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ГИПЕРРЕНИНОВАЯ АРТЕРИАЛЬНАЯ ГИПЕРТЕНЗИЯ — ТРУДНОСТИ ДИФФЕРЕНЦИАЛЬНОГО ДИАГНОЗА. КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

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Hyperreninic Arterial Hypertension — Difficulties in Differential Diagnosis. Clinical Observation

Резюме

Вторичные формы артериальной гипертензии (ВтАГ) характеризуются наличием конкретной потенциально устранимой причины повышения артериального давления (АД), более высокими его значениями, нередко рефрактерностью к гипотензивной терапии и большей распространенностью среди лиц молодого возраста. Диагностика ВтАГ предполагает поиск причин по принципу «от простого к сложному» на амбулаторном и стационарном этапах обследования. В статье описан клинический случай 44-летней женщины без факторов риска АГ, госпитализированной по поводу гипертонического криза на фоне неконтролируемой АГ. Была проведена многоэтапная лабораторная и инструментальная диагностика для исключения почечной, эндокринной, сосудистой патологии. Высокие значения ренина при нормальных показателях других гормонов надпочечников, гипофиза, щитовидной и паращитовидной желез послужили основанием для поиска ренальной и экстраренальной ренинпродуцирующей опухоли, результатом которого стала постановка диагноза гипергениновой эссенциальной АГ. В статье приводится классификация ВтАГ с перечнем рекомендованных диагностических мероприятий, принципы терапии гипергениновой АГ, имеющие практическое значение для терапевта, врача общей практики, эндокринолога, нефролога.

Ключевые слова: *вторичная артериальная гипертензия, эндокринная АГ, гипергениновая АГ, ренинома, селективный забор крови из почечных вен, диагностика, лечение*

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Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Secondary arterial hypertension (SAH) is characterised by the presence of a specific potentially treatable cause of hypertension, higher blood pressure (BP) values, often refractory to hypotensive therapy, and higher prevalence in young adults. Diagnosis of VtAH involves searching for causes according to the principle 'from simple to complex' at the outpatient and inpatient stages of examination. The article describes a clinical case of a 44-year-old woman without risk factors for AH, hospitalised for hypertensive crisis on the background of uncontrolled AH. Multistage laboratory and instrumental diagnostics was performed to exclude renal, endocrine, vascular pathology. High values of renin with normal values of other hormones of adrenal, pituitary, thyroid and parathyroid glands were the basis for searching for renal and extrarenal renin-producing tumours, which resulted in the diagnosis of hyperrenin essential AH. The article presents the classification of VtAH with a list of recommended diagnostic measures, principles of therapy of hyperreninic AH, which are of practical importance for the therapist, general practitioner, endocrinologist, nephrologist.

Key words: *secondary arterial hypertension, endocrine AH, hyperreninemic AH, reninoma, selective renal vein blood sampling, diagnosis, treatment*

Conflict of interests

The authors declare no conflict of interests

Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «Hyperreninic Arterial Hypertension — Difficulties in Differential Diagnosis. Clinical Observation» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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EH — essential hypertension, SH — secondary hypertension, BP — blood pressure, CNS — central nervous system, ECG — electrocardiogram, HR — heart rate, EF — ejection fraction, CAD — coronary artery disease, BMI — body mass index, RR — respiratory rate, HRT — hormone replacement therapy, 5-HIAA — 5-hydroxy-indole-acetic acid, RAAS — renin-angiotensin-aldosterone system, IHC — immunohistochemistry, ANF — antinuclear factor, ANCA — anti-neutrophil cytoplasmic antibodies, anti-dsDNA — anti-double-stranded DNA antibodies, anti-Scl-70 — anti-scleroderma 70 antibodies, ARBs — angiotensin II receptor blockers, MRAs — mineralocorticoid receptor antagonists, US — ultrasound, MSCT — multispiral computed tomography, MRI — magnetic resonance imaging, PET-CT — positron emission tomography — computed tomography, AC — abdominal cavity, ELISA — enzyme-linked immunosorbent assay, CVS — cardiovascular system, DP — drug product, ACEIs — angiotensin-converting enzyme inhibitors, HREH — high-renin essential hypertension

Introduction

Secondary (symptomatic) hypertension (SH) is a type of hypertension, which is defined as being caused by an identifiable root cause [1].

