



# *Pheochromocytoma* of the adrenal gland selectively secreting dopamine — a case report

Guz chromochłonny nadnerczy wybiórczo wydzielający dopaminę — opis przypadku

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## Abstract

*Pheochromocytoma* of the adrenal gland secreting catecholamines is a relatively rare endocrinological cause of secondary arterial hypertension, usually developing in people aged between 40 and 50, more often in women than in men. Each accidentally diagnosed lesion in adrenal glands is an *incidentaloma*. Incidentalomas are most commonly benign tumours: adenomas, adipomas and angiomas; less often they are of a malignant or metastatic character. Establishing the character of the lesion and its hormonal activity is of crucial diagnostic significance. Diagnostics of *pheochromocytoma* covers marking the urine output of catecholamines and their metabolites, as well as marking serum amine concentration. Possible treatment of hormonally active lesions includes their surgical removal.

This thesis presents the case of a young female suffering from arterial hypertension for several years, including organ complications, who was diagnosed with *pheochromocytoma* selectively secreting dopamine. (*Endokryol Pol* 2012; 63 (5): 391–395)

**Key words:** *incidentaloma*, *pheochromocytoma*, *arterial hypertension*

## Streszczenie

Guz chromochłonny nadnerczy (*pheochromocytoma*) wydzielający aminy katecholowe jest stosunkowo rzadką endokrynologiczną przyczyną wtórnego nadciśnienia tętniczego, rozwijającą się zwykle między 40. a 50. rokiem życia, częściej u kobiet niż u mężczyzn. Każda przypadkowo rozpoznana zmiana w nadnerczach to *incidentaloma*. *Incydentaloma* to najczęściej nowotwory łagodne — gruczolaki, tłuszczaki i naczylniaki; znacznie mniej ma charakter złośliwy lub przerzutowy. Zasadnicze znaczenie diagnostyczne ma ustalenie charakteru zmiany i jej aktywności hormonalnej. Diagnostyka guza chromochłonnego obejmuje oznaczenie wydalania amin katecholowych i ich metabolitów z moczem oraz stężenia amin w surowicy. Leczeniem z wyboru zmian hormonalnie czynnych jest ich chirurgiczne usunięcie.

W niniejszej pracy przedstawiono przypadek młodej kobiety od wielu lat chorującej na nadciśnienie tętnicze z powikłaniami narządowymi, u której zdiagnozowano guz chromochłonny wybiórczo wydzielający dopaminę. (*Endokryol Pol* 2012; 63 (5): 391–395)

**Słowa kluczowe:** *incidentaloma*, guz chromochłonny, nadciśnienie tętnicze

## Introduction

Primary arterial hypertension is a common disease, and was for many years perceived to be a disease of civilisation. In 2005 there were about 1.5 million people suffering from arterial hypertension worldwide [1]. The beginning of the disease can be deceptive, quite often with a small number of symptoms, unlike secondary arterial hypertension, which more often includes clinical symptoms characteristic for diseases causing this hypertension [2].

*Pheochromocytoma*, observed in 0.1% of patients suffering from arterial hypertension, is one of the least common reasons for secondary arterial hypertension [3].

*Pheochromocytoma* develops from chromaffin cells secreting excessive amounts of catecholamines. These cells are most commonly located in adrenal glands, and less often in other focuses of chromaffin tissue [4]. Cells within the adrenal medulla secrete and collect noradrenaline, adrenaline and dopamine. These amines influence adrenergic receptors in organs, and then in the form of metabolites they are secreted in urine. All three catecholamines are produced from tyrosine over six stages [5]. The first stage of this synthesis includes tyrosine hydroxylation to dihydroxyphenylalanine (DOPA) — this reaction is performed by tyrosine hydroxylase. DOPA



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undergoes decarboxylation (reaction executed by DOPA-decarboxylase) and creates dopamine. Dopamine is transformed into noradrenaline (reaction conducted by tyrosine beta-hydroxylase), which undergoes methylation creating adrenaline (reaction conducted by N-methyltransferase). The crucial stage of catecholamine synthesis is the first reaction, as amines influence the activity of tyrosine hydroxylase based on negative feedback.

