



# Acromegaly — a novel view of the patient. Polish proposals for diagnostic and therapeutic procedures in the light of recent reports

Akromegalia — nowe spojrzenie na pacjenta. Polskie propozycje postępowania diagnostyczno-terapeutycznego w akromegalii w świetle aktualnych doniesień

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## Abstract

Acromegaly is a rare disease caused by the secretion of growth hormone (GH) in excess, in most cases from a pituitary tumour. The diagnosis is usually delayed and is often associated with the development of various complications causing premature mortality. In patients with hypertension, heart failure, diabetes, and arthropathy that is non-specific for age, attention should be paid to the occurrence of somatic signs of acromegaly. As a screening test, insulin-like growth factor-1 (IGF-1) concentration should be assessed. Further diagnostic and treatment procedures are possible in specialised centres. The first-line therapy is selective transsphenoidal adenomectomy. Patients with a good prognosis related to a surgical removal of the pituitary tumour should be referred only to centres experienced in performing this type of procedure, after pharmacological preparation. Other patients, and those who have not recovered after surgical treatment, should be subjected to long-term pharmacotherapy with long-acting somatostatin analogues. In each case, the complications of acromegaly should be followed-up long-term and actively treated. This proposed new recommendation should be helpful for the management of patients with acromegaly. (*Endokrynol Pol* 2014; 65 (4): 326–331)

**Key words:** acromegaly; diagnosis; therapy; guidelines

## Streszczenie

Akromegalia jest rzadką chorobą spowodowaną nadmiernym wydzielaniem hormonu wzrostu (GH), zwykle przez guz przysadki. Rozpoznanie jest opóźnione i często związane z rozwojem różnych powikłań powodujących zwiększone zagrożenie zgonem. U chorych z nadciśnieniem, niewydolnością serca, cukrzycą, artropatiami, nietypowymi do wieku należy zwrócić uwagę na występowanie objawów akromegalii. Jako badanie przesiewowe należy wykonać oznaczenie stężenia insulino podobnego czynnika wzrostu-1 (IGF-1). Dalsza diagnostyka i leczenie powinny być prowadzone w wyspecjalizowanych ośrodkach. Leczeniem pierwszego rzutu jest wybiórcze usunięcie gruczolaka przysadki z dostępu przez zatokę klinową. Pacjenci rokujący wyleczenie operacyjnym usunięciem guza przysadki powinni być kierowani do ośrodków z doświadczeniem w tego typu zabiegach, po przygotowaniu farmakologicznym. Pozostali chorzy oraz ci po nieskutecznym leczeniu neurochirurgicznym powinni być długotrwale leczeni analogami somatostatyny. W każdym przypadku następstwa akromegalii winny być przez całe życie monitorowane i aktywnie leczone. Proponowane nowe zalecenia powinny być pomocne w postępowaniu z pacjentami chorymi na akromegalię. (*Endokrynol Pol* 2014; 65 (4): 326–331)

**Słowa kluczowe:** akromegalia; diagnostyka; leczenie; zalecenia

## Introduction

The symptoms of acromegaly had already been described by the end of the 19<sup>th</sup> century; surgical treatment

of somatotroph tumours has been performed since the beginning of the 20<sup>th</sup> century, and pharmacological treatment using somatostatin analogues for 25 years. In recent years, some of the diagnostic and treatment



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criteria have changed [1, 2]. New registration provisions concerning the administration of long-acting somatostatin analogues used in acromegaly have also been introduced. The way of perceiving patients with this chronic disease is also expanding, with more focus on the systemic complications that contribute to the decreased survival and reduced quality of life [3, 4].

Therefore, we present the current recommendations on diagnostic and therapeutic procedures in acromegaly, including national conditions.

## Characteristics of the disease

Acromegaly is a rare chronic disease caused by the overproduction of growth hormone (GH), in most cases by a pituitary tumour. It leads to changes in appearance, including acral enlargement (hands, feet and face), hypertrophy of soft tissues, bones and internal organs and many systemic complications adversely affecting the quality of life and decreasing patient survival [5–7]. The symptoms of acromegaly are presented in Table I.

