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OUR EXPERIENCE OF BILATERAL ADRENALECTOMY FOR CUSHING SYNDROME

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ABSTRACT

Purpose: to analyze the results of bilateral adrenalectomy for Cushing syndrome. **Material and methods.** From the analyzed 16 cases of bilateral adrenalectomy (BAE), in 14 it was performed in stages (in 11 cases with Cushing's disease (CD) after unsuccessful transsphenoidal adenomectomy (TAE), in 2 - with ectopic Cushing's syndrome (ECS), in 1 - with bilateral corticosteroma), and in two cases – simultaneously (in 2 cases with bilateral corticosteroma). The age of the patients was on average 30.14±4.13 years. In 4 cases, BAE was performed transabdominally, and in 28 cases - retroperitoneoscopically. **Results.** The median follow-up period was 35.5 months. After BAE, the vast majority (75%) of patients lost excess weight and achieved a BMI <25 ($P < 0.001$). A statistically significant improvement was also observed in arterial hypertension (from 93.75% to 50%) ($P < 0.005$). Before the operation, 56.25% suffered from diabetes mellitus, and after the operation - 18.5%. Acute adrenal insufficiency developed in 25% of patients. Death during the observation period was observed in 18.75% of cases. **Conclusion.** BAE is an effective method for treating manifestations of hypercortisolism in patients with CS. It provides good palliative treatment for CD with failed TAE and ECS. Mortality in the postoperative period is directly related to the severity of complications that develop in the preoperative period.

Key words: Cushing syndrome, bilateral adrenalectomy.

INTRODUCTION

To date, significant progress has been made in the diagnosis and treatment of endogenous hypercortisolism. The introduction of laparoscopic adrenalectomy in patients with Cushing's syndrome (CS) significantly improved their surgical treatment outcomes.

According to numerous studies, the main cause of endogenous hypercortisolysis is pituitary adenoma (Cushing's disease (CD)), in which

transphenoidal adenomectomy (TAE) is successfully performed in 70-85% of cases. In rare cases, damage to the adrenal gland itself can occur in ectopic zones of bilateral hyperplasia and cortisol production in very rare cases. The main problem today is the early and timely diagnosis of the cause of hypercortisolism. In cases of primary damage to the adrenal glands, as well as recurrence of hypercortisolism after unsuccessful TAE, the definitive solution is bilateral adrenalectomy (BAE).

The purpose of this retrospective study was to evaluate BAE results in endogenous hypercortisolysis.

Material and methods. During the period from 2009 to 2023, out of 388 patients who underwent videoendoscopic adrenalectomy (VAE) in the multidisciplinary clinic of the Tashkent Medical Academy, 67 (17.3%) patients underwent it for CS.

In our clinic, VAE (unilateral) in patients with CS was started in 2013. The first laparoscopic BAE for this pathology (with non-localized ectopic CS (ECS) and with CD after unsuccessful TAE) was performed in 2016.

The etiology of CS included patients with an ACTH-secreting pituitary adenoma after unsuccessful TAE, an unknown source of ectopic ACTH production, and a primary lesion of the adrenal glands themselves. The diagnosis was made on the basis of clinical data, biochemical analysis, radiological data and other data in accordance with the algorithm presented in Fig. 1.

Of the 67 patients, the indication for VAE in 45 (67.1%) was unilateral corticosteroma, in 17 (25.4%) it was performed with CD after unsuccessful TAE, in 2 (2.9%) - with ECS, in 3 (4.5%) – with CS due to bilateral corticosteroma.

Thus, in our observations, unilateral VAE was performed in 51 cases and BAE - 16 cases (11 (68.75%) in all cases of unsuccessful TAE and ECS and bilateral corticosteroma on CD). In this article, we analyze the results of treatment in 16 cases of videoendoscopic BAE.

