

## PECULIAR PROPERTIES OF THE ONSET OF PHEOCHROMOCYTOMAS OF ADRENAL GLANDS

**Oleksandr Kutovyi,**

*Doctor of Medical Sciences, Professor,*

**Galyna Rodynska,**

*Candidate of Medical Sciences, Assistant Professor,*

**Elyna Zhmurenko, Aspirant,**

*SI «Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine»,*

**Illia Deineko, Candidate of Medical Sciences,**

*PI «Illia Mechnikov Regional Clinical Hospital»*

**Annotation.** *Different variants of clinical and laboratory onsets of adrenal pheochromocytomas have been examined. Variability of clinical symptoms and hormonal activity of the adrenals have been shown, despite the monotypic morphological structure of the tumours.*

*In conclusion, the main clinical signs of adrenal pheochromocytoma were changes in hemodynamic parameters. Atypical course of the disease could be associated with a combined pathology or the spread of pheochromocytoma beyond the limits of the adrenal medulla. The most informative for pheochromocytoma of the adrenal glands is a high density of formation and a low rate of leaching of contrast during CT diagnosis. The level of common metanephrin urine is not a pathognomonic sign in patients with paroxysmal type of the disease.*

**Key words:** *pheochromocytoma, adrenalectomy, clinical and laboratory symptoms.*

**Relevance.** Pheochromocytoma is a tumour which consists of chromaffin cells of adrenal medulla, which are derivatives of the neural crest. The frequency of pheochromocytoma is 2 per 100,000 population [2, 5, 8]. In 90% of cases, pheochromocytoma occurs in the medulla of the adrenal glands, in 8% in paraaortic lumbar paraganglia, in less than 2% of cases it can occur in the abdominal and thoracic cavities and less than 0,1% in the neck [1, 3, 8].

The main clinical manifestations of the adrenal pheochromocytoma are, as a rule, arterial hypertension and tachycardia. According to laboratory data, the level of catecholamines in hypertensive crisis can increase by 20 times [7, 9, 10]. In the interictal period, a more than 2-fold increase in the blood content of the latter is considered reliable. The absence of laboratory changes and clinical manifestations in pheochromocytomas in rare cases is rarely observed [4, 6]. Therefore, the issue of diagnosis and, accordingly, the determination of the correct medical tactics is currently a certain problem [8].

**Objective:** to evaluate the features of clinical and laboratory manifestations of adrenal pheochromocytoma at different **stages of their treatment.**

**Materials and methods.** We analyzed the results of management of 13 patients with adrenal pheochromocytomas in the conditions of the Department of Endocrine Surgery of the I.I. Mechnikov Regional Clinical Hospital. Among them there were 8 men (61,5%), women - 5 (38,5%). The average age of patients with pheochromocytoma was  $42,4 \pm 1,7$

years.

In addition to evaluating complaints, anamnesis, and clinical data, a biochemical blood test was performed to determine the level of potassium, sodium, chlorine, lipid, glycemia, creatinine, and urea for all patients. Furthermore, hormonal studies have been made: determining the level of aldosterone, dehydroepiandrosterone - sulfate, renin and adrenocorticotrophic hormone, aldosterone - renin ratio 17 oksiprogesterone, testosterone, estradiol blood, excretion of cortisol, metanephrine daily urine, saliva level of cortisol. The presence of structural changes in the adrenal glands and abdominal organs and retroperitoneal space was diagnosed using ultrasound (US) and computed tomography (CT) with intravenous contrast. The density of the formations was determined in the native, arterial and venous phases according to the Hounsfield scale.

Patients with pheochromocytoma were divided into 3 groups: the first (n = 7 (53,8%)) - patients with paroxysmal type of arterial hypertension (AH), the second (n = 4 (30,7%)) - patients with a permanent form of AH, the third (n = 2 (15,4%)) - patients with an atypical clinical picture not typical for this type of tumor. An atypical clinical picture implied in 1 case excessive hair loss, in the second - complaints of palpitations, dizziness, general weakness, periodic increase in blood pressure to 160/90 mm Hg, the presence of a central type of obesity.

Statistical analysis of the research results was performed using the Statistica 12,5 program. Authenticity of the results was evaluated using methods of nonparametric statistics, in particular by using Mann-Whitney test. The critical level of significance was taken as  $p < 0,05$ .

**The results of the study.** Common signs of the presence of adrenal pheochromocytes in patients of all groups were changes in the hemodynamics of cardiac activity and the hormonal activity of the adrenal glands.

