ORIGINAL ARTICLE

The most common indications for measuring metanephrine and normetanephrine in plasma – a rational approach

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ABSTRACT

Aim To determine the most common indications for measuring metanephrine and normetanephrine in plasma by gender and age and to compare the concentrations of metanephrine and normetanephrine by indication, gender and age.

Methods The study was conducted on 224 patients whose plasma metanephrine and normetanephrine concentrations were measured at the Clinical Institute for Laboratory Diagnostics at the University Hospital Centre Osijek for one year, until 1st January 2020.

Results The most frequent indications for biochemical testing were adrenal incidentaloma, 138 (6.6 %), and symptoms of pheochromocytoma, 41 (18.3%). Metanephrine concentration was lower in females (p=0.009). No significant correlation was found between age and metanephrine concentration, while age and normetanephrine concentration were positively correlated (p=0.01). Of the 224 patients, only one patient was diagnosed with pheochromocytoma, whose indication for measurement of metanephrine and normetanephrine was adrenal incidentaloma.

Conclusion Adrenal incidentalomas and symptoms suggestive of pheochromocytoma are very common in the general population, while the incidence of pheochromocytoma is extremely low. Clear guidelines for the referral of patients for biochemical testing are needed to avoid unnecessary costs and to identify the correct diagnosis promptly.

Key words: adrenal glands, catecholamines, hypertension, paraganglioma, pheochromocytoma

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INTRODUCTION

Pheochromocytomas are rare neuroendocrine tumours that originate from chromaffin cells of the medulla of the adrenal gland and secrete catecholamines, most often adrenaline and noradrenaline (1). These tumours can also arise from extra-adrenal chromaffin cells of the paravertebral ganglia of the abdomen, pelvis and chest, in that case they are called paragangliomas. Paragangliomas usually do not secrete adrenaline because they have a reduced expression of the enzyme phenylethanolamine N - methyltransferase (PNMT), which converts noradrenaline into adrenaline (2). Given that this enzyme is present only in the chromaffin cells of the medulla of the adrenal gland, adrenaline is almost exclusively produced in the adrenal gland (3). Adrenaline, noradrenaline and dopamine are degraded by catechol-O-methyltransferase (COMT) to form their inactive metabolites metanephrine, normetanephrine and 3-methoxytyramine (3-MT). Measurement of their concentration in plasma or 24-hour urine represents the gold standard for the biochemical diagnosis of pheochromocytoma (4, 5, 6).

The incidence is 2-9 per million inhabitants in the general population, and it most often occurs between the ages of thirty and fifty (4). Symptoms of pheochromocytoma arise as a result of excessive secretion of catecholamines. Catecholamines exert numerous cardiovascular and metabolic effects through their receptors. They stimulate adrenergic receptors in the heart leading to pulse acceleration, increased conductivity and stronger contractility, whereas in the blood vessels they lead to vasoconstriction and an increase in blood pressure (4,6). Sudden secretion occurs occasionally meaning that the symptoms manifest in paroxysms or seizures. Attacks most often occur when getting out of bed, during physical work, excitement and after eating. The first attacks occur at intervals of several months and later they become more frequent. Alcohol, medication such as adrenaline and anaesthetics can cause it. During the attack, the patient is excited, restless, pale and sweaty (7). In 80 % of cases, they last about 1 hour, but they may last less than a minute or longer than a week. The characteristic triad of symptoms consists of headache, palpitations and sweating (7,8). Other symptoms include anxiety, panic attacks, tremors, chest pain, epigastric pain, nausea, weakness, fatigue, weight loss and dyspnoea (9). The most common sign indicating pheochromocytoma is hypertension, especially if it does not respond to therapy and occurs before the age of twenty or after the age of fifty. It can manifest as orthostatic hypotension, tachycardia, reflex bradycardia and hypertensive retinopathy. It can also manifest as new-onset hyperglycaemia or worsening diabetes (10). If cardiomyopathy, paroxysmal arrhythmias or myocardial infarction occurs where no coronary artery obstruction can be found, pheochromocytoma should be suspected (11).

Indications for biochemical testing are: signs or symptoms that may be the result of an excess of catecholamines, especially if they occur paroxysmally, hypertension resistant to therapy, hypertension that occurs before the age of twenty or after the age of fifty, adrenal incidentaloma with a density greater than 10 Hounsfield units (HU), previous treatment for pheochromocytoma or paraganglioma, hereditary risk of pheochromocytoma or paraganglioma (11,12).

