



Acromegaly treatment in Romania. How close are we to disease control?

Leczenie akromegalii w Rumunii. Jak blisko jesteśmy uzyskania kontroli nad chorobą?

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Abstract

Introduction: In Romania, no nationwide data for acromegaly treatment and control rate are available. Our objective was to assess the acromegaly control rate in a tertiary referral centre, which covers an important part of Romanian territory and population of patients with acromegaly.

Materials and methods: We reviewed the records of all 164 patients (49 males and 115 females; median age 55 [47, 63.5] years) with newly or previously diagnosed acromegaly, who have been assessed at least once in our tertiary referral centre between January 1, 2012 and March 31, 2016. This sample represents 13.6% of the total expected 1200 Romanian patients with acromegaly and covers 82.9% of the counties in Romania. Control of acromegaly was defined as a random serum growth hormone (GH) < 1 ng/mL and an age-normalised serum insulin-like growth factor-I (IGF-I) value. The GH and IGF-I values used for calculation of the control rate were those at the last evaluation. The same assays for GH and IGF-I measurement were used in all patients.

Results: There were 147 treated and 17 untreated patients. Of the 147 patients assessed after therapy, 137 (93.2%) had pituitary surgery, 116 (78.9%) were on medical treatment at the last evaluation, and 67 (45.5%) had radiotherapy. Seventy-one (48.3%) had a random GH < 1 ng/mL, 54 (36.7%) had a normalised, age-adjusted IGF-I, and 42 (28.6%) had both normal random serum GH and IGF-I.

Conclusions: In Romania, acromegaly benefits from the whole spectrum of therapeutic interventions. However, the control rate remains disappointing. (*Endokrynol Pol* 2017; 68 (5): 519–523)

Key words: acromegaly, Romania, treatment, control rate

Streszczenie

Wstęp: W Rumunii nie są dostępne ogólnokrajowe dane dotyczące leczenia akromegalii ani wskaźnika kontroli choroby. Badanie przeprowadzono w celu oceny wskaźnika kontroli akromegalii w ośrodku referencyjnym trzeciego stopnia, który obejmuje opieką zdrowotną znaczną część obszaru Rumunii i populacji pacjentów z akromegalią.

Materiał i metody: Autorzy dokonali przeglądu danych medycznych wszystkich 164 chorych [49 mężczyzn i 115 kobiet; mediana wieku 55 lat (47; 63,5)] z noworozpoznaną lub wcześniej zdiagnozowaną akromegalią, których przynajmniej jednokrotnie zbadano w ośrodku referencyjnym trzeciego stopnia (miejsce pracy autorów) w okresie od 1 stycznia 2012 roku do 31 marca 2016 roku. Ta próba stanowiła 13,6% całej rumuńskiej populacji chorych na akromegalię szacowaną na 1200 osób i reprezentowała 82,9% okręgów administracyjnych w Rumunii. Kontrolę akromegalii definiowano jako stężenie przygodne hormonu wzrostu (*growth hormone*, GH) w surowicy wynoszące poniżej 1 ng/ml oraz normalizacja odpowiednio do wieku stężenia insulinopodobnego czynnika wzrostu 1 (*insulin-like growth factor-1*, IGF-1) w surowicy. Do obliczenia wskaźnika kontroli choroby stosowano wartości GH i IGF-1 z ostatnich pomiarów. U wszystkich pacjentów używano tych samych testów do pomiarów GH i IGF-1.

Wyniki: Badanie obejmowało 147 chorych poddanych leczeniu i 17 chorych nieleczonych. Spośród 147 chorych ocenianych po terapii, u 137 (93,2%) zastosowano leczenie chirurgiczne, 116 (78,9%) w momencie ostatniej wizyty kontrolnej stosowało leczenie farmakologiczne, a 67 (45,5%) poddano radioterapii. U 71 chorych (48,3%) przygodne stężenie GH w surowicy wynosiło poniżej 1 ng/ml, u 54 (36,7%) uzyskano normalizację stężenia IGF-1 skorygowanego względem wieku, a u 42 chorych (28,6%) uzyskano normalizację obu parametrów — GH i IGF-1.

