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Research Article

Role of Pre-operative Meta-Iodo Benzyl Guanidine (MIBG) in Biochemically Proven and Anatomically Localized Adrenal Pheochromocytoma

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Abstract

Background: Radio labeled metaiodobenzylguanidine scintigraphy (MIBG) is used for used to image pheochromocytomas. While computed tomography (CECT) or magnetic resonance imaging (MRI) usually localizes the tumor, MIBG is often obtained to rule out multifocal and metastatic disease and to corroborate anatomic imaging with functional data. Since the utility of routine MIBG is questionable in the pre-operative setting, the aim of this retrospective analysis was to look at this issue.

Methods: All patients of pheochromocytoma who underwent MIBG scintigraphy at our institute between 2003 and 2013 were identified retrospectively. The findings of CECT, MIBG, operative findings and histopathological results were reviewed and compared.

Results: A total of 29 patients underwent MIBG scintigraphy for the pre-operative evaluation of pheochromocytoma for variable reasons. All patients had raised 24 hr. urinary fractionated metanephrine or nor-metanephrine. Four patients with >5 cm tumors had negative MIBG uptake and 4 patients with unilateral tumors showed bilateral uptake. MIBG did not identify any additional foci of disease or alter the surgical management in any patient but added to the confusion regarding optimum management in patients with bilateral uptake.

Conclusions: The routine use of pre-operative MIBG scintigraphy is not useful in patients with biochemically confirmed and localized apparently sporadic adrenal pheochromocytoma. Its use should be limited to the subset of patients with equivocal biochemical disease, familial disease, negative cross sectional imaging or those with recurrent or metastatic disease.

Keywords: Pheochromocytoma; Metaiodobenzylguanidine scintigraphy; Adrenal; Work up

Introduction

Pheochromocytoma (PCC) is an uncommon and deceptive neuroendocrine tumor that develops from the chromaffin cells in the sympathetic system [1]. Diverse manifestations lead to a significant delay in diagnosis and definitive treatment [2]. PCC has rightfully earned the title of "Great Mimic" and often causes morbidity and mortality if the diagnosis is missed or patients are treated inappropriately [3].

It accounts for approximately 0.05%-0.6% of patients with sustained hypertension but 50% of the patients harboring the tumor are normotensive or have paroxysmal hypertension [3-5]. However, with a high prevalence of hypertension in the general population the number of individuals harboring a potentially curable cause of hypertension would be substantial.

Approximately, 25-40% of patients have associated familial syndromes [6,7]. The number of incidentally detected adrenal masses is on the rise with the increase in number of abdominal imaging and significant proportion (1.5 to 23%) of these may be PCC [8].

MIBG introduced in the 1970's is an analogue of Guanethidine and is concentrated by specific cell membrane and vesicular transport systems in the sympatho adrenal system and it provides a functional corroboration of an anatomical image in PCC and Paraganglioma. The reported sensitivity of MIBG scintigraphy ranges from 83% to 100% and approaches specificity of 100% in some series [9].

131/123I MIBG (meta-iodo benzyl guanidine) has been used in tandem with CECT/MRI in pre-operative localization of pheochromocytoma because of its higher specificity as it provides a functional corroboration of the anatomical data [10]. Few investigators have suggested that MIBG be used as a first line imaging investigation before CECT/MRI after biochemical confirmation of PCC as it regionalizes the lesion [11].

However during the last decade some studies have questioned the routine use of pre-operative MIBG scintigraphy in patients of PCC as it is not clear if it provides significant additional information that would modify the planned operative strategy [12-16]

The objective of this retrospective analysis was to evaluate the role of pre-operative MIBG in biochemically proven and anatomically localized adrenal PCC.

Patients and Methods

Patient's characteristics

A retrospective study was carried out on 190 patients who underwent surgery for PCC between 2003 and 2013 at Department of Endocrine Surgery, Sanjay Gandhi Post Graduate Institute of medical Sciences, Lucknow, India. 24 hour urinary metanephrine and nor metanephrine were obtained in all patients.

Abdominal CECT (64 slice) was performed in all patients. MIBG scan is not routinely done in all patients at our hospital. 131I MIBG scan was performed in 29 patients in the pre-operative setting for various reasons (Table 1). Only 22 patients with adrenal pheochromocytoma were included in the analysis.