Two enzymes inactivate catecholamines: monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). MAO conducts a reaction related to transferring adrenaline into dihydroxymandelic acid, and COMT transfers it into vanillylmandelic acid (constituting 40% of the urine output of catecholamine waste products). Adrenaline and noradrenaline can be metabolised directly by COMT — as a result of this reaction we obtain metanephrine and normetanephrine. About 5% of catecholamines are secreted with urine in an unchanged form.

*Pheochromocytoma* usually develops in people who are between 40 and 50 years old, and in younger people it occurs rather in family forms [3]. Typical clinical features include paroxysmal or fixed arterial hypertension, headaches, excessive sweating, palpitations, skin paleness (in about 40% of patients), anxiety, muscle trembling and orthostatic hypotonia. Atypical symptoms may be related to systems other than the circulatory system, among others from the alimentary tract (stomach aches, constipation, vomiting, acute bowel distension) [6]. During pregnancy, *pheochromocytoma* may result in miscarriages or premature placental abruption [7, 8]. Sudden secretion of catecholamines and attack of clinical symptoms may be caused by common stimuli, such as physical effort, abdominal pressure, lavish meals, or stress [9].

Basic diagnostic tests related to tumours secreting catecholamines include marking the level of fractionated methoxy catecholamines (methoxy noradrenaline, methoxy adrenaline) or total methoxy catecholamines (both metabolites together) in daily urine output, marking the concentration of catecholamines and vanillylmandelic acid [10]. As far as blood serum is concerned, the diagnostics include marking free methoxy catecholamines and catecholamines. Results of these markings may be false due to the activity of various substances: from grocery items containing vanillin (e.g. nuts, bananas, black tea), drugs (beta-blockers, certain antibiotics, paracetamol, antihistamine drugs) and iodine shadowing agents used during radiology examinations [11]. As for diagnostics, we can also use function tests (clonidine inhibition test, glucagon test). The diagnostic value of particular markings is not identical [12–14].

## Case report

A 42-year old female was admitted to the Angiology, Arterial Hypertension and Diabetology Clinic, with a family history of circulatory system diseases (her mother died due to myocardial infarction, her father died because of cerebral stroke), suffering from arterial hypertension with RR increasing up to 200/120 mm Hg for the last 20 years. The woman mainly complained of the impossibility of obtaining optimal values of arterial hypertension despite a regular intake of several drugs (ramipril 1 × 10 mg, amilorid with hydrochlorotiaside [50/5] 1 × 1 tablet, amlodipine 1 × 10 mg, bisoprolol 1 × 10 mg, captopril 25 mg in case of increasing pressure values), and she complained about *erythema* on her face. In the past, the patient had suffered two late miscarriages, and she had given birth to one child via caesarean section (she tolerated the general anaesthesia quite well), and for the last two years she had had no menstruation.

Several months before hospitalisation, the woman underwent an ultrasound examination of her abdominal organs (within the scope of examinations after a knee injury), which revealed a nodule in the adrenal gland. The result of the above examination was confirmed using the CT method, and the nodule with smooth contours, and low, fatty densities and measuring 15 × 18 mm, was qualified as an incidentaloma. In the six months between this diagnosis and the time when the patient was referred to the Clinic, the symptoms had intensified.

Hospitalisation was designed to optimise the hypotensive treatment. Physical examination performed on the day of admittance revealed alimentary obesity, facial redness covering the nose and nasal parts of both cheeks, a scar after the caesarean section, contraction in the area of the left knee joint, and auscultatory quite numerous premature ventricular contractions making pairs. Arterial pressure equalled 180/90 mm Hg. Due to the patient's history and 'pressure resistance', diagnostics covered the secondary reason of arterial hypertension. Results of significant biochemical tests are shown in Table I.