When there is an indication for biochemical testing, metanephrine and normetanephrine metabolites are measured in plasma or 24-hour urine. Some studies showed that measurement of fractionated metanephrines in plasma has high sensitivity (97%) but lacks specificity (85%) compared to metanephrines and catecholamines in 24-hour urine (sensitivity 90%, specificity 98%). Accordingly, the measurement of total catecholamines and metanephrines in urine results in fewer false-positive results (13,14). The specificity of fractionated metanephrines in plasma decreases to 77% in patients older than 60 years (13,15).

The aim of this study was to determine the most common indications for measuring metanephrine and normetanephrine in plasma by gender and age; to investigate if gender and age affect metanephrine and normetanephrine concentration; to explore whether metanephrine and normetanephrine concentrations differ in patients with different indications for biochemical monitoring.

PATIENTS AND METHODS

Patients and study design

The study was organized as a cross-sectional study with historical data. Participants were patients whose plasma metanephrine and normetanephri-

ne concentrations were obtained by accessing the laboratory information system during one year ending on 1 January 2020 at the Clinical Department of Laboratory Diagnostics of University Hospital Centre Osijek. The study included both female and male patients older than 18 years. The study was conducted respecting the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine, Josip Juraj Strossmayer University in Osijek, Croatia.

Methods

Data were collected for each patient from the Department of Nephrology by accessing the hospital information system. The following data were collected: indications for biochemical testing, gender and age of the patient. Patients were divided according to the following indications: signs or symptoms of pheochromocytoma, hypertension resistant to therapy, hypertension that occurs before the age of twenty or after the age of fifty, adrenal incidentaloma with a density greater than 10 Hounsfield units (HU), previous treatment for pheochromocytoma or paraganglioma and hereditary risk of pheochromocytoma or paraganglioma. Plasma metanephrine and normetanephrine concentrations (metanephrine and normetanephrine reference interval 0.05–0.36 nmol/L and 0.14–1.05 nmol/L) regarding the indications for biochemical testing, gender and age were measured.

Statistical analysis

Categorical data are presented in absolute and relative frequencies. The normality of the distribution of numeric variables was examined using the Shapiro–Wilk test. Numeric data were expressed as median and interquartile range. Differences in numeric variables by indication for biochemical testing were tested with the Kruskal–Wallis's test (Conover post-hoc) and according to the gender by Mann–Whitney U test. The strength of the correlation between plasma metanephrine and normetanephrine concentration and gender was measured by Spearman's correlation coefficient, Rho. All p values are two-sided. The significance level was set at p=0.05.

RESULTS

The study included 224 patients, of whom 96 (42.9%) were males and 128 (57.1%) females. The median age of the patients was 64 years (interquartile range of 52 to 71 years) in the range of 18 to 87 years. The most common indications for biochemical testing were adrenal incidentaloma, in 138 (61.6%) and the presence of symptoms and/or signs characteristic of pheochromocytoma in 41 (18.3%) patients, while other indications were present in a smaller number of patients (Table 1).

No statistically significant difference was found in the distribution of participants according to gender and indications for biochemical testing. Patients with adrenal incidentaloma and previous treatment of pheochromocytoma were significantly older than patients with a genetic risk for pheochromocytoma and hypertension before the age of 20 (p<0.001) (Table 2).

Table 1. Basic characteristics of patients

Characteristic	
Gender (No; %)	
Male	96 (42.9)
Female	128 (57.1)
Median age (years) (interquartile range)	64 (52 – 71)
Indication for biochemical testing (No; %)	
Hypertension before the age of 20	5 (2.2)
Hereditary risk of pheochromocytoma	4 (1.8)
Symptoms and/or signs of pheochromocytoma	41 (18.3)
Adrenal incidentaloma	138 (61.6)
Hypertension after the age of 50	4 (1.8)
Therapy-resistant hypertension	26 (11.6)
Previous treatment of pheochromocytoma	6 (2.7)
Total	224 (100)

Table 2. Indications for biochemical testing regarding gender and age

Indication for biochemical testing	**No (%) of patients**			**p**	**Median (interquartile range) age**	**Min. – Max. age** (years)	**p**
	Males	**Females**	**Total**				
Hypertension before the age of 20	5 (5.2)	0	5 (2.2)	0.11	20 (19–24.5)	19–26	< 0.001*
Hereditary risk of pheochromocytoma	1 (1)	3 (2.3)	4 (1.8)		29.5 (20–45.8)	18–50	
Symptoms and/or signs of pheochromocytoma	22 (22.9)	19 (14.8)	41 (18.3)		52 (41–65.5)	29–82	
Adrenal incidentaloma	52 (54.2)	86 (67.2)	138 (61.6)		67 (60–73)	32–87	
Hypertension after the age of 50	2 (2.1)	2 (1.6)	4 (1.8)		62.5 (55.5–69.5)	54–71	
Therapy-resistant hypertension	12 (12.5)	14 (10.9)	26 (11.6)		50.5 (35–65)	30–81	
Previous treatment of pheochromocytoma	2 (2)	4 (3)	6 (3)		63.5 (58–67.5)	49–69	
Total	96 (100)	128 (100)	224 (100)				