## Epidemiology

The prevalence of acromegaly is approximately 70 per one million inhabitants. Annually, there are approximately 3–4 newly diagnosed cases of the disease per million. Acromegaly is diagnosed with a similar frequency in both genders and most commonly in patients in their 30s and 40s. The disease is usually diagnosed about 5–10 years after the onset of the first symptoms, usually earlier in women than in men [5–9]. Detailed population studies conducted in recent years suggest significantly greater prevalence of acromegaly than previously thought [10]. Therefore, the disease should be actively searched for, particularly in males and subjects with cardiovascular and osteoarticular system disorders that are non-specific for age. Early diagnosis allows for surgical cure of the disease, giving a chance to restore life expectancy comparable to that of the normal population and improve quality of life.

## Pathogenesis

Pituitary tumours secreting GH, which are the cause of acromegaly, are benign adenomas. At the diagnosis of the disease, their diameter usually exceeds 10 mm, so these are already macroadenomas which may lead to visual field defects and other endocrine disorders (hypopituitarism, hyperprolactinemia). Most of the symptoms and complications of the disease (Table II) result from an excessive effect of insulin-like growth factor 1 (IGF-1) on tissues, which is stimulated by increased GH secretion [5, 6]. As a rule, the exacerbation of clinical

**Table I. Symptoms of acromegaly**

**Tabela I. Objawy akromegalii**

General symptoms	Enlargement of: hands, feet, facial bones (nose, mandible, frontal sinuses), tongue Thickened facial features Soft tissue swelling Enlargement of internal organs (visceromegaly) Weight gain Increased sweating Hirsutism Change in voice tone
Circulatory system	Arterial hypertension Dyspnoea, swelling (heart failure) Cardiac dysrhythmia
Respiratory system	Obstructive sleep apnoea, snoring Impaired patency of the upper respiratory tract
Endocrine system	Glucose intolerance, diabetes mellitus Goitre, thyroid dysfunction Galactorrhoea Possible tumours of other glands (MEN syndrome)
Digestive system	Constipation, possible elongation and widening of the colon (megacolon) Abdominal pain, blood in faeces (polyps and colonic diverticula)
Genitourinary system	Menstrual disorders Reduced libido Erectile dysfunction (hypogonadism) Renal colic (hypercalciuria, hyperparathyroidism — MEN)
Nervous system	Headache Visual field impairment (macroadenoma may compress the optic chiasm) Paresthesias, pareses (carpal tunnel syndrome)
Osteoarticular system	Bone and joint pain and deformities Limited joint mobility

symptoms, systemic complications and concentration of GH positively correlate with the tumour size and the persistence of acromegaly. A longer duration of the undetected and untreated disease promotes the intensity of clinical symptoms, and the development of metabolic effects and systemic complications, and thus reduces the chances of a complete recovery.

## Diagnosis

The diagnosis of active acromegaly is based on clinical symptoms (Table I) and a demonstrated simultaneous increase in IGF-1 and GH secretion. Patients with clinical symptoms indicating acromegaly should undergo a screening test for IGF-1 concentration (Fig. 1). If IGF-1 values are increased (for age and sex), it is recommended to perform an oral glucose tolerance test (OGTT) after administration of 75 g of glucose. In patients with diagnosed diabetes mellitus, instead of OGTT, GH concentration should be tested several times, i.e. every 30 minutes for 2–3 hours. Active acromegaly is confirmed by an increased IGF-1 concentration and

no suppression of GH secretion below  $0.4 \mu\text{g/L}$  ( $\text{ng/mL}$ ) in OGTT. Random GH level below  $1.0 \mu\text{g/L}$  allows the exclusion of active acromegaly [2, 11, 12]. At the diagnosis of the disease, it is also necessary to evaluate the presence and degree of its systemic complications and metabolic disorders (Table II).