S. No	Indication	Number
1	B/l lesions on CT/ Familial/ Syndromic	17
2	< 20 years	5
3	Extra adrenal paraganglioma	6
4	Metastatic disease	1 (Bladder Pheochromocytoma)

Table 1: Indication for performing MIBG in Patients with Adrenal Pheochromocytoma.

All 29 patients received collosol Iodine @1-2 mg/kg in three divided doses starting 2 days before the scheduled injection and continued till 6 days after the scan for blocking the thyroid uptake of Iodine. At the time of scan all 29 patients were on alpha blockade with Prazosin (n=25) and Phenoxybenzamine (n=4). Interfering anti-hypertensive, nasal decongestants, anti-depressant and anti-psychotic medications were discontinued before the scheduled scan.

131I labelled MIBG in dose of 1 mCi was administered via slow IV injection over 5 min in a peripheral IV line and same flushed with saline. The dose of radionuclide administered was proportionately decreased in 2 patients (12 years and 11 years) to 0.5 m Ci. Whole body anterior and posterior planar scans with were acquired 48 and 72 hours after 131I MIBG injections. Spot images of the suspicious areas were obtained routinely. A dual head, large field of view gamma camera was used for obtaining the images which was of medium energy collimator.

The images were reviewed by any of the two nuclear medicine physicians with at least 10 years of experience in the field. They were aware of the clinical history of the patient. The finding of the CT/MRI scan was also known to the physicians before they prepared the reports. The intensity of the MIBG uptake relative to the hepatic uptake as suggested by Cecchin et al. [17] was taken into consideration for giving the final report. A score of 1 was given when uptake was absent or less intense then liver, score 2 for uptake equal to liver, score 3 for uptake moderately more intense than liver and score 4 for uptake markedly more intense than liver. An extra adrenal uptake or score 3-4 were classified as positive and score 1 as negative and 2 as doubtful. MIBG scintigraphy reports were classified into True positive, True negative , False positive and False negative results based on the clinical, biochemical, histopathological data and the 24 hour urinary metanephrine and nor metanephrine on POD 10 was taken as sine qua none of cure.

Results

29 patients had undergone preoperative MIBG for various indications. All these patients were biochemically proven cases of raised catecholamine secretion. 22 patients had adrenal lesion and 7 had extra adrenal lesions. The extra adrenal paragangliomas were not included the analysis.

Out of the 22 patients with adrenal PCC, the MIBG findings corroborated with CECT and intra operative findings in 14 patients. MIBG did not show any focus of increased uptake in 4 patients. All these patients had CECT findings suggestive of PCC and all the lesions were greater than 5 cms. All these patients underwent unilateral (U/L) adrenalectomy. On cut section 3 specimens were solid and homogenous. In one patient the specimen was partly cystic and solid. Histological findings were suggestive of PCC and did not reveal hemorrhage or necrosis in any of the patients with false negative scans on MIBG. All four patients who have had false negative MIBG scans are in follow up till date and remain free of recurrence. The details of these patients are provided in Table 2 and Figure 1 shows the CECT, MIBG and specimen photograph of patient no 4.

There were 4 patients in whom MIBG revealed bilateral (B/L) uptake despite unilateral lesions on CECT scans. Significantly all these patients were in the pediatric or adolescent age group ranging from 11 to 19 years. All these four patients underwent unilateral adrenalectomy and 24 hour urine metanephrine and nor metanephrine on post op day 10 were within normal range. These patients have completed 5 months to 7 years of follow up with normal annual urinary metanephrine and nor metanephrine and are free of recurrence. The details of these patients are provided in Table 3 and Figure 2 shows the CECT, MIBG and specimen photograph of patient no 1.

S. No	Age/Sex	Presentation	UMN/NMN (mcg/24 hrs)	CECT	Size (cms)	Appearance on Histopathology
1	F/20	Hypertensive	145/3745	Heterogeneous	5x3x3	Solid tumour mass
2	M/27	Hypertensive with papilloedema	150/7597	Heterogeneous	5x4x4	Solid tumour mass
3	M/21	Hypertensive	1438/10987	Heterogeneous with cystic component	7x5x3	Solid tumour mass
4	M/20	Hypertensive	593/7332	Heterogeneous	6x4x3	Solid with 30% cystic area

Table 2: Details of patients with False Negative MIBG scan - UMN- 24 hour unine metanephrine, NMN- 24 hour urine nor metanephrine.