Secondary hypertension is diagnosed in 5–25 % cases of all hypertensions [1]. Primary or essential hypertension (EH) does not require the additional search for causes, unlike the secondary one — when the latter is suspected, other conditions that can trigger stable BP elevation should be excluded. Such conditions include renoparenchymatous and renovascular diseases, endocrine diseases affecting any endocrine gland and/or dysregulating its function, CNS diseases (both focal and diffuse), drug-induced hypertension, vascular anomalies. An important aspect of hypertension etiology verification is a possibility of its complete or partial regression in specific clinical situations, including with curative surgeries.

One of the most typical SH signs is a young age of the patient (with the exception of renovascular hypertension in elderly as a result of atherosclerotic renal artery stenosis). The inefficacy of optimal drug therapy, true resistance in middle-aged and elderly patients make the clinician expand the range of diagnostic investigations to search for additional causes of stably elevated BP. Ignoring clinical SH markers threatens to

lead to a high risk of cardiovascular complications at any age.

The prevalence of SH causes varies in specific age groups. Thus, among young persons the most common pathologies causing malignant hypertension include thyroid disorders, fibromuscular dysplasia, renal parenchyma and urinary tract disorders (interstitial nephrities, glomerulopathies [including diabetic one], renal amyloidosis, urolithiasis, infrarenal chronic obstruction) [2]. Adrenal lesions are more common among persons aged 40 to 64 years [1]. Unfortunately, the obstructive sleep apnea syndrome is underestimated in this age group as a SH cause [3].Major drug products triggering BP elevation in the young cohort and among middle-aged persons definitely include non-steroidal anti-inflammatory drugs with their nephrotoxic effects. The following drugs are used less commonly in the population, but also cause hypertension: corticosteroids; oral contraceptives; nasal adrenomimetics; psychic stimulators (amphetamine, cocaine, MDMA); immunosuppressive drugs with vasospastic effects (cyclosporine, tacrolimus); licorice (stimulating mineralocorticoid receptors).

Hereby we present a clinical case of hypertension in a young female that required a detailed differential-diagnostic search for SH.

Clinical Case Study

The female patient M., 44 years old, a lawyer and a teacher, felt discomfort in the left heart of the chest (burning sensation) not associated with physical exertion, along with BP elevation to 160/106 mm Hg, tachycardia (112 bpm) on September 24, 2023. 3 days before the hospitalization, the patient for the first time developed significant general weakness, episodes of elevated BP accompanied by flushing, feverish sensation, anorexia, nausea and diarrhea. Due to inefficient hypotensive treatment and the general condition worsening, the patient was hospitalized via the ambulance to the intensive care unit of the L.A. Vorohobov CCH No. 67 with the diagnosis "Uncontrollable hypertension. Target BP values not achieved". ECG: sinus rhythm, HR 79/min, right axis deviation; negative troponin test (troponin I 0.024 ng/mL). EchoCG: cardiac contractility was preserved (EF 62 %), heart chambers were not dilated; no significant valvular lesions were detected. After BP stabilization, the patient was transferred to the Department of Cardiology with the following diagnosis: "CAD: first-detected angina. Grade 3 essential hypertension. Hypertensive crisis dated September 24, 2023". The mortality risk was assessed as low (GRACE 38 points), coronary angiography was not conducted, but repeated echocardiography, ambulatory BP monitoring, Holter ECG monitoring were scheduled. During the treatment with enalapril (2.5 mg twice daily), target BP values were achieved, however significant weakness persisted. Blood tests demonstrated hypokalemia (2.48 mmol/L) twice, which required the administration of a glucose-potassium-insulin mixture (400 mL of 5 % glucose solution + 40 mL of 4 % potassium chloride solution + 8 insulin units, three times) and a mineralocorticoid receptor antagonist (spironolactone 25 mg; due to persistent hypokalemia, the dose was increased to 50 mg daily).

Accounting for the young age and suspected SH, the patient was counseled by the employees of the Department of Acad. A.I. Nesterov Faculty Therapy Department of N.I. Pirogov RSRMU to clarify its causes.

