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Pheochromocytoma — analysis of 15 consecutive cases from one centre

Barwiak — analiza 15 kolejnych przypadków z jednego ośrodka

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Abstract

Introduction: Pheochromocytoma is a rare tumour, but one of great clinical importance as a risk factor of malignancy, cardiovascular diseases and sudden death.

Material and methods: 15 consecutive patients (eight women and seven men) were hospitalised and submitted for adrenalectomy with pheochromocytoma confirmed by histopathologic examination. Adrenalectomies were performed laparoscopically in 14 cases (93.3%): in nine by the retroperitoneal posterior mode and in five by the transperitoneal lateral approach.

Results: Molecular-genetic examination of VHL, RET, SDHB, SDHC and SDHD genes revealed inherited predisposition for PHEO in three of 15 patients (20%): RET mutations typical for MEN 2a in two patients and VHL mutation in one patient. Disturbances of the carbohydrate metabolism occurred in nine patients (60%). Ten patients (66%) reported paroxysmal symptoms. In all cases, with the exception of a von Hippel-Lindau patient, density of tumours exceeded 20 HU. In all studied patients, urine concentration of normetanephrines exceeded their normal range and greatly prevailed over metanephrines values, which were increased in six of them (40%).

Conclusions: Urine metoxycatecholamines and increased tissue density are sufficient in pheochromocytoma detection. However, taking into account clinical and supplemental biochemical data may be helpful in the diagnostic process. Laparoscopic adrenalectomy is a fully sufficient and safe method of pheochromocytoma excision. **(Endokrynol Pol 2013; 64 (3): 192–196)**

Key words: *metoxycatecholamines, adrenal tumour, tissue density, hypertension*

Streszczenie

Wstęp: Barwiak jest rzadkim guzem o dużym znaczeniu klinicznym jako guz potencjalnie złośliwy i czynnik ryzyka chorób sercowo-naczyniowych i nagłej śmierci.

Materiał i metody: U 15 pacjentów (8 kobiet i 7 mężczyzn) zdiagnozowano, usunięto i potwierdzono barwiaka badaniem histopatologicznym. Adrenalektomie przeprowadzono laparoskopowo u 14 osób (93,3%): u 9 z podejścia zaotrzewnowego tylnego i u 5 przez dostęp przezotrzewnowy boczny.

Wyniki: Badania molekularno-genetyczne genów VHL, RET, SDHB, SDHC i SDHD ujawniły wrodzone predyspozycje do barwiaka u 3 z 15 chorych (20%): mutacje RET typowe dla MEN 2a u 2 pacjentów i u jednego mutację VHL. Zaburzenia gospodarki węglowodanowej stwierdzono u 9 chorych (60%); 10 pacjentów (66%) zgłaszało objawy napadowe. We wszystkich przypadkach, z wyjątkiem chorego z zespołem von Hippel-Lindaua, gęstość guzów przekraczała 20 HU. U wszystkich badanych stężenie normetanefryn w moczu przekroczyło normę i istotnie przewyższało stężenie wartości metanefryn, które było podwyższone u 6 chorych (40%).

Wnioski: Stężenie metoksykatecholamin i zwiększona gęstość tkankowa pozwalają na rozpoznanie barwiaka, jednak wzięcie pod uwagę danych klinicznych i dodatkowych może być pomocne w procesie diagnostycznym. Adrenalektomia laparoskopowa jest w pełni skuteczną i bezpieczną metodą leczenia barwiaka.**(Endokrynol Pol 2013; 64 (3): 192–196)**

Słowa kluczowe: *metoksykatecholaminy, guz nadnerczy, gęstość tkankowa, nadciśnienie tętnicze*

Introduction

Pheochromocytomas (PHEOs) are rare cause of hypertension (about one per 1,000 cases) with an estimated prevalence in the general population of 0.5 per 100,000 per year, with equal proportions of both genders [1, 2]. We found the prevalence range of PHEO among adrenal incidentalomas to be from 1.5 up to 14% (average 7%) in our previous study 4.8% [3, 4].

