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Correlation between the size of pheochromocytoma and the level of metanephrines

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Objective. Pheochromocytomas (PHEO) and paraganglioma (PGLs) are rare neuroendocrine catecholamine-producing tumors that arise from the chromaffin cells of either the adrenal medulla or extra-adrenal paraganglionic tissues. Despite the recent advances in imaging technologies, biochemical evidence of excessive catecholamine production by the tumor is considered the most important test for the diagnosis of these tumors. The aim of the present study is to investigate the role of the catecholamine metabolites (normetanephrine and metanephrine) levels in the diagnosis of PHEO/PGLs and to evaluate if their levels correlate with the size of these tumors.

Patients and Methods. Twenty-five patients were included in the study during the time period of 10 years. Their data were compared with another set of 25 patients to obtain the sensitivity and specificity of metanephrine and normetanephrine in the diagnosis of PHEO/PGLs. The tumor size was reviewed in every patient to obtain the correlation coefficient between the tumor sizes and the plasma/24-hour urinary metanephrine levels.

Results. The sensitivity and specificity rates for plasma metanephrine were 80–92% and 92–96%, respectively; while for 24-hour urinary metanephrine were 80–90% and 95–100%, respectively. We found a strong positive relationship between the tumor size and the plasma levels of normetanephrine ($r=0.518$, $p<0.01$), and metanephrine ($r=0.577$, $p<0.01$). While the relation with the 24-hour urinary concentrations of normetanephrine ($r=0.384$, $p=0.01$) and 24-h urinary metanephrine ($r=0.138$, $p<0.01$) was low.

Conclusion. The determination of plasma and 24-hour urinary levels of metanephrines is a reliable test for the diagnosis of PHEO, as they are continuously produced by the tumor cells in contrast to catecholamines.

Key words: metanephrines, tumor size, sensitivity, specificity, correlation

Pheochromocytomas (PHEO) and paragangliomas (PGLs) are rare neuroendocrine catecholamine-producing tumors. They arise from the chromaffin cells of either the adrenal medulla (PHEO) or extra-adrenal paraganglionic tissues (Lenders et al. 2005). Although PGL can arise from both the sympathetic and parasympathetic nervous systems, they usually arise from the sympathetic chain in the chest, abdomen, and pelvis or from the parasympathetic chain in the head and neck. PHEO arising in the adrenal medulla accounts for 80% of cases, while PGLs for the remaining 15–20%. The accurate incidence of PHEO and PGLs is unknown, but it has been estimated that the annual incidence of these tumors is between two and eight cases per million (Chen et al. 2010).

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The mean age at diagnosis is approximately 43 years, but 10–20% of PHEO/PGLs are identified in children, commonly associated with underlying genetic conditions (Chen et al. 2010; King et al. 2011; Cascon et al. 2013). Although the majority of the cases are benign, Lenders et al. (2005) have reported that 5% of adrenal PHEO and 33% of PGLs are malignant.

In the past, it was estimated that about 10% of PHEO/PGLs were associated with hereditary syndromes; however, recent studies have shown that at least 25–40% of these tumors are linked to hereditary syndromes with several identified causative genes (Favier et al. 2015). The classic characteristics for hereditary PHEO/PGLs include an early age of onset, extra-adrenal disease, multiple primary tumors, and metastatic tumors (Neumann et al. 2002). Increased levels of catecholamines accounts for the typical clinical manifestations of these tumors. It is considered that PHEO/PGLs are responsible for about 0.1–0.4% of patients with sustained hypertension (Erlic and Neumann 2009).