S. No	Age/Sex	Presentation	UMN/NMN (mcg/24 hrs)	CECT	Size (cms)	Appearance on Histopathology
1	12/F	Hypertension with Papilloedema	78/2959	Heterogeneous (Unilateral)	4x2.5x1.5	Cystic and Hemorrhagic areas

2	11/M	Hypertension	82/1980	Heterogeneous (Unilateral)	5x3x3 cm	Solid
3	19/F	Hypertension with Papilloedema	789/3491	Heterogeneous (Unilateral)	4.5x3.5x1.3	Solid
4	16/F	Hypertension	77/1350	Heterogeneous (Unilateral)	5.2x5.4	Solid

Table 3: Details of Patients with False B/L Uptake on MIBG scan UMN- 24 hour unine metanephrine, NMN- 24 hour urine nor metanephrine.

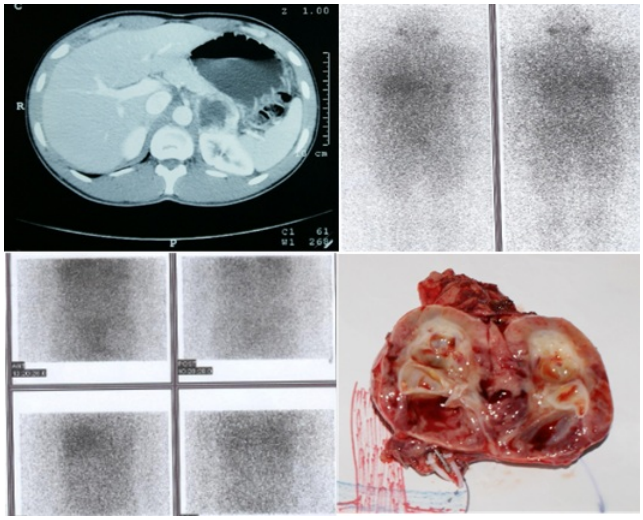

Figure 1: CECT, MIBG and specimen photograph of patient no 1.

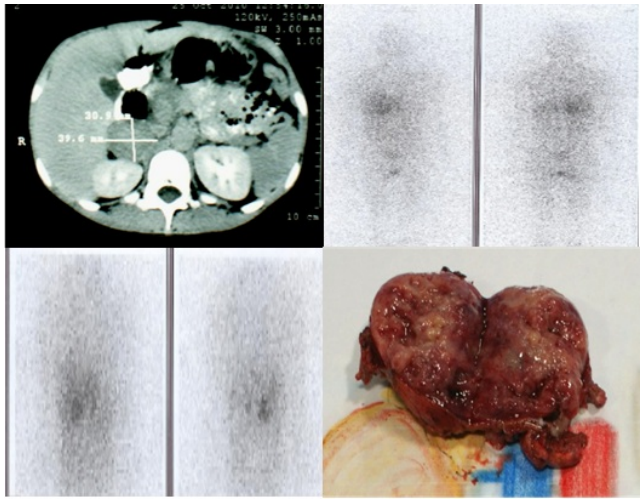

Figure 2: CECT, MIBG and specimen photograph of patient No 4.

Discussion

Biochemical evidence of increased catecholamine production in form of raised plasma or urinary catecholamine, metanephrine, nor metanephrine or their metabolites is the initial and crucial step in diagnosis of PCC. These tests have varied sensitivities and specificities and certain advantages and disadvantages. The episodic secretion of catecholamine should be borne in mind during evaluation. The next step is anatomical imaging in form of CECT and MRI which is expected to reliably pick up the side, size and location of the offending lesion with reasonable sensitivity. The sensitivity of CECT in the pre-operative period ranges from 85% to 94% for adrenal pheochromocytoma [18]. The sensitivity is lower in setting of extra adrenal pheochromocytoma, recurrent or metastatic disease or post-operative status and ranges from 77% to 90%. The specificity may be as low as 70% [19,20] MRI may be preferred over CECT in case of extra adrenal Pheochromocytoma and is the modality of choice when ionizing radiations is to be avoided as in pregnancy or children [21,22].