The history collection revealed that the first BP elevation developed during the first pregnancy initiated by the in vitro fertilization at the age of 34 years (the preparation period was not complicated). The pregnancy was accompanied by eclampsia and HELLP-syndrome, while hereditary thrombophilias and antiphospholipid syndrome were excluded. After the delivery (via cesarean section at the term of 31 weeks), persistent hypertension was preserved; the patient took hypotensive therapy (perindopril 5 mg + indapamide 1.25 mg) and isoptin 250 mg (half a tablet). The second pregnancy emerged 4 years later spontaneously and was also accompanied by eclampsia. Two healthy children were born as a result. After the second delivery, BP elevated to 145/98 mm Hg, and the patient tolerated that poorly. The attending physician administered her amlodipine 5 mg + losartan 100 mg daily. Due to early natural menopause at the age of 41, the patient had been taking Femostone (dydrogesterone 10 mg + estradiol 1 mg) for 3 years. 3 months before the hospitalization, the patient suffered from a severe distress (simultaneous death of several relatives), and hypertension became critical with maximum numbers of 160/110 mm Hg, accompanied by nausea, vomiting, and diarrhea during the high BP levels. No electrolyte disorders were reported before the hospitalization.

Physical examination in the cardiology department: satisfactory condition, clear consciousness.Skin and mucous membranes are of normal color, with preserved turgor; no cyanosis or edema were detected. BMI 19.5 kg/m^2. Peripheral lymph nodes were not palpated. The clear pulmonary sound was detected during pulmonary percussion; vesicular breathing with no rales was auscultated in lungs. RR 18/min, O2 saturation 96 %. Systolic blood pressure in both arms 118 and 120 mm Hg; diastolic BP 72 and 75 mm Hg; HR 64/min. During

cardiac percussion, heart borders were not dilated. Cardiac auscultation: weak S1 at the apex, with a soft systolic murmur irradiating to the left axillary region; split S2 over the aorta. The abdomen was not distended, soft and non-tender on palpation; the liver and spleen were not enlarged based on percussion results. Urination: 1.5–2 L/day. Endocrine system: thyroid gland consistency was elastic, it was not enlarged (WHO Grade 0) and non-tender on palpation. Parathyroid glands, adrenal glands, the pancreas were not palpated. Ocular symptoms were negative.

Standard laboratory tests detected the decrease in levels of total protein to 54.1 g/L (N 66.0–83.0); urea to 1.62 mmol/L (N 2.80–7.20); creatinine to 44.4 μmol/L (N 49.0–90.0). The sodium level was 139 mmol/L (N 136–145 mmol/L), the fasting blood glucose level was 4.2 mmol/L (N 3.5–5.5 mmol/L). Persistent hypokalemia (2.8 mmol/L) was worth noting. Lipid profile: total cholesterol 4.3; LDL 1.59; HDL 2.1; triglycerides 1.8 mmol/L. Urinalysis was normal, lacking albuminuria.

The differential diagnosis was arranged between EH and SH caused by thyroid, renoparenchymatous, renovascular, adrenal disorders, and drug-induced hypertension, including estrogen-induced hypertension (Table 2).

Accounting for laboratory capabilities of the department, levels of thyroid hormones, ACTH, renin, cortisol, aldosterone, parathyroid hormone were tested; the contrast-enhanced MRI of the abdominal cavity was arranged as well. TSH, free T3 and T4 levels were normal; adrenal hormones: serum and salivary cortisol, serum aldosterone (after discontinuing hypotensive therapy with angiotensin-2 receptor blockers and mineralocorticoid receptor antagonists a day before) levels were also normal, while ACTH levels were mildly decreased. The low-dose dexamethasone suppression test was negative. Hypercortisolism and hyperaldosteronism were excluded. Renin levels were 10-fold higher than reference values (Table 1).

Holter ECG monitoring demonstrated supraventricular and ventricular extrasystoles; the heart rate variability was normal, with average daily HR 70 bpm. Ambulatory BP monitoring (September 26, 2023) revealed that the daytime BP profile corresponded to borderline diastolic hypertension with maximum BP values of 156/104 mm Hg; nocturnal BP profile was normotensive with maximum BP values of 127/82 mm Hg; BP variability was within the reference range, while the mean daily pulse BP was normal. The Doppler renal ultrasound demonstrated a left-sided accessory artery overlying the main one, connected to the upper renal