Despite the advances in imaging technologies, including CT and MRI scans, the most important test for the diagnosis of PHEO is biochemical evidence of excessive catecholamine production by the tumor. This is usually achieved using measurements of catecholamines in plasma or urine (Bravo et al. 1979; Duncan et al. 1988). However, the catecholamine levels may be falsely negative in patients with intermittently secreting or even biochemically silent tumors. Moreover, they may be falsely elevated in patients with panic disorder or congestive heart failure (Eisenhofer et al. 2000). Metanephrines (normetanephrine and metanephrine) have been utilized as an alternative diagnostic tool (Roden 2002; Eisenhofer 2003). Metanephrines are O-methylated metabolites of norepinephrine and epinephrine which are produced by the enzyme catechol-O methyltransferase (COMT) and are rapidly metabolized to sulfate conjugates by the enzyme monoamine-preferring phenol sulfotransferase. The sulfate conjugates are present in plasma and urine in concentrations >25-fold higher than the free metanephrine levels (Eisenhofer et al. 1995). Thus, the assay of the urinary metanephrines includes mainly measurements of the sulfate-conjugated derivatives (metanephrine metabolites) (Lenders et al. 1993).

The aim of the present study is to assess the value of measurement of the plasma and 24-hour urinary metanephrine levels in the diagnosis of PHEO/PGLs and to evaluate if their levels correlate with the size of these tumors. This can help in the determining the diagnosis and making decision regarding the management of PHEO/PGL patients.

Patients and Methods

We carried out this retrospective study for all PHEO/PGL patients who had laparoscopic/open adrenalectomy in our general surgery department during the period from 2011 to 2022. Patients' data and lab results were obtained from the hospital recording system. All patients with adrenal masses on imaging or atypical presentation of hypertension had been assessed for catecholamine secreting-tumors. History taking and clinical examination were obtained for all patients. A hormonal profile was obtained for all our patient including plasma metanephrines (metanephrine and normetanephrine), 24-hour urinary excretion of metanephrines (metanephrine and normetanephrine), plasma baseline catecholamine level, plasma cortisol level, low dose dexamethasone suppression test, serum DHEAS, 17α-OH progesterone, serum aldosterone, plasma renin activity in patients with hypokalemia, and hypertension.

For plasma metanephrines, EDTA whole blood samples were preferred, minimum sample volume was 1 mL EDTA, whole blood and minimum assay volume was 100 μL plasma. Whole blood samples were transported to the laboratory in ice and arrived within 2 hours of sampling. Otherwise, frozen samples could be used for at least 6 months. The routine practice in our study was to collect samples from seated patients for plasma metanephrines. Our reference values for plasma metanephrines were: plasma normetanephrine: <1180 pmol/L, plasma metanephrine: <510 pmol/L, while reference values for 24-hour of urinary metanephrines were: urinary metanephrines <1.8 μmol/24 h and urinary normetnephrines <3 μmol/24 h.

Plasma values above the references were suspected for PHEO/PGLs, where values >4 times the upper reference interval were more consistent with PHEO/PGLs. Liquid chromatography-tandem mass spectrometers were used for analysis of the samples.

Patients were advised to abstain from caffeinated and decaffeinated beverages overnight and discontinue all medications that might affect the plasma and urinary metanephrine levels prior to sampling for at least 5 days to avoid any false positive results, i.e. tricyclic antidepressants, antihypertensive drugs (e.g. α- and β-adrenergic receptor blockers and calcium channel blockers), monoamine

oxidase inhibitors, Dopa-related drugs, and various sympathomimetic and stimulant drugs. Imaging studies used for diagnosis of the location of these tumors included computerized tomography (CT) and magnetic resonance imaging (MRI) scans. Other studies like 123I-meta-iodo-benzyl-guanidine (MIBG) and positron emission tomography (PET-CT) also have been utilized to exclude any metastatic disease.

Decision of surgery has been decided based on an endocrine MDT meeting discussion including a surgeon, endocrinologist, pathologist, radiologist and anesthetist. Preoperative blood pressure control was achieved by the use of α and β antagonists.

Twenty-five patients with confirmed diagnosis of PHEO/PGL on histopathology were eligible for our study. Their data were compared with the data of another set of 25 patients with other adrenal pathologies (cortical adenomas, metastatic cancer and adrenocortical carcinomas). 2×2 tables have been used to calculate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Histopathology results were reviewed for all patients with proven diagnosis of PHEO/PGL to obtain the exact tumor size. We ensured that the dimensions represent the actual tumor rather than the whole resected mass.

