CLINICAL FEATURES AND THERAPEUTIC OUTCOMES OF ACROMEGALY DURING THE RECENT 5 YEARS: SINGLE CENTRE EXPERIENCE

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INTRODUCTION Acromegaly is a chronic disorder characterised by hypersecretion of growth hormone (GH), which leads to the increased production of IGF-I (1). In the majority of patients (>95%) it results from a GH-secreting pituitary adenoma (1). With the incidence of 3 to 4 new cases per million and the prevalence of 40 to 125 per million, acromegaly is a rare disease (2). The aim of the present study was to determine clinical characteristics, treatment modalities and disease outcomes in patients with acromegaly followed-up at a single centre during recent five years. We also aimed to investigate association between somatostatinanalog (SSA) treatment and IGF-1 level.

PATIENTS AND METHODS It was a retrospective study conducted in the centre of Endocrinology in Vilnius University hospital Santariškių klinikos, a tertiary referral centre for endocrinology and diabetes mellitus. Data of 44 patients who were diagnosed, treated or followed-up because of acromegaly between 2007 and 2012 were extracted from the hospital's electronic database. In all cases diagnosis of acromegaly was established on the basis of characteristic clinical features, elevated for age and gender IGF-I, and failure to suppress GH < 3 mIU/l after 75 g oral glucose tolerance test (OGTT) or elevated random GH level. Magnetic resonance imaging (MRI) was performed in all patients except one in whom computerized tomography was done because of contraindications to MRI. Tumor size was classified as micro- (<10 mm) and macroadenoma. The following data were collected from medical records: demographic features, date of diagnosis, tumor size, hormonal data (initial and follow-up IGF-I and GH levels). Details on treatment were also collected: number and method of surgical treatment, previous and current medical therapy and whether it was primary therapy, radiotherapy date and method. Co-morbidities related to acromegaly or to the treatment were also registered.

Disease remission was defined according to the latest guidelines (3): normal age- and gender-adjusted IGF-I, and nadir GH < 1.2 mIU/l after 75 g OGTT or random GH < 3 mIU/l. Partial disease control was documented according local acromegaly management guidelines in cases when IGF-I level dropped, but remained <30% above upper limit of normal (adjusted for age and gender), and random GH was below 7.5 mIU/l. Uncontrolled disease was defined in cases when IGF-I level was elevated >30% above age- and gender-adjusted upper limit of normal and random GH was above 7.5 mU/l. In case of discordant IGF-I and GH results, a patient was assigned to one of study groups according to worse result.

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) 15.0 software. The chi-square and ANOVA tests were used to compare study groups. Relationships between GH and IGF-1 levels were assessed by calculating Spearman correlation coefficient. Stepwise multivariate regression analysis was used to assess determinants of IGF-1 level.

R E S U L T S

DEMOGRAPHICS AND CLINICAL DATA 44 patients (24 newly diagnosed and 20 followed-up or treated) were included in the analysis. Patient population consisted of 15 males and 29 females with a mean age at diagnosis of 53.5±13.3 years. All cases except one (empty sella) were caused by pituitary adenomas, of which 67.5% were macroadenomas and 32.5% were microadenomas(data about pituitary adenoma preoperative size were not found in the charts in three cases). The most common co-morbidities in patients with acromegaly were nodular thyroid disease (86.0%), arterial hypertension (86.0%), type 2 diabetes mellitus (27.9%), arthralgia (25.6%) and cardiac arrhythmias (25.0%) *(table 1)*.

Table 1. Characteristics of study population

Patient population	N (%)
Male	15/44 (34.1%)
Female	29/44 (65.9%)
Age at diagnosis (yr) (mean ± SD)	53.5±13.3
Tumor characteristics	
Microadenoma	13/40 (32.5%)
Macroadenoma	27/40 (67.5%)
Co-morbidities	
Visual field defects	7%
Hypopituitarism (%)	4.7%
Hyperprolactinemia (%)	14%
Nodular thyroid disease (%)	86.0%
Impaired glucose tolerance (%)	18.6%
Type 2 DM (%)	27.9%
Arthralgia (%)	25.6%
Arterial hypertension (%)	86.0%
Coronary heart disease (%)	16.3%
Cardiac arrhythmias (%)	25.0%

Table 2. Disease outcome in study population

Outcome	N (%)
Remission	16/42 (38.1%)
Partial control	12/42 (28.6%)
Uncontrolled	14/42 (33.3%)