The average age of the patients was 30.14, 4.13 (20-38) year olds, with a male-to-female ratio of 1:1.6. Before the operation, the average level of cortisol in the blood was 1055.87 and 261.22 nmol/L (range 480-2240). At the same time, a large difference in this indicator was noted between ECS and bilateral corticosteroma, and its value for pituitary CD was among them (range 1032.62.259.65 nmol/L, 502.49–2353). Patients with CD and ECS have an average preoperative blood ACTH of 75.69-22.34 (range, 19 to 92). In patients with bilateral corticosteroma, this was within normal limits.

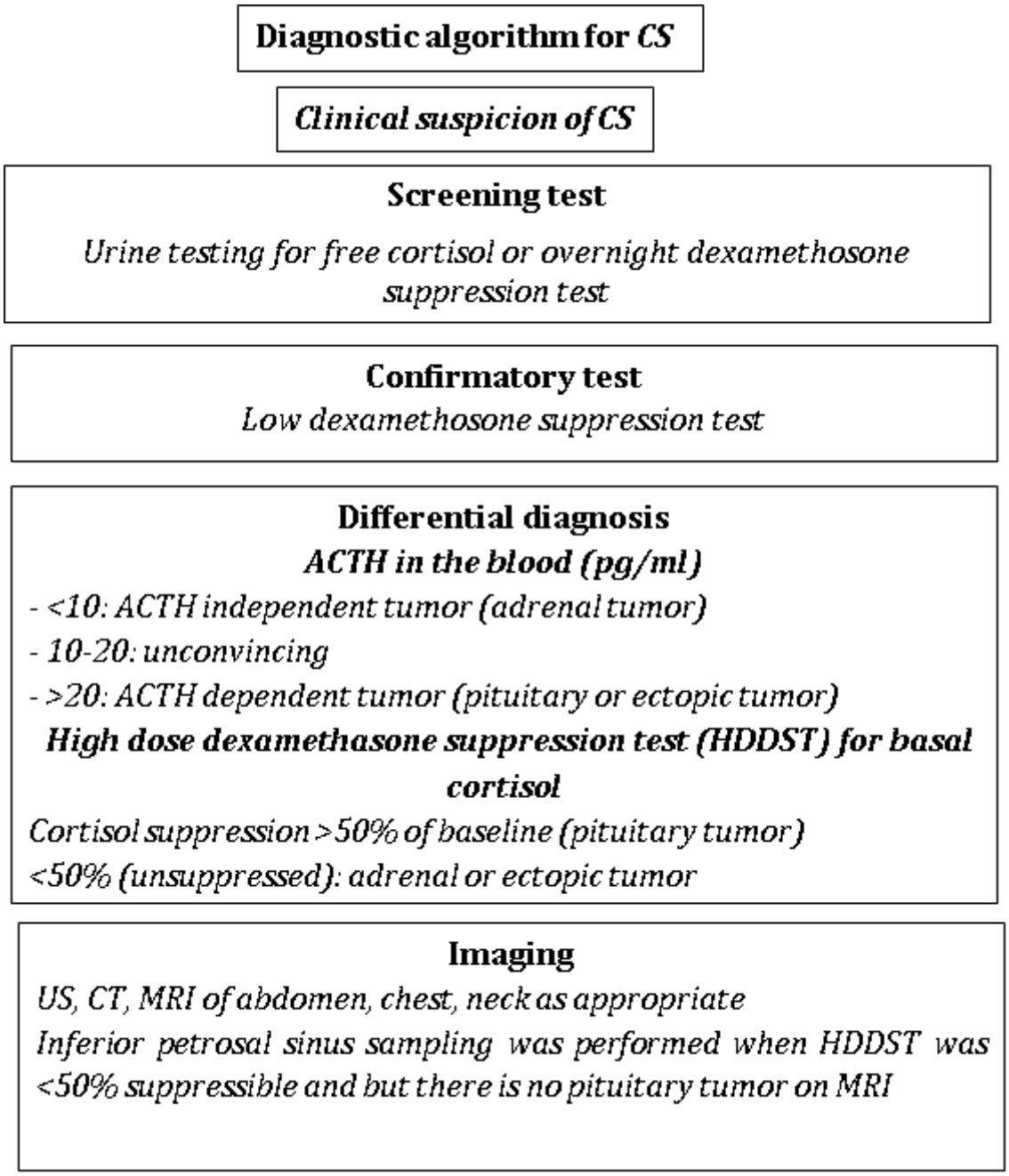

Fig. 1. Diagnostic algorithm for CS.