Statistical analysis was carried out using SPSS version 25 to obtain the correlation coefficient between the tumor sizes and the plasma/24-hour urinary metanephrine levels.

Results

Twenty-five patients with a histologically confirmed diagnosis of PHEO/PGLs were included in our study. Fourteen patients (56%) were females and 11 ones (44%) were males. The mean age at diagnosis was 58.6±17.3 years (Table 1). The youngest patient was 17 years old, while the oldest one was 82 years old. Two patients were diagnosed with PHEO during pregnancy. Twelve patients (48%) had left sided tumor and 13 subjects (52%) had right sided tumors. Twenty-three patients (92%) had histology proven PHEO, one patient (4%) had combined PHEO/PGL and one patient (4%) got PGL (Table 1). Aggressive PHEO features were detected only in one patient. Genetic associated syndromes were found in 3 patients; one patient (4%) had multiple endocrine neoplasm type 2 (MEN2) syndrome and two patients (8%) had succinate dehydrogenase subunit B (SDHB) gene mutations (Table 1). No recurrence was detected in our patients till now.

Table 1
Demographic parameters of patients

Variable		Value
Age (years)	Average	58.6±17.3
Gender	Males	11 (44%)
	Females	14 (56%)
Laterality	Left	12 (48%)
	Right	13 (52%)
Tumor size (cm)	Average	4.63±1.87
Diagnosis	PHEO	23 (92%)
	PGLs	1 (4%)
	Composite PHEO/PGLs	1 (4%)
Genetic mutation	No mutation	22 (88%)
	MEN2	1 (4%)
	SDHB	2 (8%)

Abbreviations: MEN2 – multiple endocrine neoplasm type 2; PGLs – paragangliomas; PHEO – pheochromocytoma; SDHB – succinate dehydrogenase subunit B.

Table 2
Sensitivity, specificity, positive predictive value, and negative predictive value of plasma and 24-h urinary normetanephrine and metanephrine

Parameter	Plasma metanephrines		24-hour urinary metanephrines	
	NMN	MN	NMN	MN
Sensitivity (%)	92.0	80.0	90.0	80.0
Specificity (%)	96.0	92.0	95.0	100.0
PPV	95.8	80.0	94.7	100.0
NPV	92.0	82.0	90.5	83.0

Abbreviations: MN – metanephrine; NMN – normetanephrine; NPV – negative predictive value; PPV – positive predictive value.

The mean tumor size was 4.63±1.87 cm (Table 1). The smallest tumor was 1.5 cm and the largest one was 8 cm. The sensitivity and specificity of the plasma normetanephrine was about 92% and 96%, respectively; and for plasma metanephrine was about 80% and 92%, respectively (Table 2). On the other hand, the sensitivity and specificity for 24-hour urinary normetanephrine was about 90% and 80%, respectively; and for 24-hour urinary metanephrine was about 80% and 100%, respectively (Table 2). PPV and NPV are shown in Table 2.

We found a strong positive relationship between the tumor size and the plasma levels of normetanephrine ($r=0.518$, $p<0.01$), and metanephrine ($r=0.577$, $p<0.01$); while the relation with the 24-hour urinary concentrations of normetanephrine ($r=0.384$,

p=0.01) or metanephrine (r=0.138, p=0.01) was low (Figures 1–4).

Discussion

PHEO is a rare tumor that arises from the chromaffin cells in adrenal medulla or other paraganglia in the body (Lenders et al. 2005). Although most of PHEO are sporadic, recent studies reported that PHEO/PGLs have a high degree of heritability with about 40% of the cases carrying a germline mutation (Else et al. 2008). At least 20 susceptibility genes were identified. The most common hereditary syndromes associated with PGL/PHEO include MEN2, von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF1), SDHB gene mutations, cerebellar hemangioblastoma, Sturge-Weber syndrome, and tuberous sclerosis (Neumann et al. 2002; Cascon et al. 2013). All our patients had genetic assessment; three of them had genetic mutation; one had MEN2 and two had SDHB. Although some studies reported slight predominance of male patients (Walz et al. 2006), there was no significant difference between males and females (11 vs. 14, respectively) in our study. The mean age at diagnosis in other studies was approximately 47.1 years (Guerrero et al. 2001); while in our study, it was 58.6±17.3 years. One patient in the present study had PGLs and one case had composite PHEO and PGLs. Other studies reported that 75–85% of PHEO are adrenal and the remaining 15–25% is extra-adrenal PGLs (Pacak et al. 2001). There was no major difference regarding the side of the tumor (right/left: 13/12). All cases in our study were considered benign according to the final histology reports; one patient only had aggressive features of PHEO with no evidence of any metastatic disease. Malignancy was confirmed only with the presence of local or distant metastasis (Mundschenk and Lehnert 1998).

