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ENDOGENOUS HYPERCORTICISM: ACHIEVEMENTS AND PROSPECTS IN DIAGNOSIS AND TREATMENT

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ABSTRACT: The results of examination and treatment of 647 patients with endogenous hypercortisolism were studied: pituitary corticotropinoma was detected in 494 (76.4%) patients, corticosteroma and pre — corticosteroma of the adrenal gland — in 142 (21.9%), bilateral macro-nodular hyperplasia of the adrenal glands of primary adrenal origin-in 11 (1.7%). Differential diagnosis of clinical forms of endogenous hypercortisolism was based on the assessment of the level of adrenocorticotropic hormone and cortisol, both in peripheral blood, and with selective bilateral blood sampling from the adrenal veins and lower stony sinuses, and the study of the nature of samples with 8 mg of dexamethasone. Topical diagnostics consisted in assessing the state of the adrenal glands and pituitary gland during computed tomography and magnetic resonance imaging with the use of contrast agents, and the use of special software 3D-Volume Rendering Technique allowed optimizing tactical and technical approaches to performing surgical interventions. Of the operated patients with adrenocorticotropic hormone dependent endogenous hypercortisolism, total removal according to the control magnetic resonance imaging was achieved in 92.3% of cases, subtotal — in 7.7%. However, hormonal remission was achieved only in 82.4% of cases. All patients with corticosteroma and pre-corticosteroma of the adrenal gland underwent adrenalectomy: in 6 patients by open method, in 136 patients by endovideosurgical method (in 11 patients by laparoscopic method, in 124 patients by retroperitoneoscopic method, and in 1 patient by thoracoscopic transdiaphragmatic adrenalectomy). In all patients, the operation led to recovery. Patients with benign macronodular hyperplasia of the adrenal glands needed conservative treatment with steroidogenesis blockers. Indications for surgical treatment in the volume of unilateral adrenalectomy occurred only in 2 patients.

Keywords: endogenous hypercortisolism; corticotropinoma; corticosteroma; differential diagnosis; stony sinus catheterization; transsphenoidal pituitary resection; endovideosurgical adrenalectomy.

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ЭНДОГЕННЫЙ ГИПЕРКОРТИЗОЛИЗМ: ДОСТИЖЕНИЯ И ПЕРСПЕКТИВЫ В ДИАГНОСТИКЕ И ЛЕЧЕНИИ

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Резюме. Изучены результаты обследования и лечения 647 больных эндогенным гиперкортизолизмом: кортикотропинома гипофиза выявлена у 494 (76,4%) пациентов, кортикостерома и прекортикостерома надпочечника — у 142 (21,9%), двухсторонняя макроузелковая гиперплазия надпочечников первично надпочечникового генеза — у 11 (1,7%). Дифференциальная диагностика клинических форм эндогенного гиперкортизолизма основывалась на оценке уровня адренокортикотропного гормона и кортизола как в периферической крови, так и при селективном двустороннем заборе крови из надпочечниковых вен и нижних каменистых синусов, изучении характера проб с 8 мг дексаметазона. Топическая диагностика заключалась в оценке состояния надпочечников и гипофиза при компьютерной томографии и магнитно-резонансной томографии с применением контрастных препаратов, а использование специального программного обеспечения 3D-техники объемного рендеринга позволяло оптимизировать тактические и технические подходы к выполнению оперативных вмешательств. Тотального удаления кортикотропиномы гипофиза, по данным контрольной магнитно-резонансной томографии, удалось достичь в 92,3% случаев, субтотального — в 7,7%. Однако гормональной ремиссии удалось достичь только в 82,4% наблюдений. Всем больным кортикостеромой и прекортикостеромой надпочечника выполнена адреналэктомия: у 6 открытым способом, у 136 — эндовидеохирургическим (у 11 — лапароскопическим, у 124 — ретроперитонеоскопическим способом и у 1 больного выполнена торакоскопическая трансдиафрагмальная адреналэктомия. У всех больных операция привела к выздоровлению. Больные, страдающие доброкачественной макроузловой гиперплазией надпочечников, нуждались в консервативном лечении блокаторами стероидогенеза. Показания к хирургическому лечению в объеме односторонней адреналэктомии возникли у 9 больных.

