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ADVANCES IN THE NEUROSURGICAL AND COMBINED TREATMENT OF PATIENTS WITH ACROMEGALY

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ABSTRACT — Aim. The study was carried out to identify and analyze the factors of a positive outcome of surgical and radiation treatment of acromegaly.
Methods. The work was performed on clinical material and summarizes treatment results of 256 patients (90 males and 166 females). 86% of patients underwent surgical treatment, 14% of patients received radiation therapy during 2002–2018. Significance of factors of a positive outcome of treatment was carried out using the RStudio program.
Results. The results of the study revealed that:
1. Significant factors ($p < 0.05$) of a positive outcome of surgical treatment of acromegaly are somatostatin analogs (SSA) therapy before surgery, a small tumor size (microadenomas), and the absence of extrasellar tumor spread. 2. The most significant factor in achieving remission of acromegaly after non-radical adenomectomy is postoperative therapy with SSA ($p < 0.05$). 3. Aggressive pituitary tumors invading surrounding structures, high baseline IGF-1 levels, unfavorable histological findings, macroadenomas, growth hormone levels above 10 μg/L before therapy, and extrasellar tumor spread were associated with less favorable outcomes of acromegaly radiation therapy (RT) ($p < 0.05$). The most significant factor in achieving remission of acromegaly is SSA therapy after RT ($p < 0.05$).
Conclusion. Surgical treatment is the optimal primary treatment for acromegaly. Drug therapy with SSA is effective and the preferred treatment after non-radical surgery.

KEYWORDS — acromegaly, combined treatment, surgical treatment, radiation therapy, drug therapy.

INTRODUCTION

The delay in diagnosis of acromegaly is still significant (4.5–5 years), and the disease is usually confirmed in the fifth decade of life in economically active population; this leads to loss of productivity, social and financial implications, and long-term burdens on the health system. Despite the long history of the study of acromegaly and a wide arsenal of modern methods of treatment, a complete clinical and laboratory remission is relatively rare. Hence, in February 2019, only 32% of acromegalic patients in Russia had complete clinical and laboratory remission of the disease (normalization of Insulin-like growth factor I (IGF-I)) [1]. In this regard, the search for an effective strategy for managing patients with this disease becomes relevant. Therefore, we analyzed the factors of a positive outcome of surgical and radiation treatment of acromegaly.

METHODS

The study was conducted at "N.N. Burdenko National Medical Research Center of Neurosurgery" (Moscow, Russia)

The work was performed on clinical material and summarizes treatment results of 256 patients (90 males and 166 females). 86% of patients underwent surgical treatment, 14% of patients received radiation therapy during 2002–2018.

Statistical processing of the treatment results was carried out using the RStudio program. Logit, probit, and gommit models were used. We also used McFadden's coefficient of determination, Likelihood-ratio, Kolmogorov-Smirnov test, Hosmer-Lemeshow test, error distribution graphs, and Pearson's correlation coefficient.

Besides, we calculated the marginal effects. The Student's t-test was used to assess the statistical significance of differences between samples.

To assess the effectiveness of treatment, the Cortina criteria (normal level of IGF-1 and growth hormone level after oral glucose tolerance test less than 1 μg/L) were used.

The average age of the patients was 46.03 ± 0.71 years. Endosellar adenomas were observed in 60% of cases, endo-suprasellar adenomas in 11% of cases, and endo-laterosellar adenomas also in 11% of cases. Endo-supralaterosellar tumor was observed in 8% of cases, endo-infrasellar in 10% of cases. In addition, 27 patients were admitted with a diagnosis of the condition after removal of pituitary adenoma, and in 1 case infrasellar adenoma was observed. Only 38 patients received drug therapy (SSA) before the operation, 1 patient had previously received radiation therapy.

RESULTS

There was a positive trend in the level of growth hormone (GH) and IGF-1. We noted that in the group of patients with surgical treatment, the level of GH was higher than in the group of radiation therapy (34.69 ± 2.04 ng/ml versus 26.97 ± 6.47 ng/ml).

In 93% of cases, after surgery, there was an improvement, in 4% there were no changes, and in 1% there was deterioration, recovery, and death (Fig. 1).