Table 1. *Hormonal status of the patient 'pituitary-adrenal' over time.*

	26.09.23	30.09	04.10	17.10	26.10	02.11.23	Reference values
ACTH	6,9		8,6	9,6		12,9	7,2-63,3 pg/ml
Plasma Renin	>300	252,3	400	445		150,6	2,8-39,9 μIU/mL
Aldosterone		230		lying 180 sitting 457			69,8-1085,8 pmol/l
Potassium	2,8	3,4	4,6	3,92		4,12	3,5-5,1 mmol/l
Sodium	139	142	145	143		142	136-145 mmol/l
Serum Cortisol	394,8		374	428		402	177 — 629 nmol/l
Free plasma methanephrine			0,32	0,2			0-0,49 nmol/l
Plasma Chromagranin A			55,55	45			0 — 100 mcg/ml
Serum Serotonin					0,24		0,22-2,05 mmol/l
Vanillylmindal acid					3,3		1,4-6,5 VMA mg/day
Homovanilic acid					3,1		1,4-8,8 HVA mg/day
5-HIAA (5-hydroxyindolacetic acid)					2,48		2-7 5-HIAA mg/day

segment; the parenchymal echogenicity was normal, with the normal corticomedullary differentiation; contours of both kidneys were clear and smooth. The contrast-enhanced MRI of the abdominal cavity was arranged on September 27, 2023: no pathologies were detected. The patient reached BP values of 120/75 mm Hg while taking valsartan 40 mg twice daily and amlodipine 5 mg once daily; she was discharged with the diagnosis "Grade 2 secondary hypertension (renin-induced). Premature menopause, permanent HRT (Femostone 10 mg + 1 mg)", and the recommendation to continue treatment and to consult the endocrinologist.

The next step presumed the exclusion of pheochromocytoma and paraganglioma (extraadrenal pheochromocytoma). Outpatient tests were arranged for free plasma metanephrins, plasma chromogranin A — their levels were normal. The search for an endocrine hypertension associated with renin secretion (reninoma; Robertson-Kihara syndrome) or an ectopic renin-secreting tumor (in lungs, pancreas, Fallopian tubes) was continued. The (static) scintigraphy of adrenal glands and kidneys, brain MRI (in the pituitary gland area) was recommended. If MRI, contrast-enhanced CT of the abdominal cavity, kidneys and adrenal glands, chest to exclude a small-sized reninoma had yielded doubtful/negative results, it would have been recommended to arrange the selective blood collection from renal veins to determine the renin level ratio bilaterally and in the inferior vena cava in a specialized department.

On October 20, 2023, the patient was counseled by the nephrologist in FSBI V.I. Kulakov SMRC OGP. BP 120/70 mm Hg, serum renin was elevated (400 mmol/L), metanephrines/normetanephrines, TSH were normal; C3, C4 complement levels were normal; creatinine clearance 53 mL/min, microalbuminuria 5 mg/L, urine density not decreased, potassium 3.92 mmol/L. Nephrologist counseling: "The origin of nausea and vomiting episodes with the normal BP values remains unclear; migrenologist counseling recommended". On October 24, 2024 the patient was counseled in the Scientific Center for Endocrinology, where the steroid serum profile was determined (multisteroid test using the tandem mass-spectrometry liquid chromatography (HPLC-MS/MS) method) — no pathological alterations; potassium 3.92 mmol/L (normal); renin level significantly increased (428 mmol/L). The following diagnosis was established: "Premature ovarian exhaustion, drug-induced subcompensation". Endocrine hypertension? Reninoma? Carcinoid syndrome?" The following tests were arranged for the diagnosis of neuroblastoma, pheochromocytoma, carcinoids and other neuroendocrine tumors: MSCT of kidneys; blood tests for Chromogranin A, serotonin; 24-hour urine for 5-HIAA, i.e. epinephrine, norepinephrine, dopamine, serotonin levels. The patient was counseled by the gynecologist: burning sensation in the back of the head, shoulder, chest, chills, nausea were considered menopausal signs; the dose of Femostone 2 was increase (dydrogesterone 10 mg + estradiol 2 mg). Contrast-enhanced MSCT of the abdominal cavity, kidneys, and adrenal glands was arranged on September 28, 2023 — no pathologies were detected.