Wnioski: W Rumunii u chorych na akromegalię stosuje się szerokie spektrum interwencji terapeutycznych, jednak wskaźnik kontroli choroby nadal pozostaje niezadawalający. (*Endokrynol Pol* 2017; 68 (5): 519–523)

Słowa kluczowe: akromegalia, Rumunia, leczenie, wskaźnik kontroli choroby

Introduction

Uncontrolled acromegaly is a well-known cause of increased morbidity and mortality [1]. Recent decades

have brought an improvement in acromegaly control, but, depending on the criteria used, it does not exceed 68–95% of patients after surgery [2] or 75–90% of patients on medical treatment with somatostatin ana-



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logues (SSA) [3] or pegvisomant [4]. Moreover, there is an important heterogeneity in acromegaly control rates between centres [5–7] or between industry-sponsored clinical trials and real-life studies [4, 8]. In addition, a significant number of patients need a multimodal treatment approach including surgery, various medical therapies, and radiotherapy. These patients are rarely involved in randomised clinical trials.

The best tool to measure nationwide success in the treatment of acromegaly is a country-specific database or register covering as many patients as possible over a long period of time. At present, multiple country databases are functional throughout Europe [5–7, 9, 10]. Unfortunately, Romania does not have such a register, and no nationwide data for acromegaly treatment and control rate are available.

Our objective was to assess the acromegaly control rate in a tertiary referral centre, which covers an important part of Romanian territory and population of patients with acromegaly.

Materials and Methods

Subjects

Starting on January 1, 2012 the “C. I. Parhon” Institute of Endocrinology constantly used the same assays for serum growth hormone (GH) and insulin-like growth factor-I (IGF-I) measurement, according to the Endocrine Society Guidelines for Acromegaly [11]. Hence, we reviewed the charts of all patients with confirmed acromegaly, who were assessed at least once in our tertiary referral centre between January 1, 2012 and March 31, 2016. During this period we assessed 164 patients with newly or previously diagnosed acromegaly from 34 counties. There were 49 males and 115 females, with a median age of 55 (47, 63.5) years. As the prevalence of acromegaly is considered to be around 60 cases per million [12] for an estimated Romanian population of 20 million, our centre assessed 13.6% of the total expected 1200 Romanian patients with acromegaly. Our population covered 34 of the 41 Romanian counties (Bucharest and Ilfov county taken together), i.e. 82.9% (Fig. 1A).

Of the total 164 patients, 57 (34.7%) had newly diagnosed acromegaly. There were 15 males and 42 females with a median age of 55 (43.7, 60.5) years. At an estimated incidence of 3–4 cases per million [10, 12] due in the majority of cases to a GH-secreting pituitary adenoma, and occurring with a population prevalence of 60 per million and an incidence of 3–4 per million per year. Males and females appear to be equally affected with an average age of presentation of 44 years. Younger patients may have more aggressive tumours and higher GH concentrations. There is co-existent hyperprolactinaemia in about one third of cases, and

a variable proportion of [figure: see text] tumours appear to have activating mutations of the *gsp* gene or other genetic abnormalities. Acute complications such as carpal tunnel syndrome, sweating and obstructive sleep apnoea are usually readily reversible with treatment of the condition, but chronic complications such as hypertension, diabetes and heart disease are less readily corrected and post-treatment GH levels of < 2.5 µg/L (5 mU/L per year, Romania should have 60–80 new cases of acromegaly per year. The estimated incidence for the 51 months of the study is 13.4 new cases of acromegaly per year, 16.7–22.3% of the estimated Romanian patient population. This population covered 20 counties, 48.7% of Romanian territory (Fig. 1B).

Assays

Control of acromegaly was defined according to Endocrine Society guidelines [11]: a random serum GH < 1 ng/mL and an age-normalised serum IGF-I value. The GH and IGF-I values used for calculation of the control rate were those at the last evaluation.

Serum GH was measured using a chemiluminescence assay (Liaison, Sallugia, Italy). The assay is referenced to WHO Second International Standard 98/574 for somatropin (22-kDa recombinant DNA-derived materials). The functional sensitivity is 0.05 ng/mL, and the analytical sensitivity is 0.009 ng/mL.

Serum IGF-I was measured using a Liaison IGF-I chemiluminescence assay (DiaSorin, Sallugia, Italy). The assay is referenced to the 02/254 International Standard for Insulin-like Growth Factor-I NIBSC. The assay functional sensitivity is 15 ng/mL, and the analytical sensitivity is 3 ng/mL.

Statistics

Data are presented as number (percentage) or median (25th, 75th percentile). Wilcoxon test was used to test differences between paired groups. A *p* value less than 0.05 was considered statistically significant.

