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About effectiveness of treatment by somatostatin analogues of patients with non-functional pituitary adenomas on the base of study of expression somatostatin receptor isoforms

Annotation

The aim of study is to analyze the effectiveness of treatment by somatostatin analogues (Sandostatin-LAR) in patients with non-functional pituitary adenomas (NFPA) on the base of expression somatostatin receptor isoforms SSTR3 and SSTR5.

Material and methods: A total of 272 patients with macro- and giant inactive pituitary adenomas based on the analysis of pro- (151 patients) and retrospective (121 patients) studies of the frequency of macro- and giant NFPA.

According to the size of the pituitary adenoma, prospective patients (151 patients) were divided into 2 groups: Group 1 - patients with macro- NFPA - 55 people, Group 2 - patients with giant NFPA - 96 people.

All patients underwent examinations, including examination of the fundus, measurement of visual fields every 3 months, studies of the levels of STH, IGF-1, LH, FSH, ACTH, TSH, prolactin, free thyroxine, cortisol, as well as immunohistochemical studies of operated patients.with determination of expression levels of Ki67, p53, expression somatostatin receptor isoforms SSTR3 and SSTR5.

Results: It was established that in 10 (50%) of 20 patients examined by IHC, expression of SSTR3 and SSTR5 isoforms of somatostatin receptors was established. At the same time, in 3 (30%) of 10 patients after 3 months of treatment with Sandostatin-Lar, a reliable reduction in the volume of the pituitary tumor was noted, while in 5 (50%) stabilization of the process was noted, and in 2 (20%) a relapse of growth was observed.

The clinical immunohistochemical study showed that patients with giant NFPA are recommended to undergo not only a study of Ki67 proliferation markers in the postoperative period; p53, but also the level of expression of somatostatin receptor isoforms SSTR3 and SSTR5 to justify further pathogenetic treatment with somatostatin analogues (Sandostatin-Lar).

Conclusions: 1.Analysis of SSTR subtypes is an argument in favour of introduction of novel broad-spectrum SSA that may be more effective in the treatment of NFPA. 2. In 10 patients who received Sandostatin Lar therapy, 3 months after TPA, stable preservation of the average size of the pituitary gland is observed. While in the 2nd group - without Sandostatin Lar - a tendency towards tumor growth is observed ($p<0.005$).

Keywords: macro- and giant pituitary adenomas, non-functional pituitary adenomas, SSTR3 and SSTR5

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Background

Pituitary adenomas (PA) are benign tumors adenohypophysis, which account for approximately 15% of all intracranial tumors and are responsible for approximately 25% of all surgical resections of brain tumors. Among them, NFPA may occur in 1 in 1,064 individuals with a frequency of 80-90 per 100,000 in the general population. IPA are benign tumors of the pituitary gland that arise from adenohypophyseal cells and make up one third of all pituitary adenomas.[1]

Non-fuctional pituitary adenomas (NFPA) are associated with decreased quality of life, increased incidence of comorbidities, and increased mortality. They are a benign group of neoplasms that may or may not secretetropic hormones, depending on the cell of origin. Along with this, the pathogenesis and development of giant NFPA s, often diagnosed at the latest stages of the disease, is poorly understood due to low symptoms clinics. Their postoperative treatment still remains a big problem, having a tendency to re-growth in 30-40% of cases. In addition, there is no consensus regarding optimal pre-, peri-, and postoperative management, such as the timing, frequency, and duration of endocrine, radiological, and ophthalmological evaluations, as well as the management of small tumor remnants or tumor recurrence.[2]

Despite the relevance of this study, there is currently no algorithm for correcting hormonal disorders in patients with macro- and giant NFPA in the early and late postoperative periods, taking into account immunohistochemical features. The reasons for the continued growth of NFPA and the risk factors that determine it, as well as the tactics of surgical or conservative treatment in these cases have not been established. The question that needs to be addressed is whether and how the treatment of macro and giant NFPA will change with precise

immunohistochemical diagnosis and determination of the expression of certain receptors somatostatin. The above was the reason for this study.[1]