Echocardiography revealed quite significant eccentric hypertrophy of the left ventricular muscle (IVSd 16 mm, ED 60 mm) with impairment related to the diastolic function, characteristic for relaxation disorders, and segmental contractility disorders covering the anterior and lower wall, with lowering of the global systolic function to 50%, most probably as the result of hypertensive organ injury. Ultrasound examination of carotid arteries revealed single arterosclerotic plaques posing no haemodynamic significance.

Table I. Results of main laboratory tests

Tabela I. Wyniki głównych badań laboratoryjnych

| Test  | Test result                          | Standard value   |
|---|--------------------------------------|------------------|
| Daily urinary output of 3-methoxytyramine           | Concentration 1,224 µg/d             | Up to 420 µg/d   |
| Daily urinary output of normetanephrine             | 506 µg/d                             | Up to 390 µg/d   |
| Daily urinary output of metanephrine                | 119 µg/d                             | 0–320 µg/d       |
| Daily urinary output of vanillylmandelic acid       | 3.6 mg/d                             | 0.6–6.0 mg/d     |
| Daily urinary output of 5-hydroxyindolo acetic acid | 2.4 mg/d                             | 2.0–9.0 mg/d     |
| Daily urinary output of homovanillic acid           | 3.7 mg/d                             | 0.6–9.0 mg/d     |
| Daily urinary output of Na <sup>+</sup>             | 248 mmol/d                           | Up to 220 mmol/d |
| Daily urinary output of K <sup>+</sup>              | 23 mmol/d                            | Up to 125 mmol/d |
| TSH concentration                                   | 0.53 µIU/mL                          | 0.4–4.0 µIU/mL   |
| Daily cortisol profile                              | 8.00: 12.1 µg/dL<br>20.00: 5.4 µg/dL | –                |
| RBC   | 5.6 mln/µL                           | 3.6–5.1 mln/µL   |
| HGB   | 16.8 g/dL                            | 11.2–15.2 g/dL   |
| TG  | 228 mg/dL                            | 50–150 mg/dL     |

RBC — red blood cells; HGB — hemoglobin; TG — triglycerides

During hospitalisation, the patient had complex hypotensive treatment (metoprolol 100 mg, chinapril 40 mg, telmisartan 80 mg, hydrochlorotiazyd 25 mg, doxazosin 4 mg), which on the one hand caused considerable lowering of arterial pressure, but on the other hand did not allow it to obtain optimal values. Bearing in mind the results of imaging examinations submitted by the patient (ultrasound of abdominal cavity organs and CT), next to the clinical image, result of echocardiography, and especially the co-existence of significant anomalies in secreting catechol amine metabolites, the diagnostics was expanded with MRI of the adrenal glands, which confirmed the existence of the nodule in the adrenal gland. The whole image supported the diagnosis stating *pheochromocytoma* selectively secreting dopamine. Due to the course of the arterial hypertension, especially its 'resistance' to administered complex pharmacotherapy, and most of all the existence of cardiologic complications in the form of contractility disorders and significant left ventricular muscle damage, the patient was qualified for scheduled surgical removal of the described lesion.

Three months later, the patient underwent laparotomy, during which the operating personnel removed a tumour of 2 cm diameter. The removed material was sent for histopathological test, which confirmed the diagnosis; the post-operative course was free of complications. The patient continues to be under the control of our centre: two weeks after the procedure, after de-

creasing the amount and doses of hypotensive drugs (metoprolol 1 × 50 mg, indapamid 1 × 1.5 mg, ramipril 1 × 10 mg), pressure values decreased to proper values, and the redness on the patient's skin vanished. After a further two months, regular menstruation returned. Although the patient still requires the maintenance of hypotensive treatment, values of arterial pressure remain at an optimal level.