Results

Between January 1, 2012 and March 31, 2016 we assessed 164 patients with newly or previously diagnosed acromegaly. There were 147 treated and 17 untreated patients. Of the 147 patients assessed after therapy, 137 (93.2%) had pituitary surgery, 116 (78.9%) were on medical treatment at the last evaluation (51 on octreotide LAR, 33 on lanreotide PR or autogel, 15 on pegvisomant, 30 on cabergoline, and 10 were involved in clinical trials with SSA), and 67 (45.5%) had radiotherapy (11 low-voltage radiotherapy, 27 high-voltage radiotherapy, and 36 gamma-knife; seven patients had two different radiotherapies).

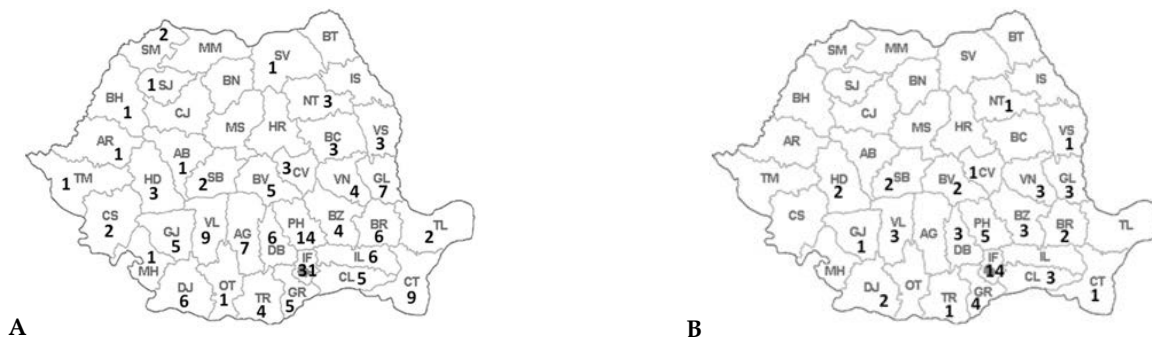


Figure 1. Geographical distribution of the prevalent (**1A**) and incident (**1B**) population of acromegalic patients from our centre between January 1, 2012 and March 31, 2016. The numbers represent individual patients from a particular county

Rycina 1. Rozkład geograficzny chorobowości (**1A**) i zapadalności (**1B**) w populacji chorych z akromegalią leczonych w ośrodku autorów w okresie od 1 stycznia 2012 roku do 31 marca 2016 roku. Przedstawiono liczę pacjentów z poszczególnych okręgów

Of the 147 patients assessed after at least one treatment, 71 (48.3%) had a random GH < 1 ng/mL, 54 (36.7%) had a normalised age-adjusted IGF-I, and 42 (28.6%) had both normal random serum GH and IGF-I.

Between January 1, 2012 and March 31, 2016 we diagnosed 57 patients with acromegaly. Of these, 42 were also assessed after at least one treatment. Of the 42 treated patients 20 (47.6%) had a random GH < 1 ng/mL, 11 (26.2%) had a normalized age-adjusted IGF-I and 8 (19.0%) had both normal random serum GH and IGF-I. Treatment efficacy for different treatments can be found in Figure 2.

Forty-one patients diagnosed after January 1, 2012 were treated by surgery. Surgery normalised random GH in 10 patients (24.4%), IGF-I in six patients (14.6%), and both GH and IGF-I in four patients (9.7%). The median random serum GH was lowered by surgery from 8.7 (4.2, 22.4) ng/mL to 2.5 (1.2, 5.1) ng/mL ($p < 0.001$). Serum IGF-I was lowered by surgery from 3.6 (3.0, 4.2) X ULN to 2.6 (1.6, 3.4) X ULN ($p < 0.001$) (Fig. 3).

Somatostatin analogues were used in 26 patients not cured by surgery. SSA analogues normalised GH in 11 patients (42.3%), IGF-I in five patients (19.2%), and both GH and IGF-I in four patients (15.4%). In these 26 patients SSA lowered serum random GH from 3.1 (2.1, 5.9) ng/mL to 1.4 (0.8, 3.7) g/mL ($p = 0.009$). Serum IGF-I was lowered from 3.0 (2.5, 3.5) X ULN to 1.5 (1.0, 2.1) X ULN ($p < 0.001$) (Fig. 3).

Discussion

Our study presents the control rate of acromegaly in a sample of 164 patients assessed in a single tertiary centre between January 1, 2012 and March 31, 2016. Also, we present here the control rate and the GH and IGF-I lowering effect of different treatments in patients diagnosed after January 1, 2012. At an estimated prevalence of 60 cases per million and an estimated

incidence of 3–4 cases per million [10, 12] per year, this population represents 13.6% of the total population of acromegalic patients and 16.7–22.3% of patients with newly diagnosed acromegaly in Romania. To our knowledge, it is the largest study on acromegaly control rate in Romania.