Ключевые слова: эндогенный гиперкортизолизм; кортикотропинома; кортикостерома; дифференциальная диагностика; катетеризация каменистых синусов; транссфеноидальная резекция гипофиза; эндовидеохирургическая адреналэктомия.

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BACKGROUND

This year marks the 180th anniversary of one of the oldest surgical clinics in Russia, the S.P. Fedorov Clinic of Departmental Surgery of S.M. Kirov Military Medical Academy (MMA), founded by N.I. Pirogov in 1841. Since then, many generations of our department's scientists, including outstanding globally renowned surgeons, have enriched various areas of surgery. In particular, their contribution to the development of endocrine surgery and, in particular, to the study and treatment of endogenous hypercortisolism (EH) should be emphasized.

The founder of this section of endocrine surgery in Russia is the great surgeon, scientist, and teacher, Sergey Petrovich Fedorov, whose name our clinic bears. It is historically accurate that the first surgery on the pituitary gland in Russia, transnasal hypophysectomy for adenoma of its anterior lobe with the development of acromegaly, was performed in our clinic in 1914 by S.P. Fedorov.

From 1903 to 1936, during the directorship of S.P. Fedorov, the departmental team performed up to 20% of surgeries on endocrine organs. The development of endocrine surgery at the MMA was so successful that, in 1926, the clinic of the then-hospital surgery was visited by the eminent American surgeon and scientist William Mayo as a sign of respect and for educational purposes. The clinic staff was actively interested in the achievements of the current leading scientists who dealt with surgical endocrinology problems. In particular, V.N. Shamov did his internship at the clinic of the famous American neurosurgeon H.W. Cushing [1].

V.M. Sitenko became the chairperson after V.N. Shamov and continued developing scientific techniques in adrenal surgery. In 1961, at the beginning of his leadership of the Department of Faculty Surgery, V.M. Sitenko performed the first bilateral adrenalectomy in Russia. The next period in the development of endocrine surgery at the department, headed by Professor A.I. Nechay, was marked by the introduction of minimally invasive technologies for examining EH patients (ultrasound, US, computed tomography, CT, magnetic resonance imaging, MRI). Also, numerous scientific publications presented the results of studies conducted jointly with neurosurgery, radiology, pathology, anesthesiology employees, and others.

Analyzing the results of studies conducted in the clinic enabled the investigators to conclude that tumor and nontumor changes in the adrenal glands have a common pathogenesis in EH. The data obtained confirmed the assumptions formulated in 1955 by the academician V.G. Baranov that hyperplasia, adenoma, and cancer of the adrenal cortex can be manifestations of a single process. It was demonstrated that with the progression of the disease, morphological changes of a focal nature (tumor), and possibly the entire tissue of the adrenal glands, can acquire functional "independence" and that the functional significance of neoplasms of the adrenal cortex is not equal. A tumor detected in the adrenal gland does not always cause manifestations of EH. When choosing a method to treat this syndrome, these aspects must be considered, especially to rule out the "autonomous" functioning of the adrenal glands that are not affected by the tumor [3]. The data obtained are presented in the thesis research of V.M. Trofimov (1986), A.G. Vavilov (1992), and L.M. Krasnov (1993). In addition, they are in the monograph "Itsenko–Cushing syndrome" (1991), ed. V.G. Baranov and A.I. Nechay, which became a handbook for endocrinologists and surgeons, were used to determine the strategy for examining and treating EH patients for many years [2–5].

The successes achieved over the past 25 years under the guidance of the Academician of the Russian Academy of Sciences, Professor N.A. Maistrenko, together with the staff of the Department of Neurosurgery, in the treatment of EH, include contemporary immunochemical studies of hormones, radiation techniques, endovideosurgical interventions on the pituitary and adrenal glands, proton irradiation, and others [6–8]. At the same time, transsphenoidal resection of the pituitary gland, as well as laparoscopic, retroperitoneoscopic, and thoracoscopic adrenalectomy, were performed by the staff of the academy for the first time in Russia [9].

