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ABSTRACT

Pituitary adenomas are one of the most common primary central nervous system tumours and have an estimated prevalence of 17%. Management of hormone-secreting pituitary adenomas involves a multidisciplinary approach that can incorporate surgical, medical, and/or radiation therapies. Acromegaly is a rare, chronic disorder that mostly results from growth hormone (GH)-secreting pituitary adenoma. We analyzed the outcomes of surgical treatment for growth hormone (GH) pituitary adenomas based on 28 cases and determine factors that lead to biochemical remission.

INTRODUCTION

Growth-hormone (GH) pituitary adenomas occur in 13-20% of all hormonally active pituitary adenomas [1, 21]. Increased levels of GH can cause the progression of cardiovascular and cerebrovascular diseases, which leads to increased mortality [4, 5]. These pituitary adenomas are invasive to the surrounding structures around the sellar area, which reduces the radicality and makes hormonal remission unattainable. [6, 15]. GH- pituitary adenomas treatment includes surgery, radiotherapy and medical therapy. Surgery allows to reduce the GH level insulin-like growth factor 1 (IGF-1) rapidly and is the primary method in GH pituitary adenomas [10, 11]. Currently, almost all pituitary adenomas are removed by endoscopic endonasal route which is highly effective and allows to achieve a high remission rate with a low number of complications [6, 12].

MATERIAL AND METHODS

A retrospective analysis of 28 patients with GH pituitary adenomas in the period from 2013 to 2019. All patients underwent surgical treatment by endoscopic endonasal route. Information about patients, tumor characteristics, clinical symptoms and biochemical remission is shown in Table 1. Patients were divided by age and gender: men – 12

Keywords
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(42.9%), women - 16 (57.1%), the average age was 40.67 years. GH pituitary adenomas were classified by size: microadenoma (up to 10 mm) - 5 (17.9%) patients, macroadenoma (10-39 mm) - 21 (75%) patients, giant pituitary adenoma (> 40 mm) - 2 (7.1%) patients. Cavernous sinus extension was classified according Knosp scale [18]: grade 0, 1 and 2 are defined as noninvasive tumors, grade 3 and 4 are defined as invasive tumors.

Age (mean, range)	40,67 (18-64)
Male	12 (42,9%)
Female	16 (57,1%)
Tumor size	
- Micro	5 (17,9%)
- Macro	21 (75%)
- Giant	2 (7,1%)
Cavernous sinus invasion	
- No invasion	18 (64,3%)
- Invasion	10 (35,7%)
Pre-GH level (mean, range)	39, (5,7 – 252) ng/ml
Symptoms and signs	
- Acromegaly	28 (100%)
- Visual field defect	9 (32,1%)
- 6 nerve palsy	1 (3,6%)
- Headache	11 (39,3%)
Long term follow-up results	
- Remission	23 (82,1%)
- Persistence	3 (10,7%)
- Recurrence	2 (7,1%)

Table 1. Patients, tumor characteristics, clinical symptoms and biochemical remission for 28 patients.

There were 18 (64,3%) cases with noninvasive cavernous sinus extension and 10 (35,7%) cases with invasive tumors. All patients were tested for GH and IGF-1 level before surgery, 3 months after surgery, and annually. Acromegaly was diagnosed on the basis of relevant clinical features: mean GH level >5 µg /l, plasma IGF-1 level greater than normal appropriate to age and gender. The serum GH level ranged from 5.7 to 252 ng / ml (at average 39), IGF-1 level ranged from 592 to 1506 ng / ml (at average 960.9). Preoperative clinical manifestations were observed in all 28 cases. All patients had clinical signs of acromegaly, visual impairment were found in 9 (32.1%) patients, oculomotor disorders in one patient (3.6%), headache was observed in 11 (39.3%) cases. All patients underwent magnetic resonance imaging (MRI) with intravenous contrast enhancement. The endoscopic endonasal

transsphenoidal (EET) approach was used in all cases. Surgery was performed using an endoscopic stand based on the HD-endoscope "Image-1HD" (Karl Storz, Germany). Rigid endoscopes "Karl Storz" 4 mm in diameter with viewing angles of 0 and 35 degrees were used as the main tool for visualization of the operating field. The follow-up ranged from 12 to 60 months, at average 25.4 (2.1 years) months. The serum level of GH and IGF-1 was determined in 3 months after surgery and annually. The criteria for endocrine remission or treatment were the lowest serum GH level of <0.4 ng/ml after oral glucose challenge, and subsequent normal IGF-1 levels appropriate to age and gender.

