

## **INACTIVE PITUITARY ADENOMAS: LONG-TERM RESULTS OF SURGICAL TREATMENT**

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### **Abstract:**

**Target.** Dynamic assessment of visual functions, symptoms of pituitary insufficiency and study of the frequency of relapses of inactive pituitary adenomas (IPA), taking into account general clinical, ophthalmological, imaging, and hormonal parameters in patients with a verified diagnosis who applied to the RSPMC of Endocrinology after transsphenoidal transnasal adenectomy.

**Material and methods.** In the period from 2018 to 2022, 427 patients with various pituitary adenomas were operated on at the Neurosurgery Department of the RSPMC of Endocrinology of the Republic of Uzbekistan using transsphenoidal transnasal adenectomy (TAG). 188 case histories of patients with IPA operated from 2018 to 2022 were retrospectively analyzed. Follow-up of patients after the first operation ranged from 1 to 3 years. Of the 188 patients, 32.4% (n=61) were men and 67.6% (n=127) were women. 151 patients had a macroadenoma (up to 40 mm), the rest - 37 - giant tumor sizes (any size over 40 mm).

**Results.** The main complaints in patients before surgical treatment were a decrease in visual acuity - in 68.8% of patients, in patients of reproductive age (men under 55 years of age and women under 50 years of age) - sexual dysfunction (81% and 83%, respectively), headaches (100%). Chiasmal syndrome in the form of optic nerve atrophy of varying degrees and bitemporal hemianopsia or hypopsia was observed in 133 (70.7%) patients. Insufficiency of one or more functions of the pituitary gland in varying degrees of severity was diagnosed in 100% of patients, including secondary hypothyroidism in 18 patients (9.6%) - 3 men and 15 women, secondary hypothyroidism with hypogonadism - in 86 (45.9%) patients - 33 men and 53 women, secondary hypothyroidism with secondary hypocorticism in 34 (18.1%) patients - 11 men and 23 women, secondary hypogonadism with secondary hypocorticism - in 37 (19.7%) patients - 10 men and 27 women and 13 (6.7%) patients (4:9) had symptoms of panhypopituitarism.

**Conclusion.** After surgical treatment, it is necessary to control the level of tropic hormones of the pituitary gland, the level of PRL and hormones of peripheral endocrine glands (cortisol, free cortisol in daily urine, free thyroxine, testosterone in men and estradiol in women), as well as urine analysis according to Zimnitsky for the diagnosis of diabetes insipidus.

**Keywords:** inactive pituitary adenomas, relapsing course, surgery.

IPA make up about 30% of the total number of pituitary formations. According to the results of epidemiological studies conducted in various countries, the prevalence of IPA, including micro- and macroadenomas, is 7–41.3 cases per 100,000 population [1,18]. Pituitary adenomas account for 10–15% of all primary brain tumors. Inactive pituitary adenomas are benign, but in some cases can have an aggressive, invasive growth pattern and have a relapsing course [2,3].

Inactive pituitary adenomas are relatively common. However, due to the absence of clinical syndromes, these tumors are diagnosed late, when patients develop compression syndromes in the form of headache, hypopituitarism, and “chiasmal syndrome” [7,11]. Although there are many reports of tumor shrinkage during dopamine agonist therapy [8,11,12,22], surgery is the first line treatment for patients with IPA [15,16,17].

These tumors can reach enormous sizes and spread locally into structures such as the cavernous sinus, sphenoid bone, dura mater, and adjoining brain [5,13] sometimes exhibiting aggressive behavior. Despite the fact that some authors report the total removal of a giant pituitary tumor, in general, the complete removal of these tumors is very rare, and they often progress [7,8,11,14]. Surgery for this pathology has been developing for several decades. Transsphenoidal adenomectomy is the main treatment for IPA, however, it is not always possible to achieve radical removal of the tumor [9,15,16].

**The aim** of our study was a dynamic assessment of visual functions, symptoms of pituitary insufficiency and the study of the frequency of recurrence of inactive pituitary adenoma, taking into account general clinical, ophthalmological, imaging, and hormonal parameters in patients with a verified diagnosis who applied to the RSSPMSE of Endocrinology after transsphenoidal transnasal adenomectomy.