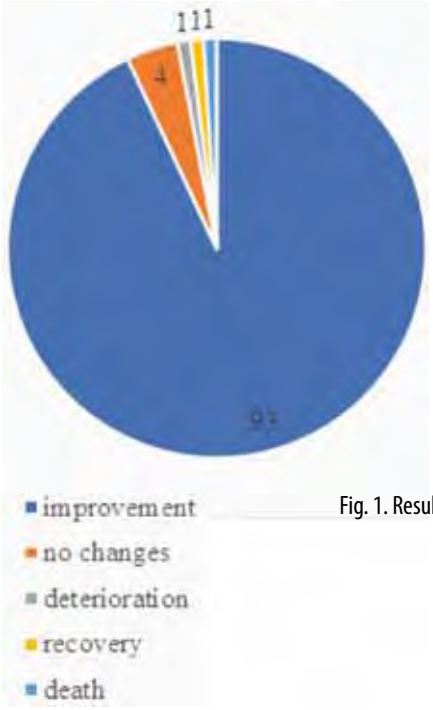

Fig. 1. Results of treatment, %

Before surgery, the level of GH was 34.69 ± 2.04 ng/ml, 12 months after surgery — 5.16 ± 0.35 ng/ml. We observed the normalization of the level of GH 12 months after the operation in 43% of patients.

In the group of patients with surgical treatment, the level of IGF-1 was lower than in the group of radiation therapy (619.08 ± 16.84 ng/ml versus 681.73 ± 27.22 ng/ml). Before surgery, the IGF-1 level was 619.08 ± 16.84 ng/ml, 12 months after surgery — 115.44 ± 4.48 ng/ml. We observed the normalization of the IGF-1 level 12 months after surgery in 41% of patients. A similar level of remission can be observed in other studies. So, Belaja J.E. et al. note that surgical treatment as the first line is 40.47% effective in achieving remission ($p < 0.01$) [1].

As a result of the study, we noted a statistically significant decrease in the levels of GH and IGF-1 against the background of surgical treatment 12 months after the operation ($p < 0.05$).

In addition, we noted a statistically significant decrease in the level of GH against the background of radiation therapy after 12 months ($p < 0.05$). Before treatment, the level of GH was 26.97 ± 6.47 ng/ml, 12 months after RT — 3.37 ± 0.82 ng/ml. We observed the normalization of the level of GH after 12 months in 38% of patients.

Before RT, the IGF-1 level was 681.73 ± 27.22 ng/ml, 12 months after RT — 130.39 ± 9.74 ng/ml. We observed the normalization of the IGF-1 level 12 months after RT in 43% of patients.

We also found a negative correlation between the level of GH before treatment and age ($r = -0.461$, $p < 0.01$). Consequently, at a younger age, higher levels of GH are noted. A similar connection is reported in the work by Molitvoslavova N.N. [2].

To optimize the treatment of acromegaly, we analyzed the key factors of the effectiveness of combination therapy. The results showed that the most significant factor was postoperative SSA therapy ($p < 0.05$). In addition, preoperative SSA therapy, tumor size, and extrasellar spread are significant factors.

DISCUSSION

Similar results were obtained by Carlsen S. M. et al. [3]. 62 patients took part in their study. The patients were divided into 2 groups: a group without pretreatment ($n = 30$) and a group with pretreatment with octreotide ($n = 32$) at a dose of 20 mg intramuscularly every 28 days for 6 months before transsphenoidal surgery. The results were assessed 3 months after the operation, mainly in terms of IGF-1 levels. As a result, 45% of pretreated patients versus 23% of patients undergoing direct surgery were cured ($p = 0.11$). At the same time, 20% of patients with microadenomas who received pretreatment were cured versus 60% using direct surgery ($p = 0.52$). 50% of pretreated patients with macroadenomas were cured, and 16% of patients with macroadenomas underwent direct surgery ($p = 0.017$).

Thus, six months of preoperative octreotide treatment may improve the surgical cure rate in patients with macroadenomas.