Despite the improvement in treatment methods and the emergence of new diagnostic technologies, differential diagnostics of the primary clinical forms of EH are still difficult. In more than 50% of patients, the cause of the disease is established with a significant delay. Gross approach errors are often made, including long-term ineffective conservative treatment and performing pathogenetically unreasonable adrenalectomies. According to many authors, the number of patients who undergo neurosurgical surgeries with a magnetic resonance-negative disease presentation does not tend to decrease, despite the achievements of modern instrumental diagnostics. The lack of an evidence base and a reasonable choice of treatment methods for these patients results in relapses, and in some cases, after bilateral adrenalectomy, to chronic adrenal insufficiency [4, 10, 11].

The study aimed to clarify rational treatment options for EH patients based on the reliable verification of its primary clinical forms using modern diagnostic technologies.

MATERIALS AND METHODS

The examination and treatment results of 647 EH patients with follow-up periods of 5 to 10 years were analyzed. The age of patients at the time of surgery ranged from 14 to 68 years, averaging 32.5 ± 4.8 years. A significant proportion of them were women. Most patients (60.8%) were active (working) from 21 to 50 years. Clinical symptoms of EH were of the same type, and the most frequent were obesity, dystrophic changes in the skin, cardiomyopathy,

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arterial hypertension, osteoporosis, diabetes, secondary immunodeficiency, and others.

For the primary diagnostics of EH, standardized methods were used: the determination of free cortisol in urine, the determination of cortisol in saliva at 11 p.m., and a small sample with dexamethasone (1 mg). After confirming EH, differential diagnostics were performed between the adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent forms of the disease by determining the level of cortisol, cortisone, and ACTH and its rhythm (at 8 a.m. and 11 p.m.) in blood plasma. Also, the nature of samples with 8 mg dexamethasone was studied. Two biochemical tests were performed simultaneously to accelerate the diagnostics in patients with high clinical predictability of the result [12, 13].

In our work, we considered the results of studies by some authors that the evening dexamethasone suppression test is not sufficiently accurate. Dexamethasone is known to suppress cortisol production in some patients with ACTH-dependent EH, but not in many patients without the disease, especially if they have other acute or chronic diseases, depression, or alcoholism. All these diseases activate the hypothalamus–pituitary–adrenal system due to stress and cause resistance to the suppression of cortisol secretion by dexamethasone. Due to such difficulties in the initial screening test for EH, the patient may need to be re-examined after some time [14, 15].

Glucocorticoid precursor levels in peripheral blood (corticosterone, 11-deoxycorticosterone, 11-deoxycortisol) were studied to rule out subclinical hypercortisolism. The excretion of free cortisol and free cortisone was determined in urine by high-performance liquid chromatography with the study of chromatographic profiles of corticosteroids [16, 17].

Neuroimaging was performed using MRI from 1.5 to 3 T. This algorithm was performed in 493 patients, except for one who had contraindications to MRI, and the diagnosis was confirmed by CT and blood sampling from the petrosal sinuses [18]. In case of doubts about the source of ACTH hyperproduction, selective angiography was performed with blood sampling from the cavernous or inferior petrosal sinuses. The gradient of ACTH level was assessed from the center to the periphery and the side of the lesion. Blood sampling was performed in 112 patients, and the diagnosis of ACTH-dependent EH was confirmed [18]. Positron emission and CT were also performed in 32 patients without tumor neuroimaging by MRI or doubtful data (in cases of differential diagnostics of recurrence or postoperative changes). The focus of hyperproduction was confirmed, and the patients subsequently underwent surgery.

Niveau diagnosis of adrenal neoplasms was performed using CT and MRI with the administration of contrast agents and special software. The 3D-Volume Rendering Technique enabled us to optimize tactical and technical approaches to perform surgical interventions [19]. The final stage of diagnostics was a morphological and immunohistochemical study of the removed adrenal and pituitary tumors [20, 21].

RESULTS AND DISCUSSION

After establishing the diagnosis of EH, the disease caused was searched. The analysis of the results of clinical and hormonal studies and changes in the adrenal glands and pituitary gland (CT, MRI) during the initial examination enabled us to establish the EH forms in the patients under study, namely ACTH-dependent form in 494 cases (76.4%), ACTH-independent form (a macronodular form of the adrenal gland disease of primary adrenal genesis) in 11 (1.7%) patients, and corticosteroma of the adrenal gland in 142 (21.9%) patients.