The expression of somatostatin receptors (ssts) on human tumours is the basis for the successful therapeutic and diagnostic application of somatostatin analogues. Manipulation of sst expression might improve the uptake of radioligand in in vivo scintigraphy of human sst-positive tumours, as well as the potential success of radiotherapy using of SRIF analogues.[3-7]

Non-functioning pituitary adenomas (NFPA) are often diagnosed late as invasive macroadenomas. The surgical resection is usually incomplete and about 50% of patients require additional surgery. Recent data suggest that somatostatin analogues (SSA), so important in the pharmacotherapy of acromegaly, can also be effective in the management of NFPA.[8,9]

Authors noted that in patients with large and invasive NFPA without neuro-ophthalmic abnormalities and a low likelihood of complete surgical resection, which are associated with mild hyperprolactinemia and positive tumor uptake on SSTR scintigraphy, combined treatment with DA and SSA may be considered as an initial therapeutic alternative to surgery.[4,10]

All of the above formed the basis for this study.

The aim of study is to analyze the effectiveness of treatment by somatostatin analogues (Sandostatin-LAR) in patients with non-functional pituitary adenomas on the base of expression somatostatin receptor isoforms SSTR3 and SSTR5.[11-13]

Material and methods

A total of 272 patients with macro- and giant NFPA based on the analysis of pro- (151 patients) and retrospective (121 patients) studies of the frequency of macro- and giant NFPA for the period 2021-2023 according to requests from three leading centers in Tashkent: RSSPMC Endocrinology of the Ministry of Health of the Republic of Uzbekistan named after academician Ya.Kh. Turakulov, Scientific Center of Neurosurgery of the Ministry of Health of the Republic of Uzbekistan and Scientific Center of Emergency Medical Care of the Ministry of Health of the Republic of Uzbekistan.

According to the size of the pituitary adenoma, prospective patients (151 patients) were divided into 2 groups: Group 1 - patients with macro- NFPA - 55 people, Group 2 - patients with giant NFPA - 96 people (Figures 1&2).