An unequivocal determination of the cause of acromegaly requires a contrast-enhanced magnetic resonance imaging (MRI) scan of the pituitary. In the case of diagnosing a pituitary macroadenoma, visual field should be evaluated. When the MRI examination does not reveal a pituitary tumour, there is a suspicion of growth hormone releasing hormone (GHRH) ectopic secretion, or less often GH secretion by neuroendocrine tumour, usually in the bronchi, thymus or pancreas [13].

An early diagnosis of acromegaly (usually a smaller tumour, less advanced clinical symptoms and complications) increases the efficacy of surgical and pharmacological treatment, reduces medical care costs, and potentially prevents premature mortality in patients with acromegaly.

## Disease management

The basic goal of acromegaly treatment is the normalisation of GH secretion which is associated with the restoration of life expectancy and improvement of the quality of life of patients. The secondary aim is to remove or significantly reduce the mass of the pituitary tumour which should result in an improvement of disorders associated with its expansion. Both objectives can be achieved by surgical and pharmacological treatment, and, less frequently, radiotherapy [6, 11, 13, 14].

The therapy choice should be based on an evaluation of possible complications and take into account the patient's condition and willingness to undergo surgery. The basic treatment method of acromegaly, which may result in a recovery, is a surgical, selective adenectomy using the transsphenoidal approach, if possible, while maintaining hormonal function of the residual pituitary gland. In the case of an extrapituitary source of the disease, the removal of neuroendocrine tumour ectopically secreting GHRH is advised. The efficacy and success of the surgical treatment of GH-secreting tumours depends on: GH concentration, the size, location and expansion of the tumour, and the surgeon's experience. In the case of microadenomas, surgical success (random GH concentration  $< 1.0 \mu\text{g/L}$ ) is achieved in about 70–90% of patients, but in the case of macroadenomas the figure is only about 30–50% [13].

Thus, the bigger the tumour, with extrasellar expansion, the lower the efficacy of neurosurgical treatment. Therefore, according to the recommendations of the Polish Society of Endocrinology, one should consider the need for

**Table II. Complications in acromegaly**

**Tabela II. Powikłania akromegalii**

Cardiovascular diseases	Hypertension (up to 60%) Cardiac hypertrophy (up to 90%) Cardiac dysrhythmia (up to 40%) Heart valve defects (up to 80%) Heart failure (up to 10%) Ischaemic heart disease (up to 40%) Sudden cardiac death Cerebral stroke
Respiratory diseases	Obstructive sleep apnoea (up to 80%) Obturation of the upper respiratory tract Bronchiectasis Emphysema
Neoplasms	Malignant — colon (2%), thyroid (5%), breast and prostate cancers Benign — thyroid tumours (up to 90%), colonic polyps, uterine fibroids, benign prostatic hyperplasia
Metabolic and hormonal disorders	Hyperinsulinaemia (up to 80%) Prediabetes (up to 40%) Diabetes (up to 20%) Hyperlipidaemia Hypercalciuria (up to 70%) Hypogonadism (up to 50%) Hyperthyroidism (up to 15%)
Diseases of the osteoarticular system	Degenerative and proliferative changes (up to 70%) Reduced bone mineral density (osteoporosis) Vertebral fractures
Diseases of the nervous system	Visual field disturbances Neuropathies Carpal tunnel syndrome (up to 50%)

the pre-surgical use of long-acting somatostatin analogues which facilitate surgical treatment by reducing the volume and changing the consistency of the pituitary tumour as well as by ensuring the clinical improvement of patients [15]. This treatment results in reduced swelling of soft tissues (easier intubation), and improved cardiovascular functions (decreased blood pressure and reduced degree of heart failure), obstructive sleep apnoea and parameters of metabolic disorders [16]. Better outcomes of surgical treatment are achieved in centres where an experienced neurosurgeon performs at least 50 transsphenoidal surgeries a year [13, 17]. Therefore, appropriately prepared patients should be referred for surgical treatment to centres specialising in pituitary surgery.