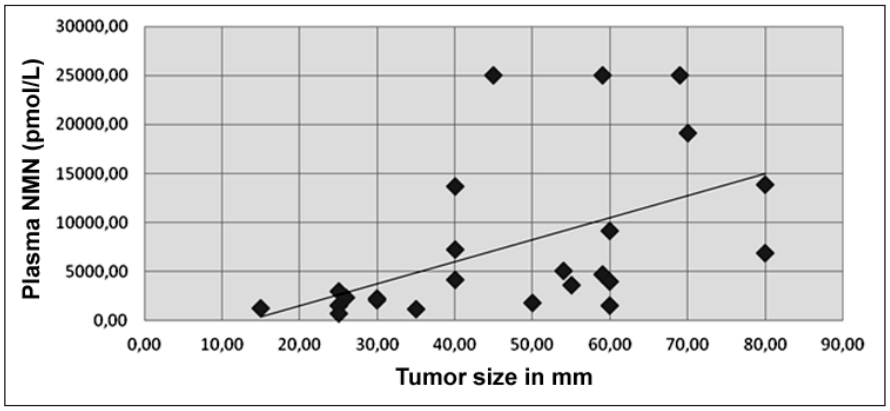

Figure 1. Correlation between free plasma normetanephrine (NMN) levels and tumor size in patients with pheochromocytoma/paraganglioma.

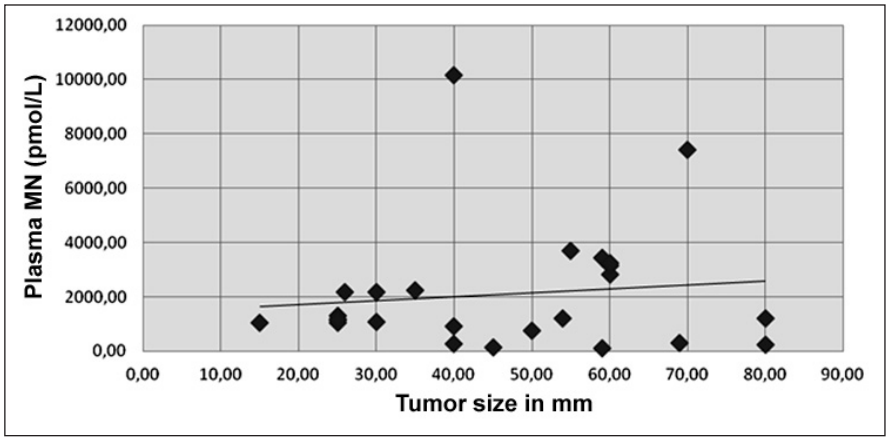

Figure 2. Correlation between free plasma metanephrine (MN) levels and tumor size in patients with pheochromocytoma/paraganglioma.

