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Challenges in the diagnosis of pheochromocytoma and paraganglioma syndrome

Aleksandra Zdrojowy-Wełna, Grażyna Bednarek-Tupikowska

Department of Endocrinology, Diabetology and Isotope Therapy, Wrocław Medical University, Wrocław, Poland

Correspondence to: Aleksandra Zdrojowy-Wełna
Department of Endocrinology, Diabetology and Isotope Therapy
Wyb. L. Pasteura 4, 50-367 Wrocław, Poland.
tel: +48 71/784 25 59; fax: +48 71 784 357 09 57; e-mail: aleksandrazdr@gmail.com

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Abstract

OBJECTIVES: Adrenal pheochromocytomas are rare neuroendocrine tumours, however their prevalence is probably underestimated – in some series 50% were diagnosed at autopsy. The clinical presentation varies among patients, that is why diagnosis might be difficult to establish. Pheochromocytoma may coexist with paraganglioma and when paraganglioma is diagnosed, the patient should be screened for pheochromocytoma too, especially in people with hypertension. We present a case of woman with pheochromocytoma, but diagnosed after incidence of stroke, who had also paraganglioma in the past. Additionally, a teratoma was diagnosed simultaneously.

CASE REPORT: 49-year old woman with hypertension was referred to the Department of Endocrinology, Diabetology and Isotope Therapy in Wrocław with suspected pheochromocytoma. She was operated twice because of paraganglioma of the right and left carotid artery, second operation was complicated with stroke. After administration of anticoagulants a bleeding from gastrointestinal tract occurred. During diagnostic process CT of the abdomen showed tumour in the right adrenal gland and a tumour in pelvis. Significantly elevated catecholamines and their metabolites in blood and urine confirmed the diagnosis of pheochromocytoma. Both tumours were removed surgically, the second was teratoma maturum. Genetic screening for hereditary pheochromocytoma was proceeded. A mutation in SDHD gene was revealed in patient's DNA and subsequently in blood samples of her sister and daughter.

CONCLUSIONS: Occurrence of paraganglioma with hypertension suggest need of screening for pheochromocytoma-paraganglioma syndrome, especially in case of paragangliomas in family history. Early treatment is crucial to avoid life-threatening cardiovascular complications. The association between pheochromocytoma and teratoma is unclear.

Abbreviations:

ACE inhibitor	- angiotensin-converting-enzyme inhibitor
KIF1Bβ	- kinesin family member 1B transcript variant beta
HIF-2α	- hypoxia-inducible factor 2α
MAX	- MYC associated factor X
MEN2 syndrome	- multiple endocrine neoplasia syndrome
NF1	- neurofibromatosis type 1
PCC	- pheochromocytoma
PGL	- paraganglioma
PHD2	- prolyl hydroxylase domain 2
SDHA/B/C/D	- succinate dehydrogenase subunits A, B, C and D
SDHAF2	- succinate dehydrogenase complex assembly factor 2
TMEM127	- transmembrane protein 127
VHL syndrome	- von Hippel Lindau syndrome

CASE REPORT

INTRODUCTION

Adrenal pheochromocytomas (PCC) and paragangiomas (PGL) are rare neuroendocrine tumours, arising from chromaffin cells of the adrenal medulla and from the extra-adrenal autonomic paraganglia, respectively. Their suggested annual incidence rate is 0.5 per 100,000 person-years (Ariton *et al.* 2000). However, some studies conclude that those numbers are underestimated (Ariton *et al.* 2000; Sutton *et al.* 1981) (50% PCC in Mayo Clinic series were diagnosed at autopsy). The diagnosis may pose a challenge due to variable clinical presentation and low frequency.