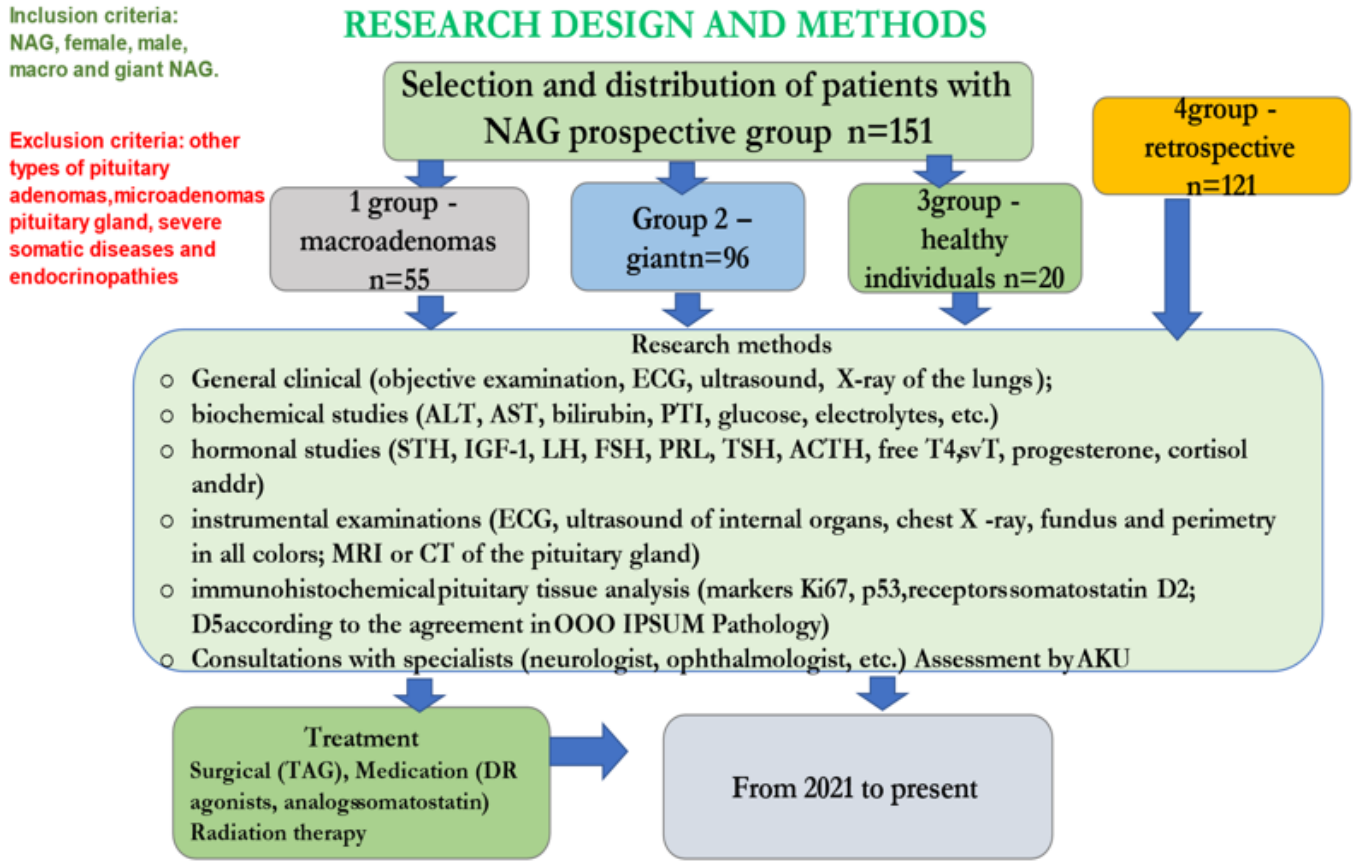

Figure 1 Study design.

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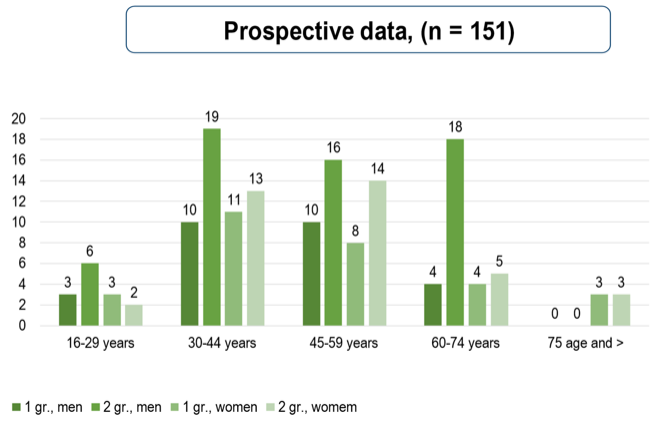

Figure 2 Distribution of patients by gender and age.

All patients underwent examinations, including examination of the fundus, measurement of visual fields every 3 months, studies of the levels of STH, IGF-1, LH, FSH, ACTH, TSH, prolactin, free thyroxine, cortisol, as well as immunohistochemical studies of operated patients.with determination of expression levels of Ki67, p53, expression somatostatin receptor isoforms SSTR3 and SSTR5. In addition, the AKU scale (2022) was introduced for the first time to predict the degree of tumor removal in the preoperative period.

Statistical analysis. The obtained data were processed using the computer programs Microsoft Excel and STATISTICA-6. The reliability of differences in quantitative indicators (n>12) was determined using the Wilcoxon method for unrelated ranges; to determine the reliability of small samples (n<12), the nonparametric Fisher component randomization criterion for independent samples was used; for qualitative values, the Fisher-Irwin exact test was used. Differences between groups were considered statistically significant at P<0.05, correlation analysis was carried out using the nonparametric Spearman rank correlation method.