## Discussion

This is the case of a young female with a family history burdened with circulatory system diseases, who was ineffectively treated due to arterial hypertension, and this treatment led to organ changes. Because of an accidental knee injury, the patient was hospitalised, and a routine ultrasound examination of the abdominal cavity revealed the presence of a nodule in the adrenal gland. The result of the examination was verified with the CT method and the diagnosis was related to *incidentaloma*. Nonetheless, 'hypertension resistance' forced the physician in charge of the patient to refer the woman to a higher reference clinic, where, based on medical history, tests and examinations submitted by the patient, she underwent diagnostics towards secondary arterial hypertension.

Adrenal gland nodules are usually diagnosed during imaging examinations of abdominal cavity organs (ultrasound or CT) performed due to various reasons, as the so-called screening examinations. Each lesion

within adrenal glands that is detected by accident is known as an *incidentaloma* [15]. Such lesions are more often diagnosed in women than in men, and the number of diagnoses increases with age [16, 17].

As far as histopathological examinations are concerned, the majority (about 90%) of incidentalomas are benign tumours: adenomas, adipomas and angiomas. They less often are of malignant (less than 10%) or metastatic (about 3%) character [18]. With CT and MRI results, it is possible to state the character of the tumour quite precisely. A possibly malignant character of the lesion may be indicated by: diameter exceeding 4 cm, irregular shape, non-homogenous structure, uneven outlines and thick, non-homogenous circumferential area, which is amplified after administering contrast, as well as dynamics of rinsing the contrasting agent (density > 10 Hounsfield Units [HU] and slow rinsing of the contrasting agent suggest a malignant character of a lesion) [19]. These features were not observed in examinations of our patient, which perhaps decreased the vigilance of the physician, who treated the patient for hypertension.

Biochemical diagnostics of *pheochromocytoma* cover marking catecholamines in serum and their derivatives in urine. Unfortunately, not all performed markings are of equal diagnostic value [20]. In the case of the described patient, a standard panel of biochemical tests in daily urine output was performed, where only concentration of 3-methoxytyramine was significantly exceeded, and concentration of normetanephrine was only slightly exceeded. These results show that, in the case of this patient, arterial hypertension was caused by an excessive amount of catecholamines. Such significant predominance of 3-methoxytyramine concentration over other metabolites of catecholamines indicated that the organism of the patient mainly produced excessive amounts of dopamine, and 3-methoxytyramine is the waste product of the above.

Another issue which was supposed to be taken into consideration was the source of dopamine. Assuming the most obvious solution, it was admitted that it was this change in the adrenal gland, which was hormonally active and secretes excessive amount of dopamine. Active hormonal changes, as well as quickly increasing lesions, constitute the recommendation for surgical procedure [21, 22]. Low-invasive surgery is a preferred treatment of functioning and non-functioning adrenal tumours [23].

The tumour was removed, a histopathological test confirmed the diagnosis, and the result of an operation supported the assumption: proper values of arterial pressure were obtained with the use of a small amount of hypotensive drugs; other ailments were also relieved, such as menstruation disorders. It can

be assumed that obstetric setbacks in the patient's history could be related to the basic disease; however, there is no direct proof.

In conclusion, it is worth noting that functional disorders of the circulatory system, especially ones resulting from environmental and social stress, quite often resemble symptoms of a chromaffin tumour. In reality, patients, and especially women referred to undergo diagnostics related to hypertension, most commonly complain of palpitations, anxiety, suddenly increasing values of arterial pressure and 'resistance' to administered drugs. Such patients constitute about 50% of patients referred to undergo diagnostics with initial diagnosis stating "suspicion of chromaffin tumour".

This extremely rare secondary form of arterial hypertension is not only related to subjective sensation of hypercatecholaminemia, but it is also usually connected to somatic organ changes reflecting a severe course of the hypertensive disease.

Patients with negative results of biochemical tests and imaging examinations are candidates to be diagnosed with initial arterial hypertension, whereas the co-existence of pathologies described by a radiology specialist as an incidentaloma should always provoke suspicion and should be the cause of expanding the diagnostics. Krawczyk et al. [24] have also suggested that each case of *pheochromocytoma* requires a DNA analysis because of a significant genetic diathesis for these tumours.

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