RESULTS

Radical removal: complete resection of somatotroph pituitary adenomas (PA) was achieved in 22 (78.6%) cases, of which in 19 (86.4%) patients - without invasive extension to the cavernous sinus, and in 3 (13.6%) patients - with invasive extension of Knosp 3. Subtotal resection was in 5 (17.8%) cases, of which non-invasive extension was found in 2 patients, in one of which the growth of PA was prolonged. The size of these tumors was from 30 to 40 mm. Invasive extension with subtotal resection of somatotroph PA Knosp 3 and Knosp 4 was revealed in 3 cases. Partial removal in 1 (3.6%) case, where there was extension to the cavernous sinus during Knosp 3.

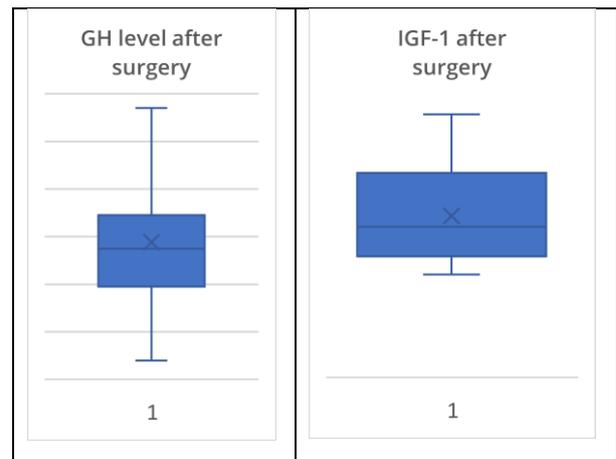


Figure 1. Range of GH and IGF-1 serum level after surgery.

Postoperative radiation therapy was performed in 4 cases, in 3 of them subtotal resection was performed, in one case due to partial removal. Growth recurrence after radiation therapy was observed in 2 (7.1%) cases, resulting in repeated

surgery. Clinical laboratory remission (CLR) was achieved in 23 (82.1%) patients. IGF-1 serum level ranged from 1 to 649 (mean 378,) GH level ranged from 0,4 to 5,7 (mean 2,9) (Fig. 1). In patients who underwent only radiation therapy after surgery, CLR was achieved in 2 patients. In patients who underwent radiation therapy and repeated surgery for a prolonged growth of PA, CLR was achieved in 1 case (out of 2 patients), which is associated with radical removal of PA. Postoperative nasal cerebrospinal fluid was observed in 3 (10.7%) cases, for which lumbar drainage was inserted in all 3 cases. Diabetes insipidus was detected in 1 (3.6%) case, which required the assignment of replacement therapy. There is no postoperative mortality.

DISCUSSION

Currently, in the treatment of tumors sellar region transsphenoidal approach is generally accepted and widely used in surgical practice [1,9,10,17]. Pituitary adenomas of various sizes and hormonal activity can be completely removed using EET approach [6, 22]. EET approach is currently the main method of surgical treatment of somatotroph pituitary adenomas [2].

The use of EET approach allows to achieve rapid decompression of the optic nerves and chiasm, affect the regression of acromegalic changes, reduce the risk of cardiovascular diseases and decrease mortality due to the rapid release of GH excess [22]. Compared to the microsurgical transsphenoidal approach, the EET approach is effective and allows one to achieve a larger number of totally removed pituitary adenomas and achieve biochemical remission surgically [6]. In our study, radical resection was achieved in 22 (78.6%) cases, of which 19 (86.4%) patients without invasive extension to the cavernous sinus, 3 (13.6%) patients with invasive extension Knosp3, subtotal resection - 5 (17.8%) cases, of which non-invasive extension was found in 2 patients. The size of these tumors was from 30 to 40 mm. Invasive extension with subtotal resection of these tumors was found in 3 cases. Partial removal in 1 (3.6%) case, where there was a spread to the cavernous sinus during Knosp3. Biochemical remission in endoscopic endonasal transsphenoidal removal of somatotroph pituitary adenomas was achieved in 23 (82.1%) patients.

According to the literature, biochemical remission in surgical series can be achieved in 60% -86% of

cases [13, 16, 22]. It is noted in studies that biochemical remission is influenced by the invasiveness of somatotroph pituitary adenomas, the level of preoperative GH [20]. In our series of observations, the radical removal of somatotroph pituitary adenomas depended on the invasive extension of these tumors to the cavernous sinus. At the same time the achievement of hormonal remission depended on the degree of removal of pituitary adenomas and their extension to the cavernous sinus. It was noted that hormonal remission was different depending on the size of somatotroph pituitary adenomas ($p < 0.05$). In pituitary microadenomas, hormonal remission was achieved in all patients (5 cases), in macroadenomas - 18 (85.7%), in giant pituitary adenomas - in one (out of two cases).