Results

We performed an analysis of neuroendocrine disorders in both groups (Fig. 1). It was found that the most common were functional hyperprolactinemia 34/91, secondary hypogonadism 23/88, panhypopituitarism - 6/70, hypopituitarism (STH, LH, FSH, IGF-1, TSH,ACTH, free thyroxine, E2, testosterone, cortisol, etc) – 49/67, bitemporal hemianopsia – 45/49, secondary amenorrhea – 22/29,isolated (GHD) growth hormone deficiency – 11/56, as well as endocrine encephalopathy – 9/26, obesity – 11/27 cases in groups 1 and 2, respectively. Less frequently observed were such disorders as postoperative panhypopituitarism - 9/11, secondary osteopenia - 5/17, Babinski's symptom - 0/3, secondary hypocorticism - 0/45 cases, respectively. Thus, there was a polymorphism of symptoms.

Disorders in the form of secondary osteopenia, endocrine encephalopathy, were detected only in patients of the 2nd group. Thus, the most pronounced neuroendocrine and ophthalmological diseases were found in patients of the 2nd group.

As can be seen from the data in Table 1, the levels of tropic hormones (LH, FSH, STH) in Group 1 were significantly reduced (p < 0.005) compared to the control group against the background of significantly increased PRL and low free testosterone (p < 0.005). The levels of free thyroxine and ACTH were within normal limits.

Table 1 Dynamics of indicators patients with NFPA with Sandostatin-Lar and without it 3-6 months after treatment.

Number of patients	Pituitary gland size after treatment	Pituitary gland size after treatment in 3 months	Pituitary gland size after treatment in 6 months	STH Blood after treatment	STH after treatment in 3 months	STH after treatment in 6 months	IGF-1 after treatment in 3 months	IGF-1 after treatment in 6 months
Patients with NFPA with Sandostatin-Lar (n= 10)	2.5 x 2.0 x 1.8 cm	2.4 x 2.0 x 1.7 cm	2.3 x 1.9 x 1.8 cm	1.1±0.4	1.4±0.2	1.4±0.2	254.8±12.2	267.6±11.2
Control (n= 10)	2.4 x 2.1 x 1.7 cm	2.6 x 2.5 x 1.8 cm	2.9 x 2.7 x 1.9 cm	1.2± 0.06	1.3± 0.07	1.2± 0.04	312± 8.9	312±8.9
Norm	1.0x1.0x1.0			2-5ng/ml			200-400ng/ml	
R	<0.005	<0.005	<0.005	>0.05	>0.05	>0.05	>0.05	>0.05

Note: p – significance of differences compared to the norm

They were characterized by the clinical picture of hypogonadotropic hypogonadism.

The most significant decrease in the average values of basal levels of plasma tropic hormones - STH, LH, FSH, ACTH was noted in patients of the 2nd group. They were characterized by a clinical picture of hypogonadotropic hypogonadism, secondary hypocorticism. Thus, the levels of cortisol and IGF-1 were significantly reduced in these patients, while ACTH and IGF-1 were within normal values in patients of group 1.

In addition, based on the comparative characteristics of the size of the sellar tumor and the level of STH, we identified a tendency for the basal level of STH in the plasma to decrease as the size of the sellar tumor increased.

Thus, in general, the average values of pituitary tropic hormones decreased in patients of both groups, but most reliably in patients with giant pituitary adenomas. In patients with giant pituitary adenoma, a decrease in the level of STH, FSH, LH (45%) is primarily observed. The most pronounced neuroendocrine and ophthalmological disorders

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occurred in patients of the 2nd group with giant pituitary adenomas. Obvious neurological disorders in the form of diencephalic-stem disorders (pyramidal symptoms, decreased reflexes and diffuse muscle tone) were observed in patients with a total growth variant, with retrosellar growth and with invasion into the brain.

We also aimed to study the degree of expression of somatostatin receptor isoforms (SSTR1–5) for more effective treatment with somatostatin analogues. It was found that somatostatin receptor isoforms 3 and 5 (SSTR5, SSTR3) were present at the highest level in the NFPA patients we studied, followed by SSTR2, SSTR1, SSTR4.