These tumours originate from tissue characterised by catecholamines production. The most frequent localisation of PHEOs is the adrenal cortex, as far as it constitutes the largest residue of the ganglionic cells [5, 6]. Pheochromocytomas are recognised in about 3% of patients with adrenal incidentaloma; extra-adrenal location is rare, involving paravertebral ganglions and paraganglionic bodies [7, 8].

Pheochromocytoma most commonly is a benign, single tumour of the adrenal cortex, causing hyperten-

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sion and usually recognised in the fourth decade of life [1, 2, 5, 6]. Exceptions to these epidemiologic rules are: malignancy, bilaterality, extra-adrenal placement and normotension are considered to occur more frequently in PHEOs determined by inherited mutations (35% of cases) [9–11]. This percentage is estimated by taking into account 10% of patients with a family prevalence of PHEOs and 25% of persons with PHEOs and no family history. A predisposition for PHEO occurrence is related to a mutation of one among nine genes that have been discovered so far: RET, VHL, NF1, SDHA, SDHB, SDHC, SDHD, TMEM127 and MAX [10, 11]. These mutations predispose to other disturbances that constitute i.a. syndromes of: Multiple Endocrine Neoplasms (MEN) type 2A and 2B, von Hippel-Lindau, neurofibromatosis type 1 and pheochromocytoma-paraganglioma syndrome (PPS) of several types [1, 2, 5, 6]. There has been a discussion as to whether PHEOs patients should be subject to genetic examination, but most experts agree that mutations in RET, SDHD, SDHB and VHL genes should be looked for in persons with a family history, plural, extra-adrenal or malignant tumours, and in those in whom PHEO was revealed before the age of 45 [11].

The purpose of the present study was to analyse clinical data of PHEO cases to assess the efficiency of diagnostics and surgical treatment of PHEO.

Material and methods

Retrospective analysis has been carried out in a group of 15 consecutive patients hospitalised between 2009 and 2012 at the Clinical Department of Endocrinology, then submitted for adrenalectomy in 1st Department of General and Endocrine Surgery of University Hospital of Białystok and confirmed by histopathologic examination to have PHEO. This group contained eight women (53.3%) mean age 46.0 years (youngest-oldest: 26–72) and seven men (46.7%), mean age 65.3 (youngest-oldest: 45–77). Ten of them were symptomatic and five were asymptomatic. In each patient, 32-row computer tomography was performed with description of adrenal tumour tissue density in Hounsfield's units (HU). In all patients, biochemical measurements of urine metanephrines and normetanephrines were done. In non-symptomatic patients diagnosed because of the presence of an adrenal incidentaloma, we performed a test of inhibition with 1 mg dexamethasone and plasma renin activity and aldosteronemia. Determinations of urine methanephrine and normethanephrine were performed by the immunoassay method using nephrines urine kits (Biosource, Nivellas, Belgium). Values expectations: methanephrins < 350 ug/ /day; normethanephrins < 600 ug/day. Sensitivity: methanephrins 5 ng/Ml; normethanephrins 13 ng/MI. CV for methanephrins 5.2%, for normethanephrines 12.2%.

Extraadrenal tumours (in patient 2 — in paravertebral L1 right ganglion and in patient 12 — near the junction of the right renal vein with main inferior vein) were revealed by CT-scanning.

Adrenalectomies were performed laparoscopically in 14 cases (93.3%): in nine by the retroperitoneal posterior approach and in five by transperitoneal lateral approach. In one case of malignant tumour (multiple metastases to the lymph nodes), a classical operation was conducted. Mean duration of laparoscopic excision was 115 min (55–180), mortality 0%, conversions 0%, mean blood loss 77 mL (20–400), no wound infections. Typical pharmacological preparation for adrenolectomy with nonselective α-adrenolytic was used in all 15 patients.

Molecular-genetic analysis of the genes: VHL (exons 1–3), RET (exons 10–16), SDHB (exons 1–8), SDHC (exons 1–6) and SDHD (exons 1–4) in blood specimens were performed in the Institute of Cardiology in Warsaw or in the University Hospital of Freiburg.