Since the majority of tumours observed at the diagnosis of acromegaly are macroadenomas, for a large proportion of patients surgical treatment does not ensure a complete cure. So it is recommended to use pharmacotherapy or, less often, radiotherapy. The removal of over 75% of the tumour mass increases the efficacy of postoperative treatment with somatostatin analogues [18]. An alternative or supplement to surgical treatment of GH-secreting pituitary adenomas is pharmacotherapy. These adenomas show the expres-

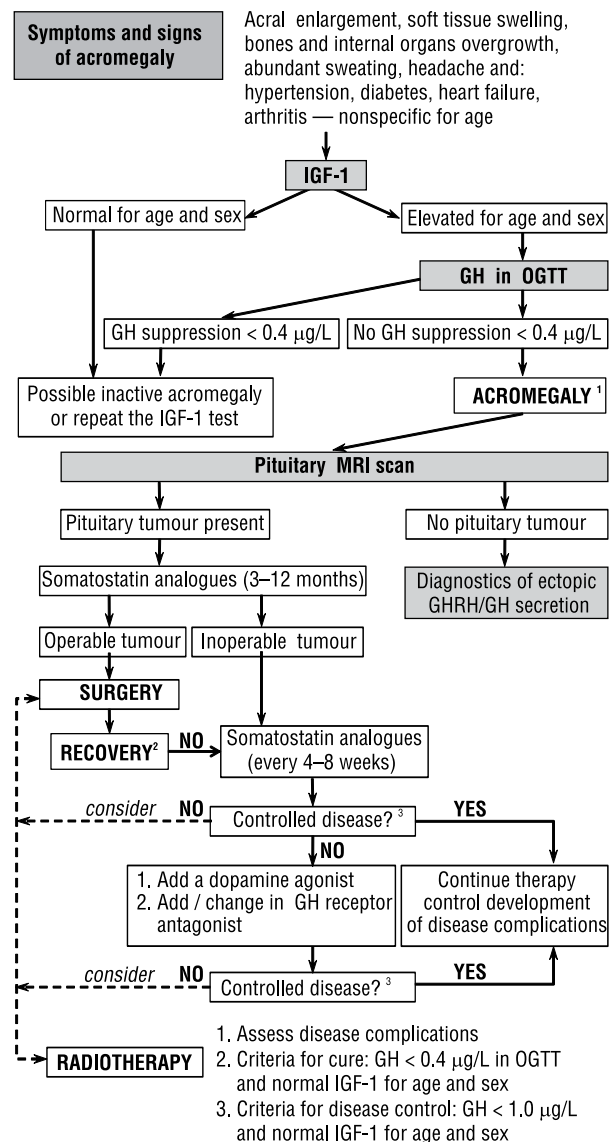
sion of somatostatin receptors; therefore, the ligands of this receptor, somatostatin analogues (lanreotide and octreotide), normalise GH secretion in 60–75% of patients with acromegaly and significantly reduce the size of the pituitary tumour in about half of patients [6].

Currently, there are two long-acting somatostatin analogues used in Poland. Lanreotide autogel is available in 60, 90 and 120 mg ampoules, for subcutaneous administration every 28 days, with a possible extension of the interval between injections to 56 days for the dose of 120 mg [9, 19]. Octreotide LAR is manufactured in 10, 20 and 30 mg ampoules, for intramuscular administration every 28 days, with a possible dose increase to 40 mg every four weeks in patients for whom a 30 mg dose is inefficient [20]. The dose of somatostatin analogue should be adjusted to the clinical and laboratory effects obtained after three months of using the drug [13]. In terms of efficacy and tolerance, there are no fundamental differences between the above-mentioned preparations [21]. Treatment with them is safe and usually well tolerated. The most frequent adverse effects are: abdominal pain, loose stools or diarrhoea. Approximately 20% of treated patients may develop cholelithiasis, and rarely, pancreatitis [9].

As mentioned before, somatostatin analogues should be used for several months in preparation for the surgical treatment, and as a long-term therapy if surgical treatment has not been used or has proved ineffective. Treatment with somatostatin analogues should be the first-line therapy in patients with significant contraindications or who refuse to undergo surgery and in patients with low chances of a cure or clinical improvement after the neurosurgical procedure (large tumours with extrasellar expansion without a significant pressure on optic nerves) [13].