On October 26, 2023, the following tests were obtained: serum serotonin 0.24 μmol/L (N 0.22–2.05 μmol/L); catecholamine metabolites in 24-hour urine — vanillylmandelic acid (final catecholamine metabolite) 3.3 mg/day (N 1.4–6.5 VMA mg/day); homovanillic acid (final dopamine metabolite) 3.1 mg/day (N 1.4–8.8 HVA mg/day); 5-HIAA (5-hydroxy-indole-acetic acid, major serotonin metabolite) 2.48 (N 2–7 5-HIAA mg/day); serum Chromogranin A (marker of the neuroendocrine tissue and other neuroendocrine tumors) 1.47 μg/mL (N 0–100 μg/mL). Additionally, levels of folic acid (7 nmol/L; N 7–39.7 nmol/L) and cyanocobalamine (478 pg/mL; N 197–771 pg/mL) were determined. Combined hypotensive treatment (losartan 50 mg twice daily; spironolactone 25 mg/day; bisoprolol 2.5 mg/day) was recommended and demonstrated positive effects; potassium was to be monitored every 3 months. Follow-up (November 2, 2023): plasma renin levels were still elevated (150 mmol/L), most likely due to MRA therapy and the addition of beta-blockers. Renal MR-angiography was arranged on November 6, 2024 — no pathological alterations. Thus, the renin-producing tumor was excluded, and the final diagnosis was formulated as follows: "Essential hypertension, hyper-renin form, Stage 1, target BP levels achieved, CVS risk 4 % (low risk as per the SCORE scale)".

The follow-up demonstrated a favorable disease course within 2 years, the patient's well-being remained normal; the Scientific Center for Endocrinology specialist recommended permanent administration of the selected hypotensive treatment with BP and pulse monitoring, annual laboratory-instrumental examinations, and follow-up by the cardiologist and endocrinologist.

Discussion

The diagnosis of symptomatic hypertensions in real clinical practice is arranged based on the "simple to complex" principle, with the order of examinations determined by the proposed SH type. Table 2 lists *screening methods* for the diagnosis and *advanced examinations*, depending on the SH type.

Table 2. *Screening methods and methods of in-depth diagnosis of SAH [1]*

SAH Variants	The main reasons	Diagnostic methods
Renault-parenchymal	– Chronic Pyelonephritis – Acute/chronic glomerulonephritis – Polycystic kidney disease – Obstructive nephropathy – Tubulo-interstitial nephritis, including medicinal – Systemic connective tissue diseases with kidney damage – Kidney dysplasia – Congenital anomalies and scarring	– Blood test for creatinine and urea, uric acid, – general urinalysis with leukocyte formula, urine analysis according to Nechiporenko, Zimnitsky, – daily albuminuria, daily proteinuria, creatinine from daily urine, daily uricosuria, GFR (calculated formula CKD-EPI, creatinine clearance according to the Rehberg-Tareev test), – ANF, ANCA, ATdsDNA, AT to Scl-70, serum IgA, immunoelectrophoresis of serum and urine proteins – Duplex examination (ultrasound of the renal arteries) (assessment of blood flow in the renal arteries), CT native, static and/or dynamic renal scintigraphy – Nephrobiopsy with IHC* including congo-mouth staining – Consultation with a nephrologist
Renovascular	– Fibromuscular dysplasia – Atherosclerosis of the renal arteries – Large cysts located at the gates of the kidney – Kidney tumor – Vasculitis of large vessels	– Duplex examination (ultrasound of the renal arteries) — peak blood flow rate> 2 m/sec (normally up to 1 m/sec) – MR angiography (3D with gadolinium) – CT aortography, angiography of the renal arteries – CT OBP with contrast
Pathology of the thyroid gland	Hypothyroidism Hyperthyroidism	Stage I — blood TSH level (ELISA) Stage II — free T4 and total T3 – ultrasound, thyroid scintigraphy
Pheochromocytoma	A tumor originating from the chromaffin cells of the adrenal glands that secrete one or more catecholamines: adrenaline, norepinephrine, dopamine	– Fractionated methanephrines (free and conjugated) in blood plasma, in daily urine (with the elimination of drugs that affect these parameters [see section "Drugs capable of causing hypertension" and [1*]) (ELISA) [4], – Direct serum renin, plasma renin activity – Serum Aldosterone and potassium – ACTH – Serum serotonin – Vanillylmindic acid, homovanilic acid and 5-OIC in daily urine – Chromogranin A of serum – Ultrasound of the kidneys and adrenal glands with Doppler, -MSCT, MRI of the adrenal glands, thoracic and abdominal cavities with contrast – PET-CT with fluorodeoxyglucose or Gallium isotope 68
Hypercorticism	Endogenous Exogenous	– Free cortisol: in blood serum, in saliva sample in the evening or in daily urine (double determination) – Suppressive test with 1 mg dexamethasone – ACTH, prolactin, serum somatostatin – Ultrasound of the kidneys and adrenal glands with Doppler, -MSCT, MRI of the adrenal glands, thoracic and abdominal cavities with contrast – PET-CT with fluorodeoxyglucose or Gallium isotope 68
Primary hyperaldosteronism	Conn's syndrome	– Potassium in blood serum – Serum Aldosterone – Renin activity in blood plasma — against the background of withdrawal of ace inhibitors, ARA, AMCR – Ultrasound of the kidneys and adrenal glands with Doppler, -MSCT, MRI of the adrenal glands, thoracic and abdominal cavities with contrast – PET-CT with fluorodeoxyglucose or Gallium isotope 68