*at the level p<0.05, there was a significant difference between hypertension before the age of 20 and all other indications; between hereditary risk of pheo chromocytoma and all other indications; between symptoms and/or signs of pheochromocytoma and adrenal incidentaloma; between adrenal incidentaloma and therapy resistant hypertension

Table 3. Plasma metanephrine and normetanephrine concentrations regarding the indications for biochemic al testing

Indication for biochemical testing	Median (interquartile range) plasma metanephrine concentration	Min. – Max.	p	Median (interquartile range) plasma normetanephrine concentration	Min. – Max.	p
Hypertension before the age of 20	0.1 (0.1 – 0.16)	0.1 – 0.18	0.87	0.300 (0.175–0.395)	0.16–0.48	0.28
Hereditary risk of pheochromocytoma	0.135 (0.065–0.205)	0.05–0.22		0.445 (0.24–0.575)	0.18–0.61	
Symptoms and/or signs of pheochromocytoma	0.14 (0.1–0.19)	0.06–4.61		0.450 (0.34–0.675)	0.14–9.93	
Adrenal incidentaloma	0.135 (0.1–0.18)	0.01–1.26		0.410 (0.29–0.553)	0.06–3.13	
Hypertension after the age of 50	0.15 (0.123–0.185)	0.12–0.19		0.415 (0.395–0.548)	0.39–0.59	
Therapy-resistant hypertension	0.115 (0.088–0.198)	0.05–0.51		0.445 (0.305–0.595)	0.24–0.83	
Previous treatment of pheochromocytoma	0.1 (0.068–0.33)	0.06–0.87		0.440 (0.2–0.635)	0.14–0.86	

No statistically significant difference was observed in plasma metanephrine and normetanephrine concentrations concerning the indications for biochemical testing (Table 3).

Plasma metanephrine concentration was significantly lower in the females (median difference of -0.02, with a 95% confidence interval of -0.04 to -0.01; p=0,009), while there was no significant difference in plasma normetanephrine concentration concerning patients' gender (Table 4).

Table 4. Plasma metanephrine and normetanephrine regarding gender

Variable	Median (interquartile range)		Difference	95% confidence interval	p
	Males	Females			
Plasma metanephrine	0.150 (0.11 – 0.20)	0.12 (0.09 – 0.17)	-0.02	-0.04 to -0.01	0.009
Plasma normetanephrine	0.43 (0.33 – 0.58)	0.41 (0.28 – 0.57)	-0.03	-0.08 to 0.02	0.23

No significant correlation between age and plasma metanephrine concentration was found. The correlation between age and plasma normetanephrine concentration was positive and significant, but weak (Rho=0.171; p=0.01). Elderly patients had a slightly higher plasma normetanephrine concentration.

Of the 224 patients, only one patient was diagnosed with pheochromocytoma, whose indication for the measurement of metanephrine and normetanephrine was adrenal incidentaloma. In plasma, metanephrine was detected at a concentration of 4.61 nmol/L.

DISCUSSION

Metanephrine and normetanephrine testing is often performed, although the prevalence of pheochromocytoma is extremely low.

This research included 224 patients whose concentration of metanephrine and normetanephrine in the plasma were measured. The median age was 64 years, which is higher than the average age at which pheochromocytoma usually occurs (between thirty and fifty years of age) (16). The most common indication for biochemical testing was incidentaloma of the adrenal gland (61.6 %). A more frequent prevalence of incidentaloma was observed in older patients (average age 67 years) and more common in females than in males. Earlier studies also recorded a higher prevalence of incidentalomas in females on average ten years older than affected males; in most cases, it is a benign formation (17). Adrenal gland incidentaloma is found as an accidental finding in 3 - 4% of abdominal CT scans (18). In a patient with adrenal incidentaloma, pheochromocytoma is found in 5% of cases (19, 20). Our results showed that among 138 patients, elevated metanephrine and normetanephrine values were observed in only one in whom the diagnosis of pheochromocytoma was confirmed. According to the results of our research, the rational approach in referring patients for biochemical testing is necessary, i.e. patients with formation density less than 10 HU on CT should not be referred for biochemical testing.

