Acromegaly : treatment and follow-up : the Leiden studies

Biermasz, N.R.

1

General introduction

I. Acromegaly
- History
- Etiology and pathogenesis
- Anatomy
- Clinical features, morbidity and mortality

II. GH physiology
- Regulation of GH and IGF-I
- Clinical effects of GH and IGF-I

III. Treatment of acromegaly
- Surgery
- Radiotherapy
- Medical therapy
- Aims of treatment, criteria for diagnosis and remission and recurrence of disease

IV. Outline of this thesis
- Treatment outcome in acromegaly
- Clinical outcome in acromegaly
- Dynamic tests in acromegaly
- GH regulation during treatment and in rare cases of acromegaly

I. Acromegaly

History

IN 1886, PIERRE MARIE was the first to describe the clinical characteristics of a disease with *'hypertrophie singuliere non congénitale, des extremites supérieures, inférieures et céphaliques'* and he named the syndrome acromegaly (1). The pituitary origin of the clinical syndrome was suggested in 1892 by Massalongo (2) and further supported by Cushing (3,4) by showing partial reversal of clinical symptoms after partial hypophysectomy and by others in animal experiments by inducing acromegaly in rats by injecting anterior pituitary extracts intraperitoneally (5).

If growth hormone (GH) hypersecretion is present before the closure of the epiphysis, GH excess also leads to a tall stature and the resulting syndrome is called gigantism. A famous historical biblical giant is for example Goliath. The longest known man ever, Robert Wadlow, the Alton giant, was 2.72 meters, while the longest living man at present according to the Guinness Book of Records lives in the Ukrain and measures 2.54 m. Well-known Dutch giants were living for example in Rotterdam and Spaarnwoude, see Fig.1, and their history was recently described by De Herder (6).

Various treatments have been proposed for acromegaly from the 20th century onwards. The first transsphenoidal operation was performed by Herman Schloffer (Austria) in 1907 and

Figure 1. Dutch giant

this treatment was rediscovered by Hardy and Guiot in the late 1960s with new microsurgical techniques (7 – 9). Conventional pituitary irradiation was first attempted in 1909 and this modality was the most effective treatment for many years. Estrogen was the first medical therapy that alleviated acromegalic symptoms in the 1930s. From 1960 onwards other drugs including progesterone and chlorpromazine were tested for efficacy in acromegaly. In 1975 the dopamine-agonist bromocriptin was the first drug that effectively reduced GH concentrations in acromegaly. In the 1980s somatostatin analogs became available, and appeared to control acromegaly in many patients. The most recent development in the field of medical treatment is the clinical application of the GH receptor antagonist Pegvisomant.

Etiology and Pathogenesis

The clinical syndrome of acromegaly is due to excessive circulating serum GH and insulin-like growth factor (IGF)-I concentrations. In most cases acromegaly is caused by a growth hormone (GH) secreting pituitary adenoma. Growth hormone releasing hormone (GHRH) secreting tumors, for example bronchial or gastrointestinal carcinoid tumors, pheochromocytoma and small cell bronchus carcinoma, causing secondary somatotrope hyperplasia, may cause acromegaly in a minority of cases (~1%).

Known genetic defects leading to hereditary syndromes with acromegaly are the inactivating mutation of 11q13 gene (multiple endocrine neoplasia (MEN) type I), and mutations leading to familial acromegaly and Carney syndrome (10,11). The molecular basis for sporadic (GH producing) pituitary tumor formation is largely unknown and is probably a multi-step process finally leading to monoclonal cellular expansion. Activating genetic mutations of the stimulatory G-protein (gsp) are present in 40% of GH adenomas, including those associated with the McCune- Albright syndrome. With this mutation the GHRH receptor is continuously activated, which eventually leads to autonomic GH secretion and GH cell hyperplasia. Stimulatory mutations in the pituitary tumor transforming gene (PTTG) and cAMP- response element binding protein (CREB) are also found in pituitary adenomas. Loss of heterozygosity of candidate tumor suppressor genes located on chromosomes 11q13, 13q14, 9p and 1p35 have been found in pituitary tumors. Overexpression of the GHRH gene in the hypothalamus or alterations in the GHRH receptor and somatostatin receptor (subtype pattern) and growth factors may also play a role in the development of pituitary GH secreting tumors.

Anatomy

The pituitary gland lies within the sella turcica, a recess in the sphenoid bone, nearby the hypothalamus and the optic chiasm. The pituitary weighs approximately 1 gram. It is connected to the hypothalamus with the pituitary stalk and consists of the adenohypophysis (80%) and the neurohypophysis (20%). The cell types in the anterior lobe of the pituitary are the somatotropes (50%), lactotropes (20%), corticotropes (10), thyrotropes (10%) and gonadotropes (10%), all producing their specific hormones.