Table 2. *(The end)*

SAH Variants	The main reasons	Diagnostic methods
Reninoma	Renin-producing kidney tumor or extrarenal localization, Multiple endocrine neoplasia	– Direct serum renin, plasma renin activity – Serum Aldosterone and potassium – ACTH – Ultrasound of the kidneys and adrenal glands with Doppler, – MSCT, MRI of the adrenal glands, thoracic and abdominal cavities – Selective blood sampling from the renal veins with lateralization and the inferior vena cava – PET-CT with fluorodeoxyglucose or Gallium isotope 68
Pathology of the parathyroid glands	Hyperparathyroidism	– Total and ionized serum calcium, parathyroid hormone – Ultrasound, scintigraphy of the thyroid and parathyroid glands, – PET-CT scan
Obstructive sleep apnea syndrome	ntermittent night snoring, sleep apnea, nocturia, sleep disorders, daytime drowsiness, morning headache, obesity	Epworth Sleepiness Scale questionnaire; pulse oximetry during sleep
Pathology of the central nervous system (neurogenic arterial hypertension)	Tumors, injuries, encephalitis, polio, focal ischemic lesions, large malformations of cerebral vessels	– CT scan of the skull – MRI of the brain, including in the cerebral mode
Medicines, food, and beverages that can cause hypertension	Hormonal contraceptives; corticosteroids; sympathomimetics; mineralocorticoids; cocaine; foods containing tyramine or monoamine oxidase inhibitors; nonsteroidal anti-inflammatory drugs; cyclosporine; erythropoietin; acetaminophen, methyldopa, tricyclic antidepressants, monoamine oxidase inhibitors, sympathomimetics, catecholamine reuptake inhibitors, mesalamine/sulfasalazine, phenoxybenzamine, levodopa, anesthetics, L-DOPA, high-dose diuretics, rauwolfia alkaloids (reserpine), theophylline, nitroglycerin, caffeine, ethanol	

Notes: * IHC — immunohistochemical study, ANF — antinuclear factor, ANCA — antineutrophil cytoplasmic antibodies, ATdsDNA — antibodies to double-stranded DNA, AT to Scl–70 — antibodies to scleroderma 70, ARA — angiotensin II antagonists, AMCR — antagonists of mineralcorticoid receptors, ultrasound — ultrasound examination, MSCT — multispiral computed tomography, MRI magnetic resonance imaging tomography, PET-CT positron emission tomography.
[1*] Do not smoke 4 hours before the study, 3 days before the analysis, exclude tea, coffee, cocoa, cola and energy drinks, bananas, pineapples, avocados, tomatoes, eggs, cheese, chocolate, vanillin-containing products (pastries, confectionery), beer from the diet [4].

When compiling diagnostic algorithms, one should account for the fact that "classic" hormones directly affecting the vascular tone and the circulating blood volume include hormones from various adrenal gland regions (cortisol, norepinephrine, epinephrine, aldosterone). Thus, hypercortisolism (increased cortisol levels) should be evaluated using the low-dose dexamethasone suppression test. Meanwhile, epinephrine and norepinephrine are short-living molecules, so the diagnosis should be based on 24-hour urine for nor- and metanephrines; the test is especially informative if urine samples are collected after the hypertensive crisis. Aldosterone levels should be ideally evaluated together with the plasma renin activity upon achieving the target serum potassium level range.

Speaking about thyroid hormones (thyroxine and triiodothyronine), one should mention their significant cardiotonic and vasodilating effects. However, they can cause BP elevation only in predisposed patients with a baseline increase in vascular tone. Hypothyroidism may also provoke hypertension, as the vascular tone increases despite negative chronotropic and inotropic effects. It is well-known that BP elevation in both hyper- and hypothyroidism is not significant, and it is not a leading clinical sign.