The diagnosis of ACTH-dependent hypercortisolism was established according to generally accepted recommendations [21]. Our earlier studies [5, 16, 20] showed that when determining the levels of adrenal hormones, the key criteria for making a diagnosis was the level of ACTH, blood plasma cortisol, and the study of their circadian rhythm, as well as a large sample (8 mg/day) with dexamethasone. For patients with ACTH-dependent EH, elevated levels of ACTH were characteristic, namely 31.8 ± 3.6 pmol/l in the morning (norm 2.2–10 pmol/l) and 28.4 ± 4.2 pmol/l in the evening, those of cortisol was 668.4 ± 36.7 nmol/l in the morning (norm 150–650 nmol/l) and 616.9 ± 39.3 nmol/l in the evening (norm 25–270 nmol/l), respectively. It was established that after an extensive dexamethasone test on day 3, the blood plasma cortisol level and the daily excretion of 17-oxycorticosteroids (OCS) in the urine decreased by 50% or more. The nature of hormonal disorders and functional tests indicated an ACTH-dependent EH and the need to identify pituitary corticotropinoma.

The main methods of topical diagnostics were CT and MRI of the pituitary and adrenal glands. CT showed bilateral hyperplasia in the adrenal glands in most cases and adenoma in the pituitary gland.

However, despite modern CT scanners in recent years, there are still difficulties in diagnosing pituitary microadenomas (less than 1 cm in diameter). CT does not allow the differentiation of small pathological neoplasms with a radiographic density close to that of cerebrospinal fluid or normal brain tissue. The difficulties in interpreting the information obtained are because of several objective reasons. The proximity of bone formations gives a significant amount of pickups and artifacts. Increased vascularization of the pituitary gland, the presence near the cavernous sinuses, internal carotid arteries, and the circle of Willis makes it impossible to rely on accurate information even with CT with intravenous contrast agents. Consequently, the small size of pituitary adenomas and the objective disadvantages of the information obtained currently prevent considering CT as the optimal method for diagnosing this pathology (sensitivity is not more than 70%) [21].

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According to the control MRI, the total removal of the pituitary corticotropinoma was achieved in 92.3% of the operated patients, and subtotal removal was performed in 7.7% of cases. However, hormonal remission was achieved only in 82.4% of cases. The results of neurosurgical treatment indicate that the total removal of pituitary adenoma, according to MRI, is not always accompanied by complete hormonal remission. Probably, with the invasive nature of growth, microfragments of the mass lesion remain in the cavernous sinus, which are not visible and are beyond the resolution of MRI. The lesions are often multifocal, and the removal of a larger manifest lesion does not always result in the recovery of patients.

The data of hormonal studies in patients with corticosteroma of the adrenal gland were characterized by normal plasma ACTH levels of 8.5 ± 2.7 pmol/l in the morning and 5.2 ± 3.1 pmol/l in the evening. At the same time, the cortisol level was elevated (840.7 ± 85.4 nmol/l in the morning and 819.6 ± 74.1 nmol/l in the evening). Daily urinary excretion of 17-OCS was 58.6 ± 9.5 μmol/l in the morning. A major dexamethasone test enabled us to establish that, on day 3, the blood plasma cortisol level and the daily excretion of 17-OCS in the urine decreased by less than 50%. At the same time, no pathological changes in the pituitary gland were detected during the MRI with intravenous administration of contrast agents. The laboratory and instrumental data obtained proved the presence of functional autonomy at the adrenal glands and the tumor level. CT and MRI enabled us to detect a neoplasm of the adrenal gland with a sensitivity of 92.5% and 100%, respectively. The data obtained coincide with the findings of other researchers [21].

All patients in this group underwent adrenalectomy, where 6 patients underwent open surgery, 136 patients underwent endovideosurgical intervention (11 patients underwent laparoscopic surgery, 124 patients underwent retroperitoneoscopic surgery, and 1 patient underwent thoracoscopic transdiaphragmatic adrenalectomy). The analysis of the results of endovideosurgical interventions showed the apparent advantages of retroperitoneoscopic adrenalectomy when there were no complications and no transitions to open surgery. With this approach, there is no need to mobilize the internal organs, and the central vein of the adrenal gland is exposed before its mobilization, which is especially important when removing hormonally active tumors.

Laparoscopic adrenalectomy appears to be less effective, especially on the left. With this localization of the adrenal gland tumor, intra- and postoperative complications developed in every second patient, and conversion was required in two cases [11, 20].