In the I group, at the time of admission, the CAD indicators were  $141 \pm 3,8$  mm Hg, the pulse was  $88 \pm 7$  beats per minute; however, when the catecholamine crisis occurred, these figures ranged from 150/80 to 200/110 mm Hg, while heart rate also increased from 96 to 120 beats per minute. Hormonal studies were conducted in all patients in the preoperative period, according to which the levels of ARS, 3-methoxytyramine blood, cortisol, and urine total metanephrine levels did not deviate from the norm.

In group II, at the time of admission, the indicators of CAD were  $185 \pm 5,1$  mm Hg, the pulse was  $76 \pm 5,2$  beats per minute while receiving combined antihypertensive therapy. According to the results of hormonal studies, the levels of ARS, blood 3 - methoxytyramine, urine cortisol were unremarkable. Urine metanephrin indices ( $327,6 \pm 1,4$  (reference range (r.r. 25-312 mkg/24 hours)) slightly exceeded permissible values.

According to the obtained results, there were no significant differences in indicators of urine cortisol, DHEA-c, APC I and II groups of comparison ( $p > 0,05$ ). The value of urine total metanephrine was higher in the second group, but its level slightly exceeded the upper limit of normal ( $p < 0,05$ ).

We can assume that the results obtained may be associated with daily intake of combination antihypertensive therapy for a permanent form of hypertension, which could

not be canceled.

In the third group, in the first male patient, the level of free testosterone and dihydrotestosterone exceeded the allowable and was respectively 55,3 (15 - 50 pg/ml) and 1927,8 pg/ml ( $\uparrow\uparrow$ ) in a two-time study, with indicators of cortisol, urine total metanephrine and APC, DHE- with blood remained normal. In the second patient, on the contrary, high levels of urine cortisol and blood aldosterone (441,7 mkg/24 hour and 367,1 pg/ml respectively) were detected against the background of an increased DHEA-c value (432 (r.r. 98-340 mkg/dl)) and total testosterone 2,49 (r.r. 0,29 - 1,67 pg/ml). The value of common metanephrine urine, blood norepinephrine were borderline with the norm.

With CT and ultrasound of the abdominal cavity and retroperitoneal space in patients with pheochromocytoma, the following results were obtained (table 1).

Table 1

**The results of instrumental studies of adrenal pheochromocytes**

Group Name	CT			US		
	Tumout size, mm	Density, HU	Erosion speed, %	Size, mm	Cyst presence, %	Presence of calcinates, %
First	44,1 ± 0,8	+22 ± 1,3	32 ± 1,6	52 ± 3,2	46	6
Second	51,3 ± 1,1	+18 ± 2,0	28 ± 1,9	38,5 ± 1,4	52	10
Third	9,35 ± 0,7	+46 ± 2,8	36 ± 2,1	Wasn't defined		

According to the presented data of CT, in all cases of adrenal gland formation were of high density with a low rate of leaching of contrast in sizes from 6 to 100 mm. According to the results of ultrasound, rather contradictory conclusions were obtained, but in most cases pathognomonic for pheochromocytes were heterogeneity of the structure with a predominance of cystic components, the presence of calcifications in the capsule and the parenchyma of the tumors. Neoplasms less than 10 mm were not visualized.

All patients underwent surgical treatment in the volume of subtotal 4 (30,8%) and total 9 (69,2%) adrenalectomy.

According to the results of histopathological studies, 100% of patients of the first and second groups had a final conclusion of pheochromocytoma, and 3 (27,3%) of them had a suspicion of a malignant nature of the tumor, which was excluded only after an immunohistochemical study. In the third group, the following conclusions were obtained: a pheochromocytoma with proliferation of the reticular zone and a pheochromocytoma with infiltration into the beam zone with pronounced hyperplasia of the reticular zone. This histological structure explains the occurrence of atypical clinical manifestations and hyperproduction of the corresponding hormones by involvement of the adrenal cortex in the process.

In most cases, the normalization of baseline blood pressure was observed for 2-3 days after surgery. On the first day after the operation, the phenomenon of uncontrolled hypotension was observed in 1 patient of the II group, clinical manifestations of adrenal insufficiency for 2-3 days in 1 patient of the III and 1 - I groups. Significant changes in the electrolyte composition of blood and cortisol levels were not detected.

After 3 months, 1 patient of the first group was operated on for carotid chemodexoma. Also, another patient resumed episodes of tachycardia, which were associated with an increase in urinary metanephrine level by 20 units, although according to the CTB OBP data, no organic pathology was detected.