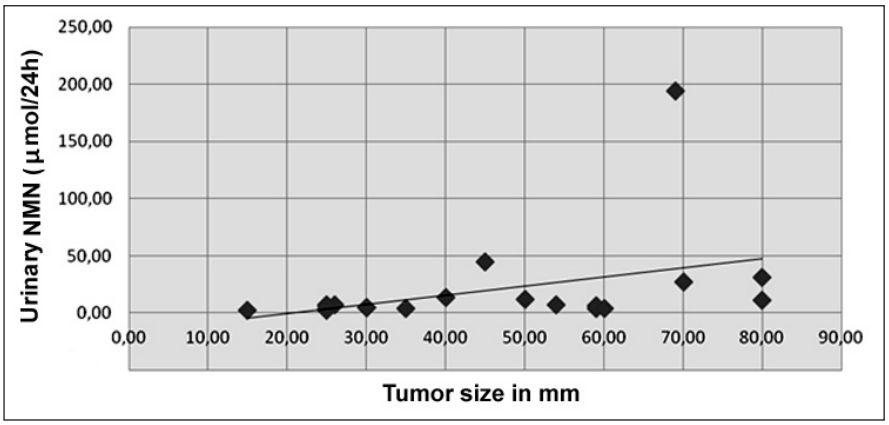

Figure 3. Correlation between 24-hour urinary normetanephrine (NMN) levels and tumor size in patients with pheochromocytoma/paraganglioma.

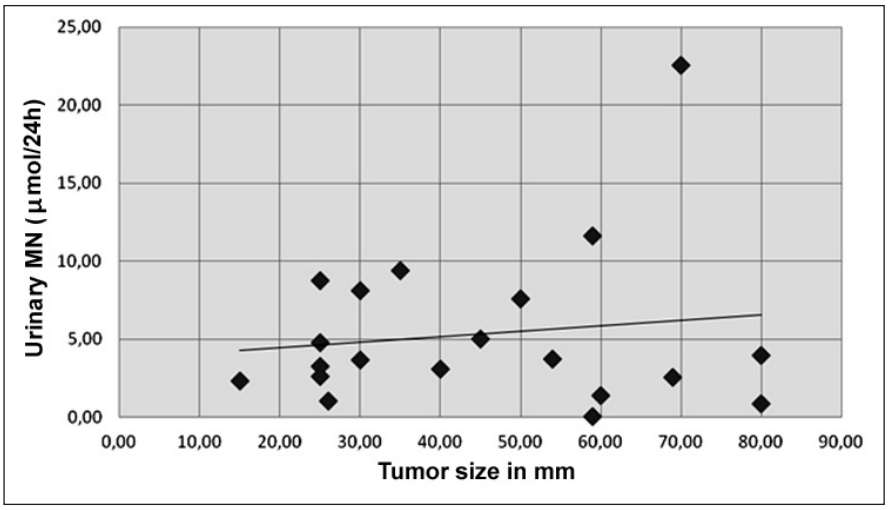

Figure 4. Correlation between 24-hour urinary metanephrine (MN) levels and tumor size in patients with pheochromocytoma/paraganglioma.

PHEO are responsible for about 0.1–0.4% of the cases of hypertension (Erlic and Neumann 2009), despite the fact that about 50% of PHEO/PGLs may present with paroxysmal hypertension or normotension. Patients with atypical presentation of hypertension should be investigated for PHEO, these include severe hypertension, hypertensive crisis, resistant hypertension, age of presentation <20 years or >50 years, family history of PHEO-associated hereditary syndromes or proven adrenal mass on imaging (Faria et al. 2007). The classical triad of PHEO includes episodic headache, sweating, and hypertension. Bravo (1991) reported that biochemical testing is mainly used to exclude PHEO. However, about 50% of PHEO/PGLs may present with paroxysmal hypertension or even normotension. It is worth mentioning that unrecognized PHEO can cause death as a result of hypertensive crisis, arrhythmia, myocardial infarction, or multisystem crisis (Nomoto et al. 2017).

The detection and localization of PHEO is potentially challenging, which have been currently facilitated by the recent advances in biochemistry and radiology. CT and MRI scans can have about 95% sensitivity and 70% specificity for adrenal PHEO. On T1 imaging, PHEO are isointense to liver, kidney, and muscle, while highly intense signal is seen on T2 images with no signal loss on opposed phase images because of the absence of fat in PHEO (Schmedtje et al. 1987; Maurea et al. 1996). Other advanced imaging modalities that can be utilized in the diagnosis of PHEO/PGLs may include MIBG, 18-fluoro-dihydroxyphenylalanine

(18F-DOPA), PET-CT, and 18-fluorodeoxyglucose (18F-FDG) PET-CT.

