome. CT (a) images reveal bilateral large adrenal masses with necrotic centre (bold arrows). 68Ga-DOTANOC PET (b) and PET-CT (c) images show intense tracer uptake in peripheral part of the masses, with no uptake in central necrotic part. Maximum intensity projection (MIP) image show bilateral adrenal masses (arrows). The diagnosis of pheochromocytoma was made and confirmed with histopathology. Note should be made of other foci of uptake in bones (arrows) due to uptake of the tracer in bone metastasis from medullary carcinoma of thyroid.
carcinoma. In a large study the sensitivities for the detection of distinct lesions and the diagnosis of metastatic organs were 90 and 93% for FDG PET-CT and 88 and 82% for CT, respectively.[43] Mackie et al[44] evaluated FDG PET-CT in locally recurrent and metastatic adrenocortical carcinoma (ACC). They concluded that most ACC accumulate and retain FDG. However, an occasional or very small tumor may not accumulate sufficient FDG to allow detection.

**Primary Hyperaldosteronism**

Primary aldosteronism can occur at all ages, although in most reported series, patients fall in the 30 to 50 year age range. Primary aldosteronism is a common cause of resistant hypertension in black and white patients.[45] It should be considered as a diagnostic possibility in any patient with spontaneous hypokalemia, moderately severe hypokalemia induced by usual doses of diuretics, or refractory hypertension.[46] The adrenal pathology underlying this syndrome is either an aldosterone-secreting cortical adenoma (usually <2 cm in diameter) or bilateral hyperplasia of the zona glomerulosa. Adrenal scintigraphy with NP59 has been employed for functional imaging of aldosterone producing tumors. Scintigraphy in hyperaldosteronism is facilitated with the use of dexamethasone administration with the goal of suppressing the ACTH-dependent component of radiocholesterol uptake occurring in the zona fasciculata. Early visualization, before the fifth day after injection, in a unilateral pattern (aldosteronoma) or bilateral pattern (adrenal hyperplasia) before day 5 after injection is the hallmark of primary aldosteronism. More recently, SPECT-CT with NP59 has been employed for evaluation of primary aldosteronism. Chen et al[47] evaluated NP59 SPECT-CT in 15 patients with CKD and atypical presentation of primary aldosteronism. Yen et al[48] evaluated NP59 SPECT-CT in 31 adrenal lesions of 27 patients who had been clinically confirmed to have PA, had inconclusive CT and adrenal venous sampling (AVS) test results, and had undergone NP-59 imaging before adrenalectomy. NP59 SPECT-CT had sensitivity of 81.8% and specificity of 66.6%. SPECT-CT performed significantly better than planar imaging \( P = 0.039 \). PET with 11C-Metomidate (MTO) has also been used for evaluation for primary aldosteronism. Hennings et al[49] evaluated dexamethasone suppression treatment MTO PET in 13 patients with adrenocortical tumors. All tumors were detected and categorised as adrenocortical by MTO-PET. SUVmax were higher in primary aldosteronism compared to nonfunctional adenomas. Normal adrenal cortex was suppressed after dexamethasone \( P < 0.05 \), but tumor SUV was not significantly decreased after suppression in either primary aldosteronism or nonfunctional tumors \( P > 0.05 \).

**Thyroid Disorders**

Approximately one-third of patients with hyperthyroidism have hypertension, which often resolves after achieving euthyroidism. Hyperthyroidism increases systolic blood pressure by increasing heart rate, decreasing systemic vascular resistance, and raising arterial pressure. In hyperthyroidism, patients usually are tachycardic and have high cardiac output with an increased stroke volume and elevated systolic blood pressure. The main indication of nuclear medicine technique is differentiation of hyperthyroidism from Grave’s disease. Radio-iodine uptake (RAIU) with I-123/I-131NaI is commonly employed for this purpose. Increased RAIU at 2 hr and 24 hrs is seen in Grave’s disease. I-131 is also commonly employed for radioablation of hyper-functioning thyroid glands in case of Grave’s disease. Hypothyroid patients have impaired endothelial function, increased systemic vascular resistance, extracellular volume expansion, and an increased diastolic blood pressure. In 32% of hypertensive hypothyroid patients, replacement therapy with thyroxine leads to a fall in diastolic blood pressure to 90 mm Hg or less. The only indication of thyroid scan in such patients is evaluation of thyroid nodules.

**Others**

Other uncommon causes of endocrine hypertension include acromegaly, insulin resistance, Liddle syndrome, Geller syndrome, pseudohyperaldosteronism, congenital adrenal hyperplasia, and reninoma. Although few case reports are present in literature, nuclear medicine modalities have no established role in management of these uncommon conditions.

**Conclusion**

Nuclear medicine techniques play an important role for evaluation and management of patients with endocrine hypertension. I123/I131-MIBG with or without SPECT-CT is routinely employed for imaging pheochromocytomas. PET-CT with FDOPA/FDA might be better than MIBG scintigraphy for this purpose. SRS with Ga-68 DOTANOC appears to be useful for extra-adrenal, metastatic and small lesions. NP 59 scintigraphy can be employed for differential diagnosis of primary hypercortisolism in doubtful cases. NP 59 scintigraphy with Dexamethasone suppression is very useful for evaluation of primary aldosteronism. Thyroid scan and RAIU are routinely employed in management of hyper-thyroidism. Development of newer tracers might further expand the role of nuclear medicine in endocrine hypertension.
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