After preoperative preparation, all patients were VAE administered under a steroid cap using one of the minimally invasive techniques (transabdominal or retroperitoneoscopic).

At the time of allowing patients to leave the house, all patients were prescribed strict follow-up by an endocrinologist. After discharge from the hospital, patients came for examinations within the prescribed period. Surveillance data was collected from patient records, letters, emails, and telephone communications.

Results. In 14 of the 16 cases of BAE analyzed, it was performed in two stages, in 2 - in one stage (in 2, it was performed in 3 of the bilateral

corticosteroma). A total of 32 Ae were performed in 16 patients. In addition, in 4 cases, VAE was transabdominal and in 28 cases retroperitoneoscopic.

There were no conversions or significant intra- and postoperative complications associated with the surgical technique.

In patients without damage to the adrenal glands, the time of the second intervention in conducting a two-stage VAE was due to the recovery time of the increase in cortisol levels in the blood. So, in 2 cases it rose again after 3 months, in 2 cases - after 6 months, in another 3 cases - after a year, in 2 cases - after two years, in one case - after three and five years. Cortisol levels were not restored after the first VAE in 2 patients, and a month later, contralateral VAE performed well.

I would like to note that 4 out of 6 patients who were not included in these analyzes and who underwent unilateral VAE due to CS against a background of unsuccessful TAE, the level of cortisol in the blood continues to be normal under our control. normal serum cortisol levels. 2 people who did not seek medical help died.

In all patients with bae adenoma and CD and ECS in histopotological CS, it was found to be adrenal hyperplasia.

The average observation period was 35.5 months (in the range of 2-80 months). Prior to surgery, 25% of patients (n = 4) were severe (body mass index [BMI] > 25), and 75% (n = 12) were clearly obese (BMI > 30). After adrenal removal, most of the total number of patients (75%) lost excess weight and reached BMI <25, and the difference was statistically significant ($P < 0.001$). A statistically significant improvement in Arterial hypertension (93.75% to 50%) was also observed ($P < 0.005$). In 37.5 percent of patients, the need for antihypertensive drugs decreased, while in 12.5 percent of patients, arterial hypertension (AH) remained. Similarly, patients with diabetes mellitus (DM) showed significant improvement. There were 56.25% (n=9) DM before surgery and only 18.5% (n=3/16) after surgery. Of the 75% (6/9) cases of improved DM after surgery, 3 patients had glucose levels in the blood in the normal range without diabetes drugs, and 3 patients had better control of blood sugar levels with low doses of oral hypoglycemic agents (insulin). Hirsutism existed in 62. It is resolved in 5% of patients (n = 10) and in all patients after VAE. 81.25% of patients (n=13) reported muscle weakness after surgery. It is worth noting that we have recorded such dynamics of symptoms even after the first stage of two-stage VAE (in 14 out of 12 cases) and after one-stage BAE.

Acute adrenal insufficiency developed in 25% of patients (n=4/16): in 2 after a one-stage bae and in another 2-after a second stage. The majority of patients (75%) did not have an adrenal crisis.

In CD cases, Nelson syndrome (NS) developed in 31.25% of cases (n = 5/16) during a 22-month follow-up period (20-60 months apart).

2 years after BAE, one patient developed a recurrence of the overproduction of endogenous cortisol. The patient had an ACTH-secreting tumor (ECS) whose localization was not determined.