Demographic, clinical and biochemical characteristics of the studied group are shown in Table I.

The statistical significance was estimated by Mann-Whitney test. To evaluate relationships between variables, Spearman's test was performed using Statistica 10.0 for Windows XP (StatSoft, Tulsa, OK, USA). Data is shown in mean ± SD.

Results

Molecular-genetic examination of VHL, RET, SDHB, SDHC and SDHD genes revealed an inherited predisposition for PHEO in three of the 15 patients (20%): RET mutations typical for MEN 2a in two patients (in exon 11; c. 634T > A; p. Cys634Ser and in exon 11; c. 634G > C; Cys634Tyr) and in one patient VHL mutation (in exon 1; c. 74C > T; p. Pro25Leu). Both MEN 2a patients had a family history of medullar carcinoma, typical for MEN 2. A male with RET mutation was thyroidectomised twice because of medullar carcinoma with lung metastases and subsequently treated with vandetanib, cyclophosmanil, doxorubicin and cisplatin. None of them had features of parathyroid glands tumours that could be expected in MEN 2a patients. In both, PHEOs were bilateral and symptomatic with paroxysms and weight loss. In a male with VHL gene mutation, signs of von Hippel-Lindau syndrome were present: retinal angioma and right kidney cortex cysts. His PHEO was found incidentally and he remained asymptomatic with steady weight. Mean age of PHEO diagnosis in the three patients with inherited PHEOs (46.3) was lower than in the other 12 patients (57.2); however, among them were two young females of 27 and 32 years of age. In five patients (33%), serious cardiovascular events oc-

Table I. *Demographic, clinical and biochemical characteristics of the studied group*
Tabela I. *Demograficzna, kliniczna I biochemiczna charakterystyka badanej grupy*

Lp	Genotype	Gender	Age (ys)	CVD	HT (ys)	T2D	Paroxysmal symptoms	Body mass	Adrenal	Diame ter [mm]	Density (HU) base→contrast	MNephr. [μg/d]	NMNephr. [μg/d]	Cholesterol Triglycerides	ECG conduct
1	VHL	m	68	CI	30	no	No	stable	R	30	7→52	100	1,260	161, 62	AV1°
2	0	f	32	no	0,5	no	↑sweating, palpitations, trembling	↑	extra adrenal	18	25→125	82	651	133, 66	PR< 120ms
3	0	m	61	2xMICI	20	+	↑RR headache/ ↓RR ↑sweating	↓	R	48	30→80	7,224	11,742	166, 92	AV1°
4	0	f	49	no	15	no	↑RR, headache, ↑sweating, weakness	↑	R	43	44→90	410	1,950	231, 173	No
5	0	m	76	2xMI	5	+	No	↑	L	42	28→88	153	941	242, 182	No
6	0	f	72	no	10	+	No	stable	R	18	22→50	92	842	251, 188	PR < 120 ms
7	0	m	72	MI	10	+	↑RR, palpitations, pallor, tinnitus, weakness	↑	R	30	44 →95 Non-homog., calcification	1,102	1,802	199, 82	RBBB
8	MEN2a	m	49	no	no	no	↑RR, headache, ↑sweating, pallor	↓	bilateral	42R/ L44	50 →105	1,020	3,848	144, 71	No
9	0	f	47	no	no	no	No	↓	R	24	45→93 Non-homog.	786	2,400	169, 89	No
10	0	m	73	MI	30	+	↑RR, palpitations	↓	R malignant	41	40→70	11,560	31,295	214, 124	AV1°
11	0	f	27	no	0.5	+	↑RR, headache, ↑sweating, pallor	↓	R	42	33→57 Non-homog.	2,550	6,807	229, 128	PR < 120 ms
12	0	f	51	no	10	no	↑RR, hot flush, weakness	↓	R + extra-adrenal	15/17	30→120/28→150326		1,225	254, 136	No
13	MEN2a	f	26	no	15	+	↑RR, palpitations	↓	bilateral	64R/ L48	55 →114	1,500	4,000	154, 89	No
14	0	f	64	no	10	+	No	stable	R	45	43→70	260	817	199, 177	PR < 120 ms
15	0	m	62	no	20	+	↑RR, weakness	↓	R	85	48→110	11,620	33,253	195, 73	No