CASE REPORT

A 49 year-old postmenopausal woman was admitted to hospital for planned surgery of left carotid PGL in November 2012. It was her second carotid PGL – the first one on the right side of the neck was surgically removed in 2002. The patient suffered from hypertension which was diagnosed in 2010. Despite receiving beta blocker and ACE inhibitor her blood pressure remained high, paroxysmal (rises up to 170/100 mmHg at home, 240/160 mmHg in hospital). She had no symptoms of hypertension and never lost conscious, however sometimes orthostatic hypotension occurred and she reported recent weight loss (around 10 kg in 2 months without diet change). Patient's sister also underwent carotid PGL operation and their father died at the age of 56 because of cardiovascular disease.

Before operation additional hypotensive treatment was given to the patient (clonidine, calcium blocker). Shortly after the procedure she suffered from transient aphasia and paresis. Computed tomography excluded cerebral bleeding and non-invasive treatment was admitted. Patient's neurological state improved and she was discharged from the hospital with anticoagulant drugs. A week later she was admitted again because of anaemia, hematemesis and weakness. Gastroscopy revealed bleeding from duodenal ulcer, which was supplied with clipping. Additionally performed computed tomography of the abdomen showed an inhomogeneous tumour in right adrenal gland (6.5×5.5×4.3 cm) and a second tumour in pelvis (20×15×10 cm) with a picture of teratoma. The patient was send to our Department.

Tab. 1. Laboratory test results.

Adrenaline in blood	**10.64** nmol/l [<0.69]
Noradrenaline in blood	**20.5** nmol/l [<3.55]
Adrenaline in urine	**1230** nmol/l [<110]
Noradrenaline in urine	**3423** nmol/l [<535]
Metoxycatecholamines in urine	**4503** µg/24h [<1000]

The hormonal tests showed elevated catecholamines in blood and urine and metoxycatecholamines in urine (Table 1). Additionally, diabetes and echocardiographical signs of heart overload were revealed. The patient was given high of dose alpha blockers and the dose of beta blockers was elevated. The blood pressure control improved. The diagnosis of PCC was made.

After three weeks the patient was operated with advanced hemodynamic monitoring and both tumours were removed simultaneously. The course of operation went uncomplicated. The histopatological examination confirmed the diagnosis of adrenal pheochromocytoma (dimension 9×7 cm) with clear surgical margin and histopatological signs of benign tumour (undamaged capsule, without angioinvasion, without necrosis, Ki67 index below 1%). Immunohistochemical findings are shown in Table 2. The ovarian tumour was confirmed as teratoma maturum. After the operation the blood pressure control improved, moreover diabetes treatment was no longer necessary.

Because of significant family history (PGLs in patient's and sister's past, early death of the father due to cardiovascular disease) the genetic screening was performed. Genes RET, VHL, SDHB, SDHC, SDHD were sequenced. The mutation in gene SDHD p. Y114C was confirmed in patient. Subsequently, the sister and patient's children were also examined – the mutation was found in patient's sister and one patient's daughter. Sister's children are currently waiting for genetic screening.

DISCUSSION

It is estimated, that around 30% of PCC/PGL are a part of familiar disorder (Mannelli *et al.* 2009; Neumann *et al.* 2002). Classic genetic disorders associated with PCC are von Hippel-Lindau (VHL) syndrome, multiple endocrine neoplasia syndromes (MEN2) and neurofibromatosis type 1 (NF1). Other mutations include succinate dehydrogenase subunits A, B, C and D (SDHA/B/C/D), succinate dehydrogenase complex assembly factor 2

Tab. 2. Immunohistochemical findings.

pheochromocytoma epinephri:
IKi67 (+)<1%
synaptophysin (+)
chromogranin A (+)
S100 (+)
CD56(–)
Melan A (–)
alfa 1 inhibin (–)
CD34 (–)
Calretinin (–)

(SDHAF2) and the more recently reported transmembrane protein 127 (TMEM127), MYC associated factor X (MAX), kinesin family member 1B, transcript variant beta (KIF1Bβ), prolyl hydroxylase domain 2 (PHD2), and hypoxia-inducible factor 2α (HIF-2α) (Jochmanova & Lazurova 2014). Those PCC are more often multifocal, smaller, extra adrenal, asymptomatic and tend to manifest earlier in life than sporadic tumours (Eisenhofer *et al.* 2011; Sutton *et al.* 1981; Szymonek & Kowalska 2013; Van Duinen *et al.* 2010) probably due to family screening. The occurrence of germline mutations predisposes patients to multifocal PPGL (SDHx, RET, TMEM127), recurrent disease (all mutations) or malignancy (SDHB mutation).