Patient of Group III, after 3 months after surgical treatment, continued to complain of palpitations, periodic increase in blood pressure to 160/90 mm Hg. Blood aldosterone was monitored - 403 (r.r. 70-300 pg/ml) and urine cortisol – 327,92 (r.r. 50-190 mkg/24 hours). Symptomatic treatment was prescribed. After 6 months, as a result of additional examination, the patient showed an increase in prolactin 29,92 (r.r. 3,74-23,3 ng/ml), total testosterone – 2,75 (0,29 – 1,57 pg/ml), normetanephrine - 262 (r.r. 21,6 – 107,6 ng/ml), aldosterone 730,6 (70-300 pg/ml), thyroid stimulating hormone - less than 0,01 (0,27-4,2 mIU/ml), while the content of ACTH, DHEA-c, metanephrine, 3-methoxymyramine did not deviate from the norm. In this regard, the patient was further examined. According to CT scan, polycystic ovarian cancer was detected. An ultrasound of the thyroid gland diagnosed with diffuse changes in the gland tissue by the type of thyroiditis and the macrofollicles of the left lobe up to 3 mm. According to MRI of the pituitary, organic pathology was not found. The patient was administered thyreostatic therapy (tiamazol 30 mg / day) for 6 weeks. After 4 weeks from the start of treatment, the patient has decreased testosterone levels (2,05 (r.r. 0,38-1,97 pg/ml)), prolactin (7,9 (r.r. 2,8-29,2 ng/ml)), normalized thyroid stimulating hormone (2,5 (0,27-4,2 mIU/ml)). Thus, the patient was diagnosed with Graves' disease and polycystic ovary.

In the second patient of Group III, after surgical treatment, the level of total and active testosterone, prolactin, cortisol and blood estradiol returned to normal after 6 months. According to the results of CT, ultrasound of the abdominal organs and MRI of the pituitary gland were not observed.

**Conclusions.** 1. In the overwhelming majority of cases (84.6%), the main clinical signs of adrenal pheochromocytoma were changes in hemodynamic parameters. Atypical course of the disease could be associated with a combined pathology or the spread of pheochromocytoma beyond the limits of the adrenal medulla.

2. For verification of the diagnosis, the most informative for pheochromocytoma of the adrenal glands is a high density of formation (more than 25 HU) and a low rate of leaching of contrast during CT diagnosis.

3. The level of common metanephrin urine is not a pathognomonic sign in patients with paroxysmal type of the disease.

Scientific novelty. Expand the understanding of the clinical and laboratory manifestations of adrenal pheochromocytoma.

Practical value. To improve the results of the diagnosis of adrenal pheochromocytoma.

Conflict of interests was absent.

### References:

1. Arora, S., Rogers, C. G., & Menon, M. (2018). Re: Each procedure matters:

threshold for surgeon volume to minimize complications and decrease cost associated with adrenalectomy. *Surgery*, 163(6), 1325-1329. DOI: <https://doi.org/10.1016/j.surg.2017.12.024>

2. Castelino, T., & Mitmaker, E. (2017). Pheochromocytoma Crisis. *Clinical Management of Adrenal Tumors*, 103.

3. Emery, R. T., Brown, H. L., Emery, K. Q., & Baker, J. R. (2017). Pheochromocytoma: A Rare Presentation. *The Journal of the Arkansas Medical Society*, 113(8), 188-190.

4. Fishbein, L., Leshchiner, I., Walter, V., Danilova, L., Robertson, A. G., Johnson, A. R., ... & Ling, S. (2017). Comprehensive molecular characterization of pheochromocytoma and paraganglioma. *Cancer cell*, 31(2), 181-193.

5. Fishbein, L. (2016). Pheochromocytoma and paraganglioma: genetics, diagnosis, and treatment. *Hematology/Oncology Clinics*, 30(1), 135-150.

6. Grona, V. N., Litovka, V. K., Zhurilo, I. P., & Latyishov, K. V. (2010). Opuholi i opuholepodobnyie obrazovaniya u detey. VN Grona, VK Litovka, IP Zhurilo, KV Latyishov—Donetsk: Nord Pres.

7. Kaulanjan, K., Blanchet, P., & Brureau, L. (2018). A Rare Location and Presentation of Pheochromocytoma. *Journal of endourology case reports*, 4(1), 111-113. doi: 10.1089/cren.2018.0025

8. Litovka, V. K., Veselyiy, S. V., Cherkun, A. V., & Latyishov, K. V. (2015). Sluchay atipichnoy feohromotsitomyi nadpochechnika u rebenka. *Hirurgiya dityachogo vku*, (3-4), 148-151.

9. Shida, Y., Igawa, T., Abe, K., Hakariya, T., Takehara, K., Onita, T., & Sakai, H. (2015). Composite pheochromocytoma of the adrenal gland: a case series. *BMC research notes*, 8(1), 257.

10. Wang, Z., Cai, Q., Li, G., Jiang, N., & Niu, Y. (2017). Giant Pheochromocytoma With Leukemoid Reaction: A Case Report. *Urology*, 99, e17-e19. DOI: <https://doi.org/10.1016/j.urology.2016.08.021>