Hyper-renin EH is characterized by high renin plasma levels within the setting of normal aldosterone levels, persistent BP elevation, and is diagnosed by excluding a true secondary renin-induced hypertension due to a renin-producing tumor [5]. The combination of hyperreninemia and hypokalemia led to thorough patient examination.

Reninoma is a benign tumor arising from the smooth muscle cells of afferent arterioles of the juxtaglomerular

apparatus producing increased renin levels, which in turn leads to secondary hyperaldosteronism and hyperkalemia [6]. It is diagnosed in adolescents and young adults. The classic symptom triad includes hypertension, increased plasma renin activity, and hypokalemia, all of which were observed in our patient for a prolonged period [7]. This type of renin-mediated hypertension is often accompanied by a prolonged history of migraine-like headache and drowsiness; it is rather sufficiently treated with drugs suppressing the activity of the renin-angiotensin-aldosterone system (RAAS) — thus, it might not be diagnosed, masquerading as a "migraine" or EH. Other relatively common symptoms include nausea, polyuria, polydipsia [8].

Imaging methods might not identify a small tumor (it is usually located superficially in the renal cortex), so it is still important to arrange an invasive selective blood collection from renal veins with lateralization (and the inferior vena cava) along with testing for renin levels in various blood samples — the closer to the renin hyperproduction source, the more probable is the tumor location; renin lateralization ratio >1.5 is maximally close to the source and region of a suspected surgical intervention.

An important aspect of the RAAS hormone hyperproduction is to exclude the use of RAAS inhibitors for at least 3 days before the laboratory test, which was not followed in the clinical case discussed (with the non-invasive diagnosis, 3 days are sufficient, while the selective blood collection from renal veins requires 2 weeks) [9]. The very-low-salt diet (<40 mmol/day) is also recommended for 4 days [9]. During this period, it is feasible to switch the drugs to alpha-blockers, calcium channel blockers, central drugs, supporting them with potassium drugs. The blood collection for plasma renin and renin activity should be arranged at room temperature maximally quickly to avoid in vitro renin activation and false-positive elevated results [10].

A Wilms tumor (nephroblastoma) is a malignant renin-producing renal tumor that is highly malignant, but more common in childhood and adolescence [6]. Multiple endocrine neoplasia is one of the prognostically unfavorable causes of renin hyperproduction.

Renin-secreting extrarenal tumors include lung carcinoma, pancreatic adenocarcinoma, Fallopian tube adenocarcinoma, with single clinical cases of vascular invading reninoma with lung metastases. If the renin-dependent tumor is suspected, PET/PET-CT with fluorodeoxyglucose is highly sensitive and specific, while PET scan with Gallium-68 is even more sensitive.

After a thorough patient examination, accounting for the favorable follow-up (no hypertension progression, preserved RAAS blocker effect), a high-renin essential hypertension (HREH) was concluded in her. Plasma renin levels widely vary in patients with EH. When analyzing the renin status in middle-aged persons with hypertension (both treated and untreated) of unknown origin in a Russian study, every fourth patient demonstrated significantly elevated renin (>39.9 μIU/mL) vs. 67 % patients with normal renin levels [2]. It is interesting to note that HREH is more common in younger persons, especially males, with hypersympathetic activation and mildly decreased circulating plasma volume; it may also form in response to the administration of angiotensin-converting enzyme inhibitors, angiotensin-2 receptor blockers, or mineralocorticoid receptor antagonists (as seen in the case presented).

Hyper-renin EH treatment includes standard regimens with the use of the aforementioned hypotensive drugs, as well as direct renin inhibitors (aliskiren) [5]. If adrenoblockers are used, alpha-blockers are preferable, with subsequent possible addition of beta-blockers to avoid paradoxical BP elevation with beta-receptor blockade. To correct resistant hypertension, bilateral sympathectomy of renal arteries using the radiofrequency ablation method is efficient provided the tumor resection is not possible [11].

Conclusion

A high-renin variant of essential hypertension requires a thorough search for the initial cause of renin hyperproduction, especially in young persons. Renal, adrenal, and extrarenal sources of renin synthesis justify a multi-step diagnosis of serum RAAS component levels with specific blood collection conditions (exclusion of drugs and food products for 3 days before the test), otherwise false-positive results may misinterpret the data. Multidisciplinary approach is complex for this patient, as it is difficult to implement in outpatient settings and requires high patient compliance with diagnosis and treatment.

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