Patients with active acromegaly after an inefficient surgical treatment of the pituitary adenoma or awaiting the effects of radiotherapy should permanently receive long-acting somatostatin analogues in doses normalising the concentration of GH and IGF-1 as a complementary treatment [12–14]. The current possibility of using lanreotide autogel 120 mg less than once a month (even every 56 days) significantly may reduce treatment costs and increase the patient's comfort and quality of life [9, 19, 22].

If the somatostatin analogue is inefficient, dopamine agonist or GH-receptor antagonist (pegvisomant) should be added to the treatment (Fig. 1) [11, 14]. In some cases, GH-receptor antagonist may be used in monotherapy. The efficacy of dopamine agonists in the treatment of acromegaly is low. The recommended doses of these drugs in acromegaly should be higher than the doses used in the case of prolactin-secreting pituitary adenomas (prolactinoma) [13, 23].



**Figure 1.** Diagnostics and treatment algorithm for acromegaly  
**Rycina 1.** Algorytm diagnostyki i leczenia akromegalii

Bromocriptine, which is easily available in Poland, normalises the concentration of IGF-1 only in 10% of patients with acromegaly. Cabergoline, which is much more expensive in Poland (no reimbursement), leads to the normalisation of IGF-1 in about 40% of cases and decreases GH secretion below 2 µg/L in 44% of patients with adenomas secreting only GH, and in 56% of patients with mixed tumours secreting both GH and PRL. Therefore, dopamine agonists may be used in the case of mixed tumours secreting GH and PRL and combined with somatostatin receptor ligands or GH receptor antagonist to improve their efficiency in patients showing resistance to maximal doses of somatostatin analogues [23, 24].

On the other hand, pegvisomant, which blocks GH action in target tissues in more than 90% of patients, normalises the concentration of IGF-1, thereby leading



to a clinical improvement and normalisation of metabolic disorders (i.e. it improves carbohydrate metabolism by increasing insulin sensitivity) [25]. Due to the systemic activity of the drug, GH concentration cannot be used to assess its efficacy. Pegvisomant does not reduce the size of the pituitary tumour, so it is necessary to control it during treatment using MRI. In the case of adenoma enlargement, additionally a somatostatin analogue may be used.

Because of the improving results of surgical treatment and the availability of efficient drugs, indications to use conventional radiotherapy in acromegaly have become controversial [26, 27]. Stereotactic radiotherapy should be considered only in the case of inefficient surgical and pharmacological treatment, bearing in mind that it leads to the normalisation of IGF-1 concentration within ten years in about 40% of patients and is associated with multiple complications. The most common of these is hypopituitarism (about 80% of patients who are subjected to conventional radiotherapy). Radial damage to optic nerves, as well as cerebral circulation disorders and the formation of secondary tumours are much less common.

The treatment of complications of acromegaly is an additional problem; these include mainly arterial hypertension and heart failure, disorders of carbohydrate metabolism and degenerative and proliferative changes of the osteoarticular system (other complications are presented in Table II) [4]. These diseases not only lead to worsening of the quality of life and decreased survival of patients, but their treatment additionally generates significant costs. An early diagnosis of acromegaly creates an opportunity for its surgical treatment, which minimises the development of complications, thereby decreasing the costs of treatment.

## Follow-up of patients

The efficacy of treatment and the course of the complications should be controlled in each patient with acromegaly based on the clinical evaluation, as well as laboratory and imaging tests. The efficacy of surgical treatment can be evaluated by examining the GH concentration soon postoperatively (after one week), while a reliable assessment of the IGF-1 concentration should be carried out approximately three months after the surgery. The criterion of recovery is IGF-1 concentration within reference values for age and sex, as well as GH level  $< 0.4 \mu\text{g/L}$  in OGTT [2]. If the efficiency of surgical treatment of acromegaly is confirmed in laboratory tests, and there are no clinical disorders of vision and pituitary function, there is no need for an MRI examination.

