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Clinical and Laboratory Features of Adrenal Macronodular Hyperplasia

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RATIONALE. Adrenal macronodular hyperplasia (AMH) is a benign adrenal lesion that, in some cases, leads to hypercorticism. Due to its low detectability, nonspecific and blurred clinical picture, and slow, multi-year progression, it is difficult to assess the true prevalence of AMH. These are thoughts based on very limited literature data. Detailed analysis of laboratory, radiological parameters, clinical presentations, particularly the identification of the course of comorbid diseases (arterial hypertension (HTN), diabetes mellitus (DM), osteoporosis), is necessary to determine the management tactics for patients with AMH.

OBJECTIVE.To study the clinical and laboratory picture of AMH in adult patients, as well as to search for factors contributing to its clinical heterogeneity.

MATERIALS. A single-center cross-sectional study was conducted. A total of 110 patients with adrenal macronodular hyperplasia (AMH) who presented to the National Medical Research Center of Endocrinology between 2014 and 2022 were examined. Comparative and sequential analyses of hormonal (nighttime cortisol suppression test (NCT), 24-hour urinary cortisol (24hUC), adrenocorticotropic hormone (ACTH)), biochemical (glycated hemoglobin), radiological data (volume of nodular tissue), and the course of concomitant diseases (metabolic syndrome, diabetes mellitus (DM), hypertension (HTN), osteoporosis) were performed in three groups of patients: those with manifest Cushing's syndrome (CS), those with functional autonomous cortisol production (FACP) and comorbidities, and AMH without hormonal activity.

METHODS.All patients underwent abdominal and pelvic computed tomography (CT) imaging using the Optima CT660 multi-detector computed tomography scanner from General Electric. The slice thickness was 0.625 mm. The scanning range extended from the diaphragm to the pubic symphysis. When necessary, intravenous bolus contrast enhancement was performed using non-ionic contrast agent (iodixanol 400 mg/mL). Assessment of arterial and venous contrast phases was conducted at 5 and 20 seconds after reaching the threshold of aortic contrast enhancement. Evaluation of the delayed phase was performed at the 10th minute from the start of contrast agent administration.

Radiological Examination. During the radiological examination, a differential diagnosis was performed between adrenal macronodular hyperplasia (AMH), cysts, and myelolipomas. Cystic

formations typically exhibit complete absence of contrast enhancement. The diagnosis of bilateral myelolipomas is established in the presence of formations containing areas of solid tissue with markedly negative native attenuation (<0 Hounsfield units (HU)), and myeloid components, characterized by high native attenuation (>20 HU). In cases with a history of malignancy, the possibility of secondary metastatic adrenal involvement arises. This is primarily assessed based on CT findings (high native attenuation, rapid growth of the formation), as well as an increase in the efficacy of tumor markers. Additionally, in corresponding pathologies, the characteristic adrenal tissue hyperplasia outside the nodule, typical of AMH, is absent.

Diagnosis of Hormonal Activity. The diagnosis of hormonal activity was conducted in accordance with the domestic recommendations of the Ministry of Health of Uzbekistan for the differential diagnosis of adrenal incidents.To confirm the hormonal activity of adrenal macronodular hyperplasia (AMH), cortisol levels were determined during the overnight 1 mg dexamethasone suppression test (NCT1). The procedure for conducting NCT1 involved the administration of 1 mg dexamethasone between 23 and 24 hours, followed by blood collection for cortisol levels the next morning between 8:00–9:00. Cortisol level measurements were performed using electrochemiluminescent analyzers from Roche (Cobas 6000 Modulee601) with standard kits from F. Hoffmann-La Roche Ltd. According to current recommendations, the threshold point is determined at the level of 50 nmol/L.

Results of NCT1 (cortisol >50 nmol/L). Additionally, all patients were further examined for the level of free cortisol in 24-hour urine using the immunochemiluminescent method on the Vitros Eci analyzer with prior ether extraction. The protocol for collecting biological material involved collecting 24-hour urine in a single container. The total urine volume was recorded. Patients were instructed to adhere to their usual drinking habits, discontinue the intake of medications affecting cortisol levels in the urine, as well as diuretics, and to avoid physical exercise and emotional stress. Laboratory reference values for free cortisol in 24-hour urine were 60–413 nmol/24h.