Surgery was the mainstay of acromegaly treatment. In our study, 95.1% of treated patients had pituitary surgery, a slightly higher figure compared with data from national registries: 89.3% in Germany [5], 83.8% in Spain [9], 70.3% in UK [7], and 68% in Belgium [6]. Medical treatment for acromegaly came into widespread use in Romania only in the last 5–10 years and is reimbursed only in surgically treated patients, and this could explain the high percentage of surgery. On the other hand, 78.9% of patients were on medical treatment at the last evaluation (SSA, GH receptor antagonists, dopamine agonists, or clinical trials) as compared with 74.7% in Spain [9], 60.2% in UK [7], 58% in Belgium [6], and 42.6% in Germany [5]. The high percentage of patients on medical treatment in Romania is probably due to the very low cure rate of surgery (see below). Radiotherapy was used in 45.5% of patients as compared with 22.2% in Germany [5], 34% in Belgium [6], and 44.7% in UK [7]. In all of these countries the percentage of radiotherapy fell dramatically in recent decades, primary radiotherapy being practically absent. In Romania, of the 67 patients with radiotherapy, only seven (10.4%) were diagnosed after 2012, the remaining 60 (89.6%) being diagnosed prior to 2012.

We found an overall disease control rate (GH < 1 ng/mL and age-normalised IGF-I) of 28.6%. This would increase to 36.7% if only an age-normalised IGF-I were considered and to 48.3% if only random GH < 1 ng/mL were used to define disease control. The UK acromegaly Register [7] reported a rate of age-normalised IGF-I of 59% for patients assessed after 2000. The rate of GH and IGF-I control was 49%, but in this register normal GH

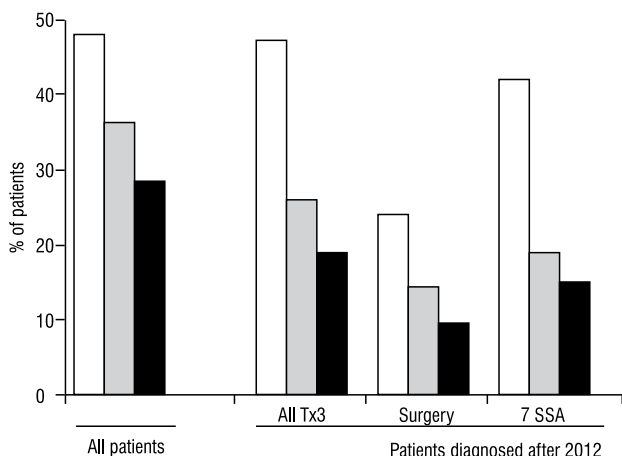


Figure 2. Percentages of patients with normalised random GH (white bars), IGF-I (grey bars), or GH and IGF-I (black bars) in all treated patients (n = 147) or patients diagnosed after 2012 (all treatments, n = 42; surgery, n = 41; somatostatin analogues, n = 26)

Rycina 2. Odsetek pacjentów z normalizacją stężeń hormonu wzrostu (growth hormone, GH) (białe słupki), insulinopodobnego czynnika wzrostu 1 (insulin-like growth factor-1, IGF-1) (szare słupki) oraz GH i IGF-1 (czarne słupki) w pomiarach przygodnych u wszystkich leczonych pacjentów (n = 147) oraz u pacjentów, u których rozpoznano chorobę po 2012 roku (wszystkie metody leczenia, n = 42; leczenie chirurgiczne, n = 41; analogi somatostatynny, n = 26)

was defined as < 2 ng/mL. The German Acromegaly Register [5] reported a rate of age-normalised IGF-I of 71.9%, a figure two times higher than in our results; GH data are not reported. The rate of age-normalised IGF-I was 56% in AcroBel [6] and 76% in the Spanish Acromegaly Registry [9]. Overall, the rates of disease control in patients from European national registers are 20–40% higher than in Romania, probably due to the poor result of surgery (see below) in our country. Also, the pre-treatment GH but not IGF-I levels are known to have an impact on the disease control rate of medical therapy [8, 13]. However, in the subgroup of patients from our study submitted to somatostatin analogues the pre-treatment GH and IGF-I levels were 3.1 ng/mL and 3.0 X ULN, lower than in this meta-analysis [13].