During the observation period, mortality was observed in 18.75% (n=3) cases. Patients died 2, 9 and 36 months after the operation. Most of the 16 patients (82.25%) reported their health at the last observation. The average survival after BAE was 71.75 and 13.24 months. The Kaplan-Meier survival curve is shown in fig. 2.

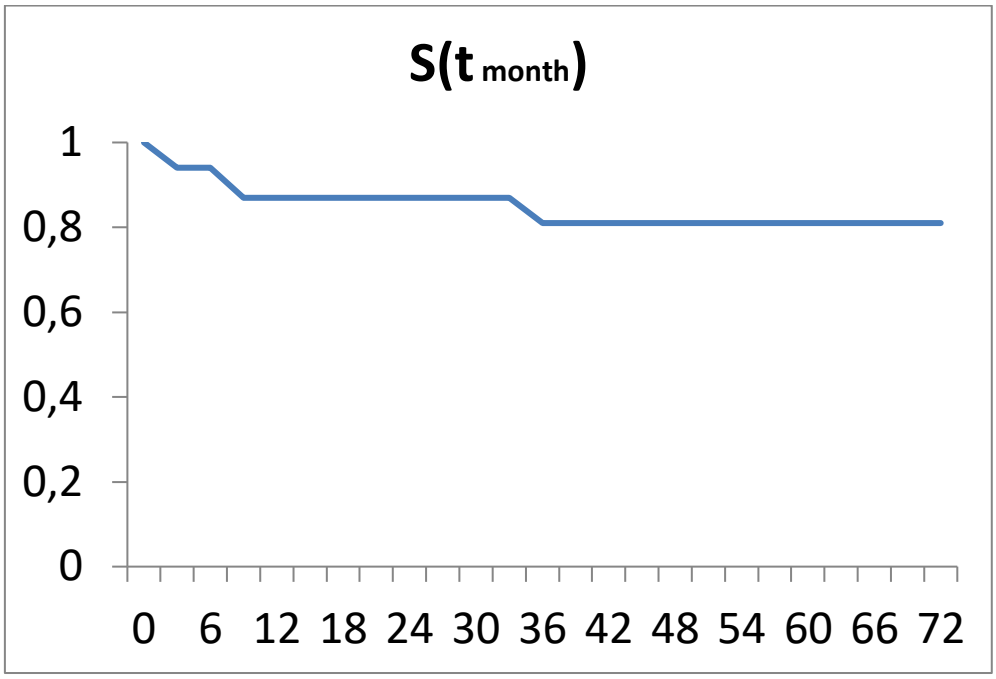

Fig. 2. Kaplan-Meier survival curve.

Discussion. One of the main causes of CS in our observations was adrenal corticosteroma, for which VAE is successfully used. Another common cause in our observations, as well as in other researchers, was unsuccessful TAE in CD. Of 17 such cases, 11 underwent BAE. Removing both adrenal glands for CS is not as dangerous as previously thought. Our data indicate that in the vast majority of patients it is effective with proper postoperative management.

It is known that TAE is the main method of treating patients with NIC. As a rule, most patients experience remission after it has been performed [2]. If relapse occurs after Tae with BIC, the following four treatments are used in the future: 1 - repeat TAE, 2 - sella turcica radiation therapy, 3 - ketoconazole and pasireotide uptake, and 4-double AE. And although re-surgery is recommended for these patients, many recommend other treatments, the causes of which are: the technical complexity of re-surgery and the high risk of complications [4]. So, in our

observations, liquorrhea appeared in 2 patients after repeated TAE, which was interrupted by repeated tamponade. At the same time, a decrease in the symptoms of the main disease was not recorded, and later they were transferred to the laparoscopic BAE stage.

When choosing an adrenalectomy method, we believe that the VAE method has undoubted advantages over open surgery. At the same time, the posterior retroperitoneoscopic approach is more justified for this purpose due to its specific advantages over the transabdominal and the absence of the need to change the position of the patient on the table.