Due to symptoms and signs, 18.3% of our patients were biochemically tested; the average age was 52 years and symptoms occurred more often in males than in females. It was observed in our study that due to the symptoms of pheochromocytoma, younger and middle-aged people were tested more often. A possible explanation for this is the highest prevalence of anxiety disorders, panic attacks, and thyroid disease at that age, considering that the symptoms are very similar and sometimes impossible to distinguish (21, 22). Due to the variety of symptoms, pheochromocytomas are called "great imitators", therefore there are many conditions and diseases that can be a differential diagnosis of pheochromocytoma (23). It is necessary to set clear guidelines on when to refer the patient for biochemical testing and whether

other, more common conditions that can lead to the different symptoms should be ruled out first.

In this study, the hereditary risk of pheochromocytoma was present in 1.8% of patients, with an average age of 29.5 years. Pheochromocytoma most often occurs sporadically, but in 35% it is part of a hereditary syndrome. The most common inherited syndromes include multiple endocrine neoplasia type 2 (MEN 2), Von Hippel Lindau (VHL) syndrome, neurofibromatosis type 1 (NF1) and mutations in genes encoding succinate dehydrogenase B and D subunits (SDHD and SDHB) (10,42). Genetic testing is necessary if pheochromocytoma occurs at a younger age with multifocal, extra-adrenal, bilateral tumours and with a positive family history of pheochromocytoma (25,26). Furthermore, any hypertension that occurs before the age of 20 should arise the suspicion of pheochromocytoma (16,26).

In our study, 2.2% of patients were tested for hypertension that occurred before the age of 20. Hypertension occurs in 60-90% of children and adolescents with pheochromocytoma (16,27). Other more common causes of secondary hypertension in young people are diseases of the renal parenchyma and coarctation of the aorta (28). Pheochromocytoma in children and adolescents is in 80% of cases associated with gene mutations (27). The average age at which it occurs is 11-13 years, and it is twice as common in male children. It is the cause of hypertension in 0.5-2% of cases. Genetic testing and follow-up of the patient throughout his life are necessary (2).

Due to previous treatment for pheochromocytoma, 2.7 % of patients, with an average age of 63.5 years, were tested in this study. When the diagnosis is made, especially in younger patients, it is necessary to decide on a need for genetic testing. It is useful due to the possibility of identifying patients who have an increased risk of multifocal, recurrent, and metastatic disease (29). Although the prognosis of benign tumours is excellent, recurrence rates in 10 years are 16%, therefore biochemical monitoring is required once a year (30).

Therapy-resistant hypertension was the indication for testing in 11.6% of our patients. The median age of onset was 50 years, with a slightly higher prevalence in females. Only 5-10 % of hypertension is secondary hypertension; it should be suspected if it occurs at a younger age (< 30 years), with unexplained blood pressure variability and unexpected response to medication or anaesthesia (31,32).

In our study, no significant differences in the metanephrine and normetanephrine concentration in the plasma about the indication was found. The patients' findings were mostly within the reference values. Levels of normetanephrine in plasma that are 4 times higher than the reference value and metanephrine 2.5 times higher, indicate with great certainty that the cause is a pheochromocytoma (33). Our patients' plasma metanephrine values increased 12 times, and normetanephrine 9 times the reference value. Also, urinary catecholamine levels 2-3 times higher than reference values support this diagnosis (34). Medication such as tricyclic antidepressants, antipsychotics, serotonin and noradrenaline reuptake inhibitors and levodopa can lead to false positive results, so they should be discontinued two weeks before the test (11).

Our results showed that metanephrine in plasma was significantly lower in females, while no difference was observed for normetanephrine in regards to gender. This is confirmed by earlier studies, but it is not necessary to adjust the reference values of metanephrine and 3-methoxytyramine, even though they are higher in males than in females (19). On the other hand, normetanephrine reference values must be adjusted to the patient's age. In young people, the upper limit value of normetanephrine is 0.47 nmol/L, in middle-aged (40 - 49 years) 0.79 nmol/L, in 50-59 years 0.87 nmol/L and elderly (≥60 years) 1.05 nmol/L (19,35). In our research, the association between age and plasma normetanephrine concentration was confirmed - significantly higher values were observed in the elderly; no correlation between age and plasma metanephrine concentration was observed. Earlier studies report that there is weak relationship between age and metanephrine concentration (35).

This study was conducted to determine the most common indications for biochemical testing of pheochromocytoma and to examine the difference in the concentration of metanephrine and normetanephrine in regards to indication. Given that the indications for biochemical testing are very common in the general population, research should be repeated on a larger sample of patients.

In conclusion, pheochromocytoma is a rare dia-

gnosis, but if it remains unrecognized, it can lead to complications. Given the wide spectrum of conditions that have similar symptoms to pheochromocytoma, a rational approach and clear guidelines are needed when biochemical testing of patients is required.

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