Experimental data and accumulated practical experience indicate the need for broader use of endovideosurgical interventions on the adrenal glands, which proved effective in 87.3% of cases. The exception is patients with tumors larger than 8 cm and signs of malignant growth.

In three cases, adrenalectomy was ineffective (histologically, it was clear cell adenoma and extratumor hyperplasia of the adrenal cortex). In these patients, in the long-term after surgery (5 years or more), the clinical presentation of EH was noted with hyperproduction of cortisol (845 ± 28.7 nmol/l in the morning and 664 ± 26.5 nmol/l in the evening). When conducting a test with 8 mg of dexamethasone, they suppressed blood cortisol production by more than 50%. Along with this, attention was drawn to an increase in the blood plasma level of ACTH to 16.8 ± 3.4 pmol/l in the morning and 12.3 ± 3.6 pmol/l in the evening. A repeated MRI of the pituitary gland with an intravenous contrast agent revealed a microadenoma. Therefore, the initial diagnosis of adrenal corticosteroma in these patients was changed to ACTH-dependent EH. After proton therapy in the area of the identified pituitary microadenoma, all patients recovered.

A special group consisted of patients who had a normal level of plasma ACTH of 9.1 ± 2.1 pmol/l in the morning and 4.6 ± 2.8 pmol/l in the evening, as well as elevated cortisol levels of 712.1 ± 27.8 nmol/l in the morning and 684.6 ± 31.3 nmol/l in the evening. Daily urinary excretion of 17-OCS was 46.4 ± 6.1 μmol/l in the morning [22]. The major dexamethasone test result was negative, and the daily excretion of 17-OCS in the urine decreased by at least 50% of the background level. A CT detected no tumor in the adrenal glands in these patients, and their macronodular bilateral hyperplasia was noted. MRI with intravenous injection of a contrast agent did not reveal adenomas in the pituitary gland. The data obtained indicated an ACTH-independent EH. In order to reduce the manifestations of EH in these patients, adrenalectomy was performed (unilateral in 9 patients on the side of the most altered adrenal gland, bilateral in 2 patients). After unilateral adrenalectomy, all patients showed a short remission of the disease with its subsequent progression, and after bilateral adrenalectomy, Nelson syndrome developed. A morphological examination of the removed adrenal glands revealed signs of macronodular hyperplasia.

Along with this, there was an increase in blood ACTH levels to 18.2 ± 4.8 pmol/l in the morning (norm 2.2–10 pmol/l) and 15.3 ± 4.1 pmol/l in the evening in patients after both unilateral and bilateral adrenalectomy. Repeated MRI of the pituitary gland in these patients revealed a pituitary microadenoma (corticotropinoma). After transsphenoidal removal of the pituitary microadenoma, the signs of EH regressed. The analysis of the obtained results of the examination and treatment of patients enabled revision of the initial diagnosis of macronodular hyperplasia of the adrenal glands of the primary adrenal genesis and to establish corticotropinoma of the pituitary gland in these patients.

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Thus, the presented analysis of the results of the examination and surgical treatment of 647 EH patients enabled the establishment of the final diagnosis of ACTH-dependent form of the disease in 505 (78.1%) patients and corticosteroma in 142 cases (19.9%).

CONCLUSION

The diagnostic difficulties in identifying the primary clinical forms of EH are evident despite the improvement of laboratory and instrumental research methods. Suppression of blood cortisol secretion after a test with 8 mg of dexamethasone by more than 50% and a normal plasma ACTH level, the absence of a tumor in the adrenal glands or their bilateral macronodular hyperplasia necessitates a targeted search for a pituitary microadenoma using high-field targeted MRI using contrast paramagnetic agents.

The main aim of treating EH patients is the normalization of the levels of adrenal cortex hormones and, as a result, the reduction in the clinical manifestations of hypercortisolism. At the same time, early surgical intervention is important before severe complications develop, which determine an unfavorable prognosis. Compliance with the diagnostic algorithm will allow the timely detection of corticotropinoma in EH and effective transsphenoidal adenomectomy and adrenalectomy in cases of corticosteroma. This approach, which can only be implemented in a specialized hospital, provides a rational treatment approach, good treatment results, and a high quality of life.

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