**Materials and methods.** We retrospectively analyzed 188 case histories of patients with IPA operated from 2018 to 2022. The diagnosis of IPA was verified using imaging methods, data from a study of the hormonal status of patients. Follow-up of patients after the first operation ranged from 1 to 3 years. Of the 188 patients, there were 61 (32.4%) men and 127 (67.6%) women. 151 patients had a macroadenoma (up to 40 mm), the remaining 37 had giant tumors (any size over 40 mm).

The main complaints in patients before surgical treatment were a decrease in visual acuity - in 68.8% of patients, in patients of reproductive age (men under 55 years of age and women under 50 years of age) - sexual dysfunction (81% and 83%, respectively), headaches (100%). "Chiasmal syndrome" in the form of atrophy of the optic nerve of varying degrees and bitemporal hemianopsia or hypopsia was observed in 133 (70.7%) patients. Insufficiency of one or more functions of the pituitary gland in varying degrees of severity was diagnosed in 100% of patients, including secondary hypothyroidism in 18 patients (9.6%) - 3 men and 15 women, secondary hypothyroidism with hypogonadism - in 86 (45.9%) patients - 33 men and 53 women, secondary hypothyroidism with secondary hypocorticism in 34 (18.1%) patients - 11 men and 23 women, secondary hypogonadism with secondary hypocorticism - in 37 (19.7%) patients - 10 men and 27 women and 13 (6.7%) patients (4:9) had symptoms of panhypopituitarism. Thus, clinical signs of pituitary insufficiency (from

panhypopituitarism to loss of only one tropic function of the pituitary gland) had all the patients who were in our observation. In 50% (n=94) of patients, a subclinical increase in blood prolactin levels was noted.

In 100% of patients, adenomectomy was performed by a transnasal-transsphenoidal approach in our center by a neurosurgeon, Ph.D. Akbutaev A.M. According to the conclusion of the neurosurgeon, 69/188 (36.7%) patients underwent total tumor resection, 119/188 (63.3%) - partial, 79 (66.4%) of the latter underwent postoperative radiation therapy.

**Results.** In the postoperative period, in general, there is a positive trend in the clinical picture of the disease, although the number of complaints of headache remained the same, which is probably due to the surgical intervention itself.

The same can explain the increase in complaints of general weakness. Improvement of visual functions is considered to be the main criterion for the quality of the effectiveness of surgical treatment of IPA. Chiasmal syndrome in our analyzed series was observed in 133 (70.7%) patients, and in the postoperative period (after 6 months) improvement in visual acuity was detected in 48/133 (36.1%) patients, no improvement in 85/133 (63.9%), there was no deterioration. As mentioned above, according to different authors, this criterion (i.e., improvement) is observed in 31.5-84% of cases 6 months after surgery [9,15,24], while the same authors also note cases of deterioration vision in 1.1-7.8% of cases after surgery.

In our analyzed groups, visual impairment was not observed. Most of the authors associate the degree of visual recovery with the size of the tumor [15,24], therefore, a lower percentage of improvement in visual functions can probably be explained by the fact that the tumors were large or gigantic. According to our data obtained in our study, normalization of vision after transsphenoidal surgery was observed in 36.1% of cases.

The size of the removed tumor, the radicalness of the operation performed, and the age of the patient did not statistically significantly affect the frequency of vision improvements after the operation. The only factor that statistically significantly affects the possibility of improving vision after endoscopic removal of pituitary adenomas is the severity of initial visual disorders. In the analyzed patients, hypopituitarism of varying degrees, which was present before surgery, persisted after surgery, and an increase in the number of patients with panhypopituitarism was observed, which is also noted by other authors after adenomectomy [15,19]. So, before the operation, panhypopituitarism was in 13/188 (6.7%) patients, after the operation the number of patients increased to 55 (29.3%), i.e. the number of patients with panhypopituitarism after surgery increased by 22.6%. Also, the same authors note that the highest level of development of hypopituitarism is observed in patients who received a combination of surgical and radiation methods of treatment (91.0%). In the early postoperative period, there was a decrease in prolactin in 82/94 (87.2%), of which, in 69 patients, the hormone level returned to normal within 6 months after surgery - in all these cases, the tumor was radically removed.