CVD — cardiovascular diseases; HT — hypertension; T2D — type 2 diabetes; MNephr — metanephrines; NMNephr — normetanephrines; CI — cerebral insult; MI — myocardial infarction; BP — blood pressure; ↑/↓ — increased/decreased; AV1° — atrio-ventricular 1° block; RBBB — right bundle branch block

curred: in four myocardial infarctions (in two double) and in two ischaemic cerebral insults. Hypertension of various duration (from six months to 30 years) was present in all with the exception of one patient. Disturbances of carbohydrate metabolism were present in nine patients (60%): in six, glucose intolerance and in three overt diabetes. Ten patients (66%) reported paroxysmal symptoms: blood pressure increases (nine) and decreases (one), excessive sweating (five), palpitations (four), headache (four), weakness (four), pallor (three), trembling (one), tinnitus (one) and hot flushes (one). These attacks occurred in both MEN2a patients but not in the patient with von Hippel-Lindau syndrome. Eight patients experienced body mass decrease, four gained weight and in three body mass remained stable.

As mentioned above, both of the MEN 2a patients had bilateral tumours, in 12 tumours were localised unilaterally: in 11 in right adrenals (one malignant) and in one in the left adrenal gland. In two cases, PHEO had extra-adrenal localisation (in one of them accompanying right adrenal tumour). In all cases, with the exception of the von Hippel-Lindau patient, density of tumours exceeded 20 HU and increased markedly after contrast infusion. In all studied patients, normetanephrines exceeded their normal range and greatly prevailed over metanephrines values, which were increased in six of them (40%). Triglycerides were relatively decreased (< 90) in eight (53.3%) and total cholesterol was relatively low (< 170 mg%) in six (40%). In eight (53.3%) various conduction abnormalities in ECG were found: in four PR shortening (< 120 ms), in three 1°atrioventricular block, and in one RBBB.

We found statistically significant differences between patients with and without paroxysmal symptoms in urine concentrations of metanephrines (in µg/24 h) respectively: 3,740 ± 4,622 and 278 ± 292 ($p < 0.02$) and normetanephrines (in µg/24h) respectively: 9,657 ± ± 12,367 and 1,252 ± 666 ($p < 0.05$). There were negative correlations between body mass reduction and metanephrines ($R = –0.66$; $p < 0.01$) and normetanephrines ($R = –0.71$; $p < 0.01$). There were positive correlations between tumour diameter and metanephrines ($R = 0.59$; $p < 0.01$) and normetanephrines ($R = 0.55$; $p < 0.01$). A high-degree positive correlation was found between metanephrines and normetanephrines themselves ($R = 0.94$; $p < 0.001$).

Discussion

The percentage with inherited PHEO among our patients (20%) was comparable to those found in other populations (20–35%) and greatly exceeded other previous reports (10%) [9–13]. However, the percentage of causative mutations diagnosed in persons with PHEO under 50 years of age (33%; both in the MEN2a patients) was lower than the prevalence, estimated as over 80%, in this age group in another setting [10].

Adrenalectomies in our patients were performed laparoscopically in 93.3% of cases: by the retroperitoneal posterior approach and by the transperitoneal lateral approach. Laparoscopic adrenalectomy is the method of choice for benign tumours of less than 8 cm. They are superior compared to the classical open method for adrenal tumours excision as they allow hospitalisation time to be cut from five days to three and to reduce by 50% the complication rate [14]. Both retroperitoneal posterior and transperitoneal lateral approaches are effective, but the latter has some advantages: time of surgery is one third shorter, blood loss is diminished by nearly a half, and hospitalisation duration and complications percentage are reduced by more than half [15].