Table 3. Treatment modalities and disease outcomes

Transphenoidal surgery	**29/42 (69.0 %)**
Remission	14/29 (48.3%)
Uncontrolled	15/29 (51.7%)
Primary medical therapy	**11/42 (26.2%)**
Remission	2/11 (18.2%)
Partial control	3/11 (27.3%)
Uncontrolled	6/11 (54.5%)
Primary radiotherapy	**1/42 (2.4%)**
Combination therapy	**15/42 (35.7%)**
Remission	2/15 (13.3%)
Partial control	6/15 (40.0%)
Uncontrolled	7/15 (46.7%)

RESULTS OF TREATMENT Based on the latest GH and IGF-1 results, in the whole study population the outcomes were: 38.1% cured or controlled, 28.6% partially controlled, and 33.3% uncontrolled *(table 2)*. In 25% of the study population latest GH and IGF-1 were discordant.

Transsphenoidal operation was applied as the first-line therapy in 29 (69%) patients and it led to disease remission in 14 (48.3%) of them (table 3). Primary medical therapy with low to moderate doses of SSAs, cabergoline or bromocriptinewas administered in 11 (26.2%) of cases due to contraindications or refusal of surgery. One patient was not administered any treatment because of severe comorbidities, one was treated with primary radiotherapy. In two cases data about treatment is not available as the patients are lost to follow-up. Of surgically treatedpatients,15 (51.7%)were diagnosed with disease recurrence and received medical therapywith SSA, cabergoline or bromocriptine. Radiotherapy as a third-line treatment was applied in the 4 (17.2%) patients with a postoperative desease recurrence. Control and partial control were achieved in 2 (18.2%) and 3 (27.3%) cases in primary medical therapy group, and in 2 (13.3%) and 6 (40.0%) cases in combined therapy (surgery and medical therapy with / without radiotherapy) group *(table 3)*.

IGF-1 AND GH LEVELS IN MEDICALLY TREATED PATIENTS Although we observed higher mean observational period IGF-1 in the primary medical treatment group (672.8 [534.1; 811.5] µg/l) as compared to combined (surgery and medical therapy with / without radiotherapy) treatment group (556.4 [412.8; 700.0] µg/l), the difference did not reached statistical significance (p=0.148) *(figure 1)*. Median GH in these groups were also not statistically significantly different (22.0[3.3; 40.8]mIU/l vs. 13.0[6.9; 19.1]mIU/l, p=0.281) *(figure2)*.

Figure 1. Observational period mean IGF-1 in medical treatment and combination treatment groups, p=0.148

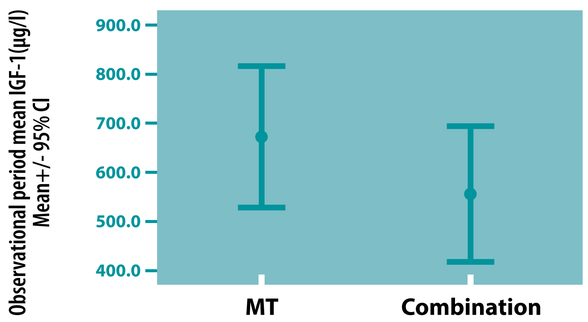
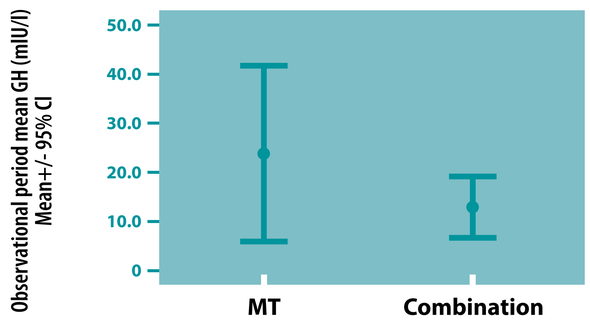


Figure 2. Observational period mean GH in medical treatment and combination treatment groups (P=0.281)



DETERMINANTS OF IGF-1 VARIABILITY

We observed stronger correlation of IGF-1 and GH in samples taken without medical therapy (rs=0.667) than in those taken while on SSA treatment (rs=0,416). In our regression analysis age, gender and GH level, but not SSA treatment, were significan determinants of IGF-1 level variability (B = 67.2 (-31.4;165.9); p=0.181).

CONCLUSIONS **Acromegaly is associated with an increased morbidity. Control of the disease remains a challenge in our institution as one third of the patients remain uncontrolled despite availability of transsphenoidal surgery, SSA, dopamine agonists and conventional radiotherapy. SSA may have direct effect on IGF-1 secretion, but this association remains to be further studied.**

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