Studies found that the secretion of catecholamines from these tumors is not constant; thus single estimation of urinary or plasma epinephrine and norepinephrine is likely to miss the diagnosis of PHEO in many cases, especially in familial cases with false negative results in up to 29% of the cases (Eisenhofer et al. 1999). On the other hand, assessment of metabolites of epinephrine and norepinephrine, metanephrine and normetanephrine, respectively, is currently considered the best screening test for PHEO. The hypothesis for the superiority of plasma free metanephrines over other tests is that in patients with PHEO, free metanephrines are produced mainly from metabolism of catecholamines within the tumor (which is a constant process), not from catecholamines metabolized after their secretion into the circulation (Eisenhofer et al. 1998; Lenders et al. 2002).

In the present study, our threshold level for plasma normetanephrine was 1180 pmol/L and for plasma metanephrine was 510 pmol/L. We reported high sensitivity and specificity rates for the plasma metanephrines test, (80–92%) and (92–96%), respectively. Other studies reported higher (97–100%) sensitivity, but lower specificity rates (85–96%) (Lenders et al. 1995; Sawka et al. 2003). Again, our reference values for urinary metanephrines were 1.8 μmol/24 h, and for urinary normetnephrines was 3 μmol/24 h. The sensitivity and specificity rates for 24-hour urinary metanephrines in our study were about (80–90%) and (95–100%), respectively. Other studies demonstrated urinary total metanephrines sensitivities rates between 65% and 89% and specificities rates between 89 and 95% (Lenders et al. 2002; Eisenhofer et al. 2003). Urinary metanephrines mainly reflect the sulfate-conjugated metabolites, which are formed in gastrointestinal tissue. Consequently, they are not related only to the PHEO, which may explain the reduced accuracy compared with plasma metanephrines (Eisenhofer 2001).

The strong relationship between the size of PHEO and the plasma/24-hour urinary levels of the catecholamine metabolites (metanephrine and normetanephrine) was reported in many studies despite reporting no or poor relationships between the tumor mass and the urinary or plasma concentrations of catecholamines (Crout and Sjoerdsma 1964; Stenstrom and Waldenstrom 1985; Eisenhofer et al. 1999). These differences reflect the variable and intermittent secretion of catecholamines by the tumor, compared with the continuous production of free metanephrines within the tumor cells by the enzyme, catechol-O methyltransferase (COMT), this process that is independent of the catecholamine release (Eisenhofer et al. 1998).

In the present study, we have found the positive relationship between the tumor diameter and the plasma concentrations of free normetanephrine ($r=0.518$, $p<0.01$), and metanephrine ($r=0.577$, $p<0.01$). In addition, the relationship between the tumor size and the 24-hour urinary concentrations of normetanephrine and metanephrine was low positive ($r=0.384$, $p=0.01$) and very weak positive ($r=0.138$, $p=0.01$), respectively.

Consequently, the high sensitivity and specificity of the plasma and urinary metanephrines and the strong relation between these levels and the tumor size have many implementations in management of PHEO. It would help not only in the diagnosis of PHEO/PGLs, but also to predict the tumor size. Additionally, it would help to predict the difficulties in controlling the blood pressure of patients with very high levels of plasma/24-hour metanephrines with consequently large volume tumors. Moreover, it would help to avoid unnecessary costly tests and imaging procedures.

Conclusion

The determination of plasma and 24-hour urinary levels of metanephrines is a reliable test for the diagnosis of PHEO as they are continuously produced by the tumor cells in contrast to catecholamines that may be intermittently produced. We concluded a strong relation between the size of these tumors and the plasma/urinary concentration of metanephrines, which can help to predict the size of the tumor even before imaging. Proper implication of the information obtained from these measurements together with the results of high quality imaging techniques can be of great value, especially in diagnosis of patients with adrenal tumors of unknown etiology.

Conflict of interest: *The authors declare no conflicts of interest.*

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