The number of patients with hyperprolactinemia also increased by 16.5%. Of note, 10 of 49 men with postoperative secondary hypogonadism, despite androgen replacement therapy, restoration of sexual function did not occur, and moderate

hyperprolactinemia was detected in hormonal blood tests. The appointment of cabergoline (5-15 mg/week) in combination with hormone replacement therapy in 50% (of 10 men) of patients led to the restoration of erectile dysfunction. Diabetes insipidus after surgery was observed in 101/188 (53.7%) patients. Its duration was different: in 31/101 (30.7%) patients this complication was permanent, in 41/101 (40.6%) patients the effects of diabetes insipidus persisted for 2-8 months (usually 6 months) after surgery, in 13 (12.9%) - 1-4 years and in 16 (15.8%) diabetes insipidus had a transient character - signs were present for several days (from 3 days to 1 month).

There is no doubt that hypopituitarism (and often panhypopituitarism) that occurs after surgery or radiation therapy in almost all patients with giant adenomas requires replacement (sometimes lifelong) or corrective hormonal therapy. In our study, hormone replacement therapy with one or more drugs after surgery was required by 79% of patients.

Thus, after adenomectomy in the long-term after surgery, 36.1% of patients with IPA show improvement in visual functions, 16.5% of patients who had normoprolactinemia before surgery have moderate hyperprolactinemia; in 50% of patients, erectile dysfunction is restored while taking cabergoline drugs in combination with hormone replacement therapy, but at the same time, the number of patients with total hypopituitarism (29.3%) and with a permanent form of diabetes insipidus (up to 30.7%) increases. An increase in hypopituitarism, the need to prescribe hormone replacement therapy with glucocorticoids, thyroid and sex hormones in 90% of patients, and desmopressin in 30.7% requires constant endocrinological monitoring of patients after surgery.

To date, the number of recurrences of tumor growth remains high during the removal of pituitary adenomas. First of all, this applies to giant and invasive forms of pituitary adenomas. According to various authors, recurrence or continued growth of IPA is observed in 12-47% of cases [4,10,21,23]. Factors that significantly affect the duration without a relapse period are the degree of radical removal and tumor morphology [4,6,25,26] notes a high recurrence rate (67.8%) during the first 5 years, which is due to the invasive nature of tumor growth and insufficient radicalism of the operation. It is among patients with giant pituitary adenomas that the number of postoperative complications and adverse outcomes is high. More than 50% of patients become disabled due to visual and endocrine disorders [15,19,26]. Do not forget about the disorder of the reproductive function, which sometimes causes severe moral trauma to both men and women. All this indicates the need for further improvement of treatment methods, especially for this group of patients.

In our series of patients, tumor recurrence was found in 32 (17.0%) operated patients (23 women and 9 men), whose cytological analysis of the removed adenoma showed a null-cell tumor. Signs of recurrence of the disease were a decrease in visual acuity - in 6 patients, in 19 women menstrual irregularities (they had menstruation restored after the 1st operation), in 7 women relapse was detected as a result of systematic control MRI studies and all patients had persistent headaches. pain.

**Conclusions.** Thus, in patients with IPA after adenomectomy, there remains a relatively high risk of developing relapses of the disease, the time of development of

which depends on the size and timing after surgery. Therefore, MP-imaging of the hypothalamic-pituitary region, examination by a neuro-ophthalmologist after surgical treatment should be carried out annually with a subsequent increase in the observation interval. After surgical treatment, it is necessary to control the level of tropic hormones of the pituitary gland, the level of PRL and hormones of peripheral endocrine glands (cortisol, free cortisol in daily urine, free thyroxine, testosterone in men and estradiol in women) , as well as urinalysis according to Zimnitsky for the diagnosis of diabetes insipidus. According to electron microscopy, a null-cell tumor most often recurs. In the material analyzed by us, in those patients who underwent radiation therapy after surgery (and all of them had partial removal of the tumor), no relapses were found, there were 51 (27.1%). According to the literature, radiation therapy as a postoperative combined treatment, having relatively good efficacy (68%), has extremely high complication rates (up to 94% hypopituitarism) [15,19,20,21], which significantly worsens the quality of life of patients. However, the need for postoperative radiotherapy continues to be debated. Considering the high percentage of disease recurrence among null cell tumors, radiation therapy after adenectomy can be recommended in the first place for patients with this type of tumor.

#### LITERATURE

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