In case of coexistence of PCC with PGL the mutations in the SDH genes must be taken into consideration. They compose the mitochondrial complex II, which is a tumour suppressor gene involved in the electron transport chain and the tricarboxylic-acid cycle. In German-Polish registers of 417 patients with PCC or PGL, 12% showed a mutation in SDHD or SDHB genes (Neumann *et al.* 2004). Our patient presented the most common mutation – in SDHD subunit, which seems to predispose to multifocal PGL, but less often malignant than in case of SDHB mutation (Neumann *et al.* 2004). In patients with SDHD and SDHAF2 mutations, the disease is not manifested when it is inherited from the mother but is highly penetrant when inherited from the father (maternal imprinting). We can conclude then, that both patient and her sister inherited the mutation from their father. Their children with inherited mutation will probably not manifest the disease, until male offspring transmits the mutation to his children. That is why genetic screening is important to monitor the mutations spread in the family.

The diagnosis of PCC/PGL syndrome was made in the patient after severe complications of PGL operation. However, due to the recent indications for biochemical screening for PCC/PGL (Van Berkel *et al.* 2014) (Table 3), patient fulfilled at least two criteria even before operation (paroxysmal hypertension, episodes of hypotension), other two occurred in course of treatment (adrenal incidentaloma, new onset of diabetes in lean patient). Measurements of metanephrines in plasma or urine are the tests of first choice, offering the best diagnostic performance because of continuous intratumoural production and secretion of metanephrines into the circulatory compartment (Van Berkel *et al.* 2014). However, in case of our patient both metanephrines and catecholamines were helpful in diagnostic process.

Another interesting aspect is the coexistence of pheochromocytoma with teratoma. We couldn't find any reported correlation between development of those tumours in literature. There is one case report describing occurrence of dermoid cyst and pheochromocytoma in male patient, our case would be the second (Soyupek *et al.* 2004). Recently there is increasing evidence that hypoxia-inducible factor 2α gene (*HIF2A*) mutations predispose to PCC/PGL and also stimulates tumorogenesis in general (Jochmanova & Lazurova 2014). cybS, encoded by SDHD, is a critical component of the oxygen-sensing system of paraganglionic tissue, and that its loss may lead to chronic hypoxic stimulation and cellular proliferation. That may be a possible explanation of a tendency to tumorogenesis in patients with genetic predisposed PCC/PGL, however we cannot exclude a simple coincidence of those diseases.

Tab. 3. Indications for biochemical testing for pheochromocytoma (after Van Berkel *et al.* 2014).

Symptomatic patients
• paroxysmal headaches, sweating, tachycardia, pallor, nausea, flushing, hypertension
• unexplainable variability of blood pressure
• paradoxal blood pressure response to anesthesia, surgery or drugs
• orthostatic hypotension in a hypertensive patient
Non-symptomatic patients
• adrenal incidentaloma
• predisposition for hereditary PPGL[1]
• new onset diabetes mellitus in a young lean hypertensive patient

[1] Defined as: presence of syndromic features or proven pathogenic mutation in one of the known susceptibility genes in one of the family members, one or more family members with PPGL, recurrent or metastatic PPGL.

CONCLUSIONS

Occurrence of paraganglioma with hypertension suggests need of screening for pheochromocytoma-paraganglioma syndrome, especially in case of paragangliomas in family history. Following indications for biochemical screening, proper treatment may had been managed few years earlier, which is crucial to avoid serious complications. The association between pheochromocytoma and teratoma is unclear, however recent studies suggest hypoxia-inducible factor 2α gene mutations important role in development of PCC/PGL and tumoregenesis in general.

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