After AE, most patients (75%) experienced clinical improvement in obesity and diabetes status, and more than 90% of patients showed improved blood pressure control, proximal myopathy, and hirsutism. At the same time, despite the normalization of cortisol levels after surgery (mental disorders, chronic fatigue), a number of symptoms of hypercortisolism remain.

Adrenal crisis remains a devastating consequence of BAE and remains the main cause of deterioration in general condition and sometimes mortality in these patients [5]. In our cases, 25% of patients developed at least one episode of adrenal crisis during a mean follow-up period of 20 months, which was managed by intravenous corticosteroids after hospitalization. According to Ritzel K. et al. the frequency of adrenal crisis after BAE was 9.3/100 patient-year, which is approximately comparatively lower than our observations [6].

Patients who experience their first episode of adrenal crisis are much more likely to die than those who have already experienced it but survive. So, unfortunately, 2 patients who suffered the first attack of the crisis died on the way to the hospital. At the same time, the remaining two suffered multiple attacks of adrenal crisis. We believe that against the background of an adrenal crisis, it is possible to achieve survival, which is achieved by adequate glucocorticoid replacement therapy, regulated by the control of blood cortisol.

In 1 patient with ECS, the source of hypercortisolism was not initially known, but was detected during postoperative follow-up. After detecting a tumor, which was an ectopic focus of hypercorticholism, patient successfully underwent surgery to remove it. Given this case, the question arises: is BAE necessary in these patients? Perhaps, on the one perspective, repeated studies over a certain period of time will be able to identify the primary source and it can later be removed by surgical intervention. On the other hand, if surgery is delayed, the course of CS will worsen, and, consequently, the quality of life will worsen. Therefore, the answer to the above question remains, in our opinion, controversial. In our opinion,

if the quality of life worsens and the likelihood of death increases due to an undetected primary ectopic tumor, then it is better to perform BAE.

Altogether, during our observation period, death occurred in 18.5% of cases. In 2 cases, death occurred due to adrenal crisis, and in one - progressive multiple organ failure in a patient with ECS.

Conclusion. In patients with CS, BAE is the main method of treating manifestations of hypercortisolism. BAE is an effective palliative treatment for patients with CD after unsuccessful TAE and ECS. After BAE, in most cases there is good survival and good quality of life. Mortality after surgery directly depends on the severity of complications that develop in the preoperative period. Despite not a small rate of morbidity and mortality in the postoperative period, BAE is a necessary intervention, when other treatment options are ineffective. Due to the difficulties associated with diagnosis, management, postoperative care and follow-up after BAE, it should only be performed in specialized centers, where the necessary equipment and specialists are available.

REFERENCES

1. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2008;93:1526–40.

2. Prajapati OP, Verma AK, Mishra A et all. *Indian Journal Endocrinology and Metabolism.* 2015; 19(6):834-840.

3. Locatelli M, Vance ML, Laws ER. Clinical review: The strategy of immediate reoperation for transsphenoidal surgery for Cushing's disease. *J Clin Endocrinol Metab.* 2005;90:5478–82.

4. Trainer PJ, Lawrie HS, Verhelst J, Howlett TA, Lowe DG, Grossman AB, et al. Transsphenoidal resection in Cushing's disease: Undetectable serum cortisol as the definition of successful treatment. *Clin Endocrinol (Oxf)* 1993;38:73–8.

5. Thompson SK, Hayman AV, Ludlam WH, Deveney CW, Loriaux DL, Sheppard BC. Improved quality of life after bilateral laparoscopic adrenalectomy for Cushing's disease: A 10-year experience. *Ann Surg.* 2007;245:790–4.

6. Ritzel K, Beuschlein F, Mickisch A, Osswald A, Schneider HJ, Schopohl J, et al. Clinical review: Outcome of bilateral adrenalectomy in Cushing's syndrome: A systematic review. *J Clin Endocrinol Metab.* 2013;98:3939–48.