There are studies showing that SSTR5 and SSTR3 are the most frequently expressed SSTR subtypes in NFPA, supporting the potential role of SSTR subtypes in stabilizing the tumor remnant from NFPA (84, p.571-8).Thus, the authors conclude that SSTR3 and SSTR5 in NFPA may be a potential target for somatostatin analogues (Sandostatin-Lar).

So, it was established that in 10 (50%) of 20 patients examined by IHC, expression of SSTR3 and SSTR5 isoforms of somatostatin receptors was established. At the same time, in 3 (30%) of 10 patients after 3 months of treatment with Sandostatin-Lar, a reliable reduction in the volume of the pituitary tumor was noted, while in 5 (50%) stabilization of the process was noted, and in 2 (20%) a relapse of growth was observed.

Next we performed an analysis of IHC studies regarding the levels of Ki67; p53 markers and performed a comparative analysis with the expression of somatostatin receptor isoforms of SSTR3 and SSTR5. It was found that 3 patients with tumor shrinkage after Sandostatin treatment had normal Ki67 levels (< 2%), while 2 patients with tumor recurrence had elevated levels (> 4%).

Thus, the clinical and immunohistochemical study showed that patients with giant NFPA are recommended to undergo not only a study of proliferation markers Ki67; p53, but also the level of expression of somatostatin receptor isoforms in the postoperative period. SSTR3 and SSTR5 to justify further pathogenetic treatment with somatostatin analogues (Sandostatin-Lar).

The next stage of our research was to study the efficacy of Sandostatin-Lar in patients with giant NFPA after transnasal pituitary adenomectomy (TPA) in comparison with a similar group who did not receive conservative therapy after TPA. A total of 150 transnasal pituitary adenomectomy were performed (Dr. Fayzullaev R.B., Prof. Makhkamov K.I., Ph.D. Akbutaev A.M., and Prof. Michael Powell from the UK). Repeated pituitary surgeries were performed in 5 patients (7.3%). 87 (57.6%) patients received radiation therapy of the pituitary gland after TAH.

From these patients, we selected 20 patients (13 men and 7 women) with NFPA. Subgroup 1 - 10 patients with NFPA in the postoperative period received Sandostatin-Lar 20 mg once every 4 weeks, intramuscularly, for 3-6 months. Subgroup 2 did not receive such treatment.

Table 1 shows the dynamics of MRI parameters of the pituitary gland and hormonal data of 10 patients without GHR after 6 months of observation.

As can be seen from the data presented in Table 1, in 10 patients receiving Sandostatin Lar therapy, stable preservation of the average size of the pituitary gland is observed. While in group 2 - without Sandostatin Lar - a tendency towards tumor growth is observed ($p<0.05$).

Thus, our results showed that all patients with giant pituitary adenomas have neuroendocrine disorders of varying severity, worsening as the pituitary tumor grows. The nature of the disorders has a number of specific (bitemporal gemianopsiya, scotomas, hypopituitarism, cranial nerve damage) and non-specific symptoms (pyramidal symptoms, diffuse decrease in muscle tone, reflexes) depending on the side of growth, tumor size. The most pronounced neuroendocrine, neurological and ophthalmological disorders were observed in patients with a total growth variant in patients of 2 groups.

Thus, a clinical immunohistochemical study showed that patients with giant NFPA are recommended to undergo not only a study of Ki67 proliferation markers in the postoperative period; p53, but also the level of expression of somatostatin receptor isoforms SSTR3 and SSTR5 to justify further pathogenetic treatment with somatostatin analogues (Sandostatin-Lar).

Conclusions

Analysis of SSTR subtypes is an argument in favor of introduction of novel broad-spectrum SSA that may be more effective in the treatment of NFPA. 2. In 10 patients who received Sandostatin Lar therapy, 3 months after TPA, stable preservation of the average size of the pituitary gland is observed. While in the 2nd group - without Sandostatin Lar - a tendency towards tumor growth is observed ($p<0.005$).

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