Fougner S. L. et al. [4] in their study also divided patients with acromegaly into 2 groups: the direct surgery group ($n = 30$) and the group with pretreatment with octreotide LAR for 6 months ($n = 32$). The analysis of the treatment results was carried out 1 and 5 years after the operation. The criteria for cure were normal IGF-1 levels and normal IGF-1 levels on an oral glucose tolerance test. 38% of macroadenomas were cured in the pretreatment group with octreotide versus 24% in the direct surgery group 1 year after surgery ($p = 0.27$) and 41% versus 27% of macroadenomas, respectively, 5 years after surgery ($p = 0.34$).

In addition, the results of our study are supported by two other prospective randomized studies showing the advantage of preoperative SSA treatment by doubling the remission rate and higher remission for tumors with invasion of the cavernous sinus [5, 6].

We also noted a statistically significant decrease in GH and IGF-1 levels 12 months after RT ($p < 0.05$). We found that the percentage of patients in remission usually increases with time after RT. For example, in the work of Powell J. S. et al. [7], 9 out of 13 patients (69.2%) observed at least 6 years after radiation therapy had normal IGF-1 levels without drug therapy. In 26 patients, IGF-1 levels decreased from 268 ± 32% (from the upper limit of normal) to 122 ± 12% after radiation therapy ($p < 0.001$).

The frequency of remission after different forms of radiation therapy probably differs [7], but the number of patients in each group and the number of follow-up periods in our study were very different. Therefore, we did not get a statistically significant difference between the groups.

In the Powell J. S. et al. [7] study, IGF-1 normalization was achieved in 14 out of 32 (43.7%) patients after remote radiation therapy (the average follow-up period was 5.6 years), in 3 out of 6 (50%) after stereotactic radiosurgical interventions (the average follow-up period was 2.9 years), in none of 4 patients after gamma knife LT (the average follow-up period was 1.2 years) and in none (1 patient) 3.6 years after proton beam radiotherapy.

In our study, hypopituitarism after RT was observed in 13% of patients. At the same time, we did not observe the development of new visual anomalies or secondary malignant neoplasms of the brain. In a study by Powell J. S. et al. [7] before receiving radiation therapy, 11 of 43 patients (25.6%) had a deficiency of at least 1 pituitary hormone, and 2 had panhypopituitarism. Pituitary hormone deficiency developed after radiation therapy in 13 of 41 patients (31.7%).

According to Minniti G., Scaringi C., Enrici R. M. [8], the main complication of radiation therapy is hypopituitarism, which is observed in 0–47% of patients. Pollock et al. [9] in their study noted that one-third of 39 patients with acromegaly had new hormone deficiencies after stereotactic radiosurgery (SRS), with a frequency of new hormone deficiencies in the anterior pituitary gland of 10% after 2 years and 33% after 5 years. In a series of 95 patients, hormone deficiency was observed in 5% 12 months after SRS but increased to more than 1/3 in patients with follow-up for more than 49 months. A similar incidence of hypopituitarism (20–40%) after 5 years has been observed in several other studies [10, 11]. Thus, we can assume that the incidence of this complication increases over time.

To optimize the treatment of acromegaly, we analyzed the key factors of the effectiveness of RT. As a result, it was revealed that the most significant factor in the positive outcome of RT is the administration of SSA after therapy ($p < 0.05$). Aggressive pituitary tumors with invasion of the surrounding structures, a high baseline IGF-1 level, an unfavorable histological picture, macroadenomas, a pretreatment GH level above 10 μg/L, and extrasellar tumor spread were associated with a less favorable RT outcome. For comparison, there are no similar data or research results on RT in the available literature.

CONCLUSION

The analysis made it possible to conclude that for patients with microadenomas of the pituitary gland and tumors of small sizes, with the absence of extrasellar growth, it is advisable to undergo surgical treatment, which has high efficiency in achieving remission of acromegaly. In agromegalic patients with pituitary macroadenomas and extrasellar spread, in most cases, combined treatment is necessary (therapy with SSA and/or radiation therapy). To increase the effectiveness of treatment in patients with macroadenomas and extrasellar tumor spread, it is advisable to use SSA therapy before and after the operation. Subsequent SSA therapy is required to improve the effectiveness of radiation therapy.

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