The study of ACTH levels was conducted using electrochemiluminescent analyzers from Roche (Cobas 6000 Modulee601) with standard kits from F. Hoffmann-La Roche Ltd. Blood samples were collected from peripheral veins in the fasting state between 8:00 and 09:00. The laboratory reference values were: ACTH — 7.2–66 pg/mL. Differential diagnosis between ACTH-dependent and ACTH-independent forms of CS was performed according to ACTH recommendations. A decrease in ACTH levels below 5 pg/mL confirmed the ACTH-independent nature of hypercortisolism.

The manifest form of CS was established when:In the absence of laboratory-confirmed hormonal activity and presence of characteristic changes (nodular adrenal hyperplasia) on CT imaging, a "hormonally inactive form of AMH" was diagnosed.Exclusion of bilateral pheochromocytoma was conducted in patients with high-density formations on CT (>20 HU) based on normal levels of methylated catecholamine excretion. In the presence of hypertension, primary diagnosis of primary hyperaldosteronism (PHA) was performed — including assessment of aldosterone, renin, and potassium levels.In cases of suspected Cushing's disease, levels of ACTH (if absent, 150 pg/mL) and cortisol (less than 500 nmol/L) were measured. If results were obtained, further investigation was conducted according to current recommendations.

RESULTS. The study included 110 patients, of whom 79.1% were women, with a mean age of 60 years [51; 68]. The proportion of hormonally inactive forms of AMH was 37.3%, manifest CS was detected in 25.4% of cases, and FACP was diagnosed in the remaining patients (37.3%). According to hormonal examination: cortisol level during NCT was 173.8 nmol/L [86.0; 441.0], ACTH was 3.35 pg/mL [1.00; 8.00], 24hUC was 445.5 nmol/24h [249.0; 900.0]. Statistically significant moderate positive correlations were found between the volume of nodular tissue and cortisol level after NCT ($r=0.40$; $p<0.001$), 24hUC ($r=0.29$; $p<0.004$), as well as a moderate negative correlation between ACTH level and the prognosis ($r=-0.40$; $p<0.001$). In the analysis of the prevalence and clinical expression of comorbid conditions, DM was diagnosed in 22 patients (53.7%), HTN in 36 patients (87.8%), obesity and disorders of mineral metabolism in 23 (56%) and 3 (7.8%) patients,

respectively. Associations with CS-related diseases (DM, HTN, osteoporosis) and body mass index values were not statistically significant in the respective groups.

Treatment plan for patients:Body weight was measured using medical scales, and height was measured from a distance using a wall-mounted stadiometer. Body mass index (BMI) was calculated using the formula:BMI = m/h^2,where m is the body mass (kg), and h is the height (m).During examination, the presence/absence of signs of Cushing's syndrome (CS) was assessed: weight gain, "Cushingoid" obesity type, purple striae, moon facies (prominent facial redness), hyperandrogenism, muscle weakness, limb muscle atrophy.The diagnosis of arterial hypertension (AH) was established with repeated elevation of blood pressure above 140/90 mmHg. All patients with concomitant AH received consultation from a cardiologist regarding the degree of hypertension, stage of AH, and initiation/correction of antihypertensive therapy.In the presence of elevated fasting blood glucose levels (>6.1 mmol/L), an oral glucose tolerance test was used to exclude carbohydrate metabolism disorders. Upon diagnosis of diabetes mellitus (DM), glycated hemoglobin (HbA1c) levels were assessed. HbA1c was measured using high-performance liquid chromatography on the D10 analyzer (BioRad, USA) with kits from the same manufacturer following standardized procedures; the method was certified by the NGSP (National Glycohemoglobin Standardization Program). Reference values were 4–6%.

CONCLUSION. The results of the study indicate that AMH is a heterogeneous pathology with various hormonal and radiological manifestations. Hormonally active forms of AMH dominate in our hospital cohort. A relationship between the volume of nodular tissue and the degree of hormonal activity in AMH was identified. The findings take into account the complexity of defining clear indications for surgical intervention in specific patient groups with FACP.Keywords: adrenal macronodular hyperplasia, Cushing's syndrome.

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