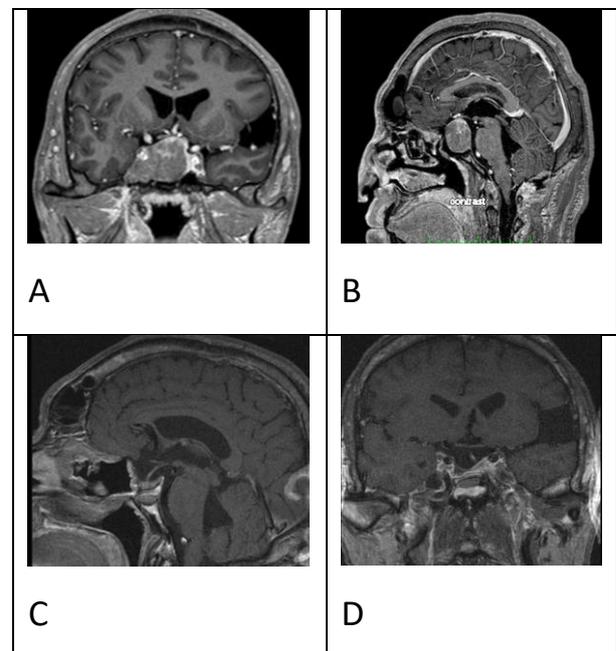


Figure 2.

A-B preoperative MRI scans with gadolinium. Macroadenoma 27x25x38 mm in size with Knosp 3B extension into the cavernous sinus.

C-D MRI scans with gadolinium after surgery, follow-up 5 years. GH level - 4,6 ng/ml.

Among invasive GH pituitary adenomas, biochemical remission was achieved in 8 (72.7%) patients, among noninvasive tumors, biochemical remission was achieved in 16 (94.1%) patients. As a clinical case we illustrate outcome of surgical treatment patient with large GH pituitary adenoma (Fig. 2). Patient with clinical manifestation of acromegaly, visual

disturbances, high level of GH -233 ng/ml and increased IGF-1 - 1288 ng/ml. Preoperative MRI scans with gadolinium shown large pituitary adenoma 27x25x38 mm in size with Knosp 3B extension into the cavernous sinus. Endoscopic endonasal approach was used to remove the tumor. Visual disturbances regressed after surgery. CLR was achieved after surgery in a few months and stay stable during all follow-up period (5 years). MRI scans with gadolinium after surgery and 5 years after shown gross-total tumor resection and no recurrence. Serum GH level – 4,6 ng/ml, IGF-284 ng/ml.

Recurrence and low level of hormonal remission are associated with the volume of tumor removal, its extension to the cavernous sinus. Thus, in 6 patients there was incomplete resection of GH pituitary adenoma. The size of these tumors was more than 3 cm in diameter. In 4 cases there was an invasive extension to the cavernous sinus. In two cases, there was a prolonged growth of tumors which were operated on at another center.

Adjuvant therapy, which includes drugs that reduce GH, repeated surgery or radiation therapy, plays an important role in the long-term treatment of patients who have not achieved hormonal remission after surgery [8, 9]. Postoperative radiotherapy was performed in 4 cases. Recurrence of growth after radiation therapy was observed in 2 (7.1%) cases, resulting in repeated surgery. Thus, hormonal remission in the group of patients with incomplete resection of GH-pituitary adenoma was achieved in 4 (66.7%) patients.

According to the literature, complications during pituitary adenoma surgery occur on average in 10% of cases, hypopituitary syndrome is manifested in less than 10% of cases, nasal cerebrospinal fluid - 13.9%, oculomotor nerve injury- in 6% [3, 17, 19]. Postoperative nasal cerebrospinal fluid was observed in 3 (10.7%) cases. Diabetes insipidus - 1 (3.6%) case, for which was prescribed the replacement therapy. There is no postoperative mortality.

CONCLUSIONS

1. Endoscopic endonasal transsphenoidal approach in the treatment of GH pituitary adenomas is effective, allowing to achieve hormonal remission in 82.1%, and is safe method reducing the number of postoperative complications.

2. Cavernous sinus extension of GH pituitary adenomas reduces the possibility of radical removal of these tumors, clinical and laboratory remission can be achieved in 85.7% of patients.

3. Radiotherapy can reduce the number of recurrences, while clinical laboratory remission was achieved in 66.7% of patients.

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