In patients who do not recover after surgery, imaging of the pituitary area using MRI should be performed after 3–4 months, and in patients treated with

**Tabela III. Ocena przebiegu powikłań akromegalii**

**Table III. Evaluation of the course of complications in acromegaly**

Examination	Frequency of evaluation
Blood pressure	Every 3–6 months, more frequently when treatment is changed
ECG	Every year
Exercise ECG	In the case of stenocardial symptoms
Echocardiography	Every year
Polysomnography	Every year
OGTT	In the case of suspicion of diabetes mellitus
Fasting glucose	Every 6–12 months
HbA1c	Every 6–12 months in the case of diabetes
Lipid profile	Every year
Ca, P	In the case of symptoms of nephrolithiasis
TSH, fT4	Every year
PRL, testosterone (♂)	Every year
PRL, LH, FSH, E2 (♀)	Every year
Thyroid ultrasound	Every 1–2 years
Colonoscopy	Every 2–3 years
DXA (in hypogonadism)	Every 2–3 years

the pharmacotherapy 6–12 months from its beginning. Further control MRI examinations should be repeated once a year (fast-growing tumours may be an exception). When evaluating the efficacy of pharmacological treatment, the clinical condition of the patient should be taken into account (together with an assessment of the visual field and the quality of life), as well as the results of basal IGF-1 (primarily), and random GH (additionally) concentrations (there is no need to perform OGTT). It is assumed that an efficient pharmacological treatment (managing the course of the disease) is a treatment which maintains the IGF-1 concentration within reference values for age and sex, and GH  $< 1.0 \mu\text{g/L}$  [2].

Clinically, complications (Table II) should be identified, actively monitored (Table III) and effectively treated in every patient with acromegaly. Taking into consideration the complications in the cardiovascular system, blood pressure should be measured during every examination of a patient with acromegaly, and ECG and echocardiographic examinations should be performed once a year. Bearing in mind the most common complications in the respiratory system, it is recommended to perform a polysomnographic test. Due to common metabolic and hormonal complications, it is necessary to exclude disorders of glucose, lipids, calcium and phosphorus metabolism, as well as disorders of the thyroid and gonad functions. Due to the increased predisposition to tumourigenesis in acromegaly, it is first necessary to exclude proliferative

changes in the colon and thyroid [4]. Detailed suggestions for the monitoring of complications in acromegaly are presented in Table III.

## Prognosis

Untreated acromegaly causes an average reduction in survival of about ten years. The risk of earlier death doubles in a patient with active acromegaly. The most common causes of death are cardiovascular complications (60%), respiratory complications (25%) and neoplasms (15%). A decrease in GH secretion to 2.5 µg/L and normalisation of IGF-1 secretion are associated with the restoration of life expectancy in patients [24, 28].

## Conclusion

Acromegaly is a rare chronic disease caused by the overproduction of GH, usually by a pituitary tumour. Despite the fact that the disease leads to characteristic changes in the appearance and the development of multiple systemic complications, its diagnosis is greatly delayed. A late diagnosis of acromegaly contributes to the development of complications in the cardiovascular and respiratory system, and malignant neoplasms. They are responsible for a 30% increase in the mortality rate among non-treated patients compared to the general population.

An important role in improving the diagnosis of acromegaly within the Polish health service is played by general practitioners. In patients with hypertension, heart failure, diabetes, and arthropathy, non-specific for age, they should pay attention to the occurrence of somatic signs of acromegaly and perform a screening test for IGF-1 concentration if the signs occur. A lack of inhibition of GH secretion below 0.4 µg/L in OGTT and the presence of a pituitary tumour in MR imaging confirm active acromegaly. It is indicated to perform these tests in reference centres which should also assess complications of the disease and establish a treatment plan.

Patients with a good prognosis related to the surgical removal of the pituitary tumour should be referred only to centres experienced in transsphenoidal adenomectomy, after a pharmacological preparation. Other patients, and those who have not recovered after surgical treatment, should be subjected to long-term pharmacotherapy with long-acting somatostatin analogues. In each case, in addition to the evaluation of therapeutic efficacy, the complications of acromegaly should be followed-up and actively treated.

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