In our cohort of PCC patients MIBG was performed in the pre-operative setting in 29 patients and 15 patients in post-operative period.

Of these 22 patients, MIBG caused or added to the dilemma in 8 patients. 4 patients had a false negative scan and 4 had false bilateral up take (in spite of unilateral lesion on CECT). However, all these patients had a biochemical diagnosis of PCC and anatomical localization had been made on CECT. False negative scans can be expected in those not stopping medications interfering with MIBG scan for recommended periods or tumors that have undergone necrosis or de differentiation [15,23,24] The sensitivity also drops down in smaller lesions. All the 4 patients with false negative scans had lesions larger than 5 cm and did not show significant necrosis or hemorrhage on histopathology and all were reported as benign PCC. MIBG uptake is lower in PCCs that subsequently prove to be malignant [15,24]. An implication of this would be keep patients with negative MIBG scans on closer follow up even if the histopathology is suggestive of benign PCC. Another reason for large number of false negative in our cohort could be use of 131I. Studies have however shown that 123IMIBG has a higher sensitivity compared to 131I [25-27].

Our cohort showed a high rate of false B/L positive uptake of MIBG. There were 4 patients with biochemical diagnosis of PCC with unilateral lesion on CECT but pre-operative MIBG revealed B/l uptake. Significantly all these patients belonged to the pediatric or adolescent age group and B/l uptake on MIBG added to the dilemma of performing unilateral/bilateral adrenalectomy keeping in mind lifelong steroid dependence and the socio economic and educational standards. Hence, a decision of U/L Adrenalectomy was taken and all these 4 patients underwent unilateral adrenalectomy and the post-operative 24 hour urine metanephrine and nor metanephrine values were within normal limits and have remained asymptomatic with normal yearly urinary catecholamine during follow up till date ranging from 5 months to 7 years. This strategy has avoided steroid dependence in these patients.

131IMIBG uptake may be seen in normal adrenal medulla in as much as 16% at 48 hours [28]. Corresponding figure for 123I may be as high as 32-75% at 24 hours [26,27]. Scoring system for the intensity of uptake of MIBG in PCC with respect to liver, may increase the specificity for PCC. Another possible reason for the normal B/L uptake could have been the more than ideal dose of 131IMIBG. Brown et al had reported clear visualization of B/L adrenal medulla after administration of 2mci of 131I MIBG [29]. Other causes of false positive uptake on MIBG includes non pheo lesions like adrenal hemangioblastoma, anigiomyelolipoma, hemangioma, adreno cortical carcinoma, adenomas, lymphoma, actinomycosis and dilated renal pelvis have been reported to take up I MIBG in literature [14,30,31].

MIBG did not find any additional lesions or altered the management strategy in any patient. Longer follow up may be needed for the correct characterization of opposite adrenal. Though the numbers included in this study are small, based on the observations we would like to conclude that the routine use of pre-operative MIBG in biochemically proven apparently sporadic pheochromocytoma patients with anatomical localization on cross sectional imaging is not useful. Routine pre-operative MIBG is un warranted and may in fact add to the diagnostic dilemma in a significant proportion of patients. Similar observations have been made in other studies [12-14,16]. However, few investigators routinely do pre-operative MIBG after biochemical diagnosis of PCC for regionalization followed by CECT/MRI of the area for anatomical details or with CECT/MRI followed by MIBG for functional corroboration of anatomical findings [10,11,32]. However, cost effectiveness of either approach needs to be ascertained before coming to any firm conclusion.

MIBG would continue to have role in management of malignant, recurrent, extra adrenal pheochromocytoma or in those with equivocal biochemical diagnosis [32,33]. It would also have a definite role in post-operative patients with suspected recurrence where tissue scarring would obscure findings on CECT/MRI [19]. There may be a role of MIBG in work up of familial cases but it merits further studies [35,36]. The fusion MIBG images with of CECT/MRI and PET may have a greater diagnostic potential compared to MIBG alone [33,34].

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