Challenges in the diagnosis of pheochromocytoma and paraganglioma syndrome

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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
SDHAB/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

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INTRODUCTION

Adrenal pheochromocytomas (PCC) and paragangio-
mas (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 stud-
ies 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 hyperten-
sion 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 symp-
toms 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 sup-
plied 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.

The hormonal tests showed elevated catecholamines
in blood and urine and metoxycatecholamines in urine
(Table 1). Additionally, diabetes and echocardiographi-
cal 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 histopathological examination
confirmed the diagnosis of adrenal pheochromocytoma
(dimensions 9×7 cm) with clear surgical margin and
histopathological 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 daugh-
ter. 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 endo-
crine neoplasia syndromes (MEN2) and neurofibroma-
tosis type 1 (NF1). Other mutations include succinate
dehydrogenase subunits A, B, C and D (SDHA/B/C/D),
succinate dehydrogenase complex assembly factor 2

<table>
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<tr>
<th>Tab. 1. Laboratory test results.</th>
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<tr>
<td>Adrenaline in blood</td>
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<tr>
<td>Noradrenaline in blood</td>
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<tr>
<td>Adrenaline in urine</td>
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<tr>
<td>Noradrenaline in urine</td>
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<tr>
<td>Metoxycatecholamines in urine</td>
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<tr>
<th>Tab. 2. Immunohistochemical findings.</th>
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<tr>
<td>pheochromocytoma epinephri:</td>
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<tr>
<td>IKi67 (+)&lt;1%</td>
</tr>
<tr>
<td>synaptophysin (+)</td>
</tr>
<tr>
<td>chromogranin A (+)</td>
</tr>
<tr>
<td>S100 (+)</td>
</tr>
<tr>
<td>CD56(-)</td>
</tr>
<tr>
<td>Melan A (-)</td>
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<tr>
<td>alfa 1 inhibin (-)</td>
</tr>
<tr>
<td>CD34 (-)</td>
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<td>Calretinin (-)</td>
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(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 2a gene (HIF2A) mutations predispose to PCC/PGL and also stimulates tumorigenesis 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 tumorigenesis in patients with genetic predisposed PCC/PGL, however we cannot exclude a simple coincidence of those diseases.

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 2a gene mutations important role in development of PCC/PGL and tumorigenesis in general.

REFERENCES


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

<table>
<thead>
<tr>
<th>Symptomatic patients</th>
<th>Non-symptomatic patients</th>
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<tr>
<td>• paroxysmal headaches, sweating, tachycardia, pallor, nausea, flushing, hypertension</td>
<td>• adrenal incidentaloma</td>
</tr>
<tr>
<td>• unexplainable variability of blood pressure</td>
<td>• predisposition for hereditary PPGL1</td>
</tr>
<tr>
<td>• paradoxal blood pressure response to anesthesia, surgery or drugs</td>
<td>• new onset diabetes mellitus in a young lean hypertensive patient</td>
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<tr>
<td>• orthostatic hypotension in a hypertensive patient</td>
<td>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.</td>
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