In the subgroup of patients diagnosed after 2012 surgery normalised GH, IGF-I, or both GH and IGF-I in 21.9%, 14.5%, and 9.7% of patients, respectively. The rate of normalised age-adjusted IGF-I by surgery alone is over 30% in national registers [5–7, 9]. This low control rate is unexpected because most of the surgical interventions on our patients were carried out in a university tertiary neurosurgical unit with more than 50 pituitary surgeries per year. The number of pituitary surgical interventions is a well-accepted and important factor in surgical success [14–16]. However, although active

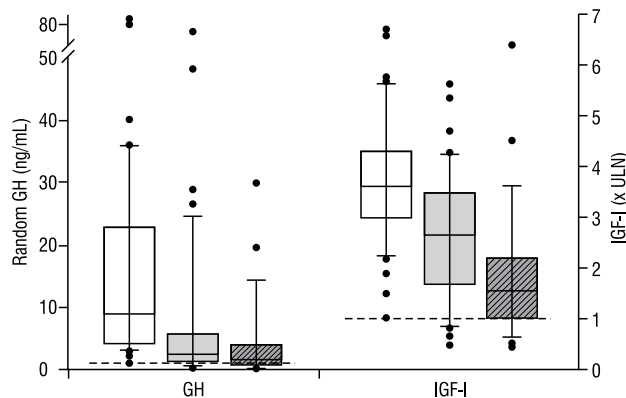


Figure 3. Effect of surgery (n = 41, grey bars) and somatostatin analogues (n = 26, shaded bars) compared with baseline (n = 41, white bars) on random serum GH (left Oy axis) and IGF-I (right Oy axis)

Rycina 3. Zmiana stężeń w surowicy hormonu wzrostu (growth hormone, GH) (lewa strona osi Y) i insulinopodobnego czynnika wzrostu 1 (insulin-like growth factor-1, IGF-1) (prawa strona osi Y) w pomiarach przygodnych pod wpływem leczenia chirurgicznego (n = 41, szare słupki) oraz terapii analogami somatostatynny (n = 26, zakreskowane słupki) w stosunku do stanu wyjściowego (n = 41, białe słupki)

postsurgical disease was the most frequent scenario, median random GH and IGF-I serum levels were significantly lowered by pituitary surgery.

Somatostatin analogues seemed to have a lower efficacy in our population compared with published national registers [5–7]. However, not all patients were on maximal doses of SSA. Also, the number of the patients in the subgroup diagnosed after year 2000 is too small (n = 26) to draw firm conclusions. As for surgery, SSA were able to significantly lower random GH and IGF-I serum levels.

Although our sample population represents 13.6% of the total population of acromegalic patients in Romania and covers most of its territory, the main limitation of our study is the absence of a real registry for acromegaly. In the European countries where a nationwide registry is functional [5–7, 9] it includes most of the acromegalic population and many practicing offices, from university centres to smaller regional hospitals. However, there are countries where acromegaly treatment is restricted to university centres [10]. Unfortunately, in our study, the practicing bias of a single centre cannot be ruled out. Also, there are 15 patients who were diagnosed after 2012, who were not reassessed after any kind of treatment. It is possible that some of these patients were cured by surgery and never returned to our centre, thus artificially lowering the cure rate.

To our knowledge it is the largest study on acromegaly control rate in Romania. Also, our study showed consistency in patient assessment because we used the same assays

for ultrasensitive GH and IGF-I measurement during the whole period of the study, as recommended by the last acromegaly guidelines [11]. Moreover, we defined acromegaly control based on the latest guidelines by using random GH instead of mean 24-h GH or minimum GH during an oral glucose tolerance test (OGTT) and age-normalised IGF-I [11]. There is a study on a larger population of 336 acromegalic patients in Romania [17] containing also data on cure rate. However, it focused on mortality, used different criteria for acromegaly control definition, and GH was measured using an immunoradiometric assay. Unfortunately, also national registries from European countries use slightly different criteria for defining disease control. For example, the German Acromegaly Register [5] does not use GH levels (random, mean, or minimum during OGTT), and the UK Acromegaly Register uses a random GH cut-off value of 2 ng/mL for the definition of acromegaly control [7].

Conclusions

In conclusion, in Romania acromegaly benefits from the whole spectrum of therapeutic interventions: pituitary surgery in high-volume centres, long-acting somatostatin analogues, GH receptor antagonist, and modern radiotherapy. However, the control rate remains disappointing.

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