Pheochromocytoma is well-known risk factor for myocardial infarction and cerebral insult [14]. In our PHEO group, 33% experienced serious cardiovascular events and half of the patients with myocardial infarctions had it twice.

Hypertension is reported in nearly all PHEO cases, usually as a permanent condition, but in half of patients it occurs in attacks (with maintained hypertension or normotension in the meantime) [5, 6]. In our group, nearly all patients had chronic hypertension (two normotensives) and 60% had spells of blood pressure increases, accompanied by other paroxysmal symptoms. Rarely (about 10%), PHEO may provoke hypotension with collapses, especially orthostatically. In our setting, in one patient with chronic and paroxysmal hypertension, we also observed symptomatic hypotension. 66% of our PHEO patients complained of paroxysmal symptoms. Apart from blood pressure increases, other complaints constituting a classical triad of PHEO symptoms occurred: excessive sweating, palpitations and throbbing headaches. Other reported paroxysmal symptoms were: weakness, trembling, tinnitus, pallor and hot flushes. The latter two are rare, however very typical complaints of PHEO patients [1, 2, 4, 5].

The reported incidence and severity of diabetes is highly variable but most commonly it ranges between 40 and 65% [5, 17]. Disturbances of carbohydrate metabolism were present in 60% of our PHEO cases.

Typically, catecholamines excess leads to hypercatabolism and weight loss as was observed in most of our patients, however nearly one in four of them gained weight and in another 20% body mass remained stable. This may be explained by an increase of appetite and overcompensation of metabolic expenses [1, 6].

A typical tumour phenotype for PHEO is characterised by unilateral occurrence, diameter exceeding 4 cm and irregular shape, nonhomogeneity of structure

with calcifications, cysts, haemorrhages and increased vasculature, increased density (> 20 HU) and delayed contrast wash-out (< 50% after 10 min) in computer tomography and increased signal in T2-dependent images in magnetic resonance [4, 7, 18, 19]. In positron emission tomography, usually increased uptake of 18-fluorodeoxyglucose (SUV > 2.5) is observed [20]. However, it is not rare that smaller tumours, with no typical phenotype, are finally diagnosed as PHEO. This makes mandatory biochemical screening in all cases of adrenal incidentalomas [18]. Determination of urine metoxycatecholamines plays a crucial role in PHEO diagnostics as far as their sensitivity and specificity reach 98% [21].

In all the cases in our settting, with the exception of the von Hippel-Lindau patient, density of tumours exceeded 20 HU, however in 33% of PHEO their diameter was less than 4 cm. Majority of PHEO (73.3%) were localised in right adrenal glands of our patients and this is in line with the report of Bednarek-Tupikowska et al. [22].

In all the patients in our study, urine level of normetanephrines exceeded their normal range and greatly prevailed over metanephrines values, which were increased in 40% of cases, suggesting the superiority of metanephrines measurement in confirming a diagnosis of PHEO. In a cohort of PHEO analysed by Przybylik-Mazurek et al., urine metanephrines determination had a higher positive predictive value than normetanephrines measurements [23].

We found higher values of both urine metoxycatecholamines in patients with paroxysmal symptoms and negative correlations between body mass reduction and both catecholamine metabolism. Moreover, we found positive correlations between tumour diameter and both metanephrines and normetanephrines. This suggests a close relation between urine metoxycatecholamine levels, tumour size and clinical picture in PHEO patients.

Data from routine clinical work-out: relatively decreased triglycerides (53.3% in our study) and total cholesterol (40% in our analysis), as well as various conduction abnormalities in ECG may make the suggestion of PHEO stronger, as likely consequences of catecholamine excess.

In summary, as PHEO is a potent risk factor of serious cardiovascular events, sudden death and malignancy, it is of importance to suspect this condition in terms of paroxysmal attacks and biochemical screening in all cases of adrenal incidentaloma. Urine metoxycatecholamines are sufficient in PHEO detection, although taking into account clinical and supplemental biochemical data may be helpful in the diagnostic process. Laparoscopic adrenalectomy is a fully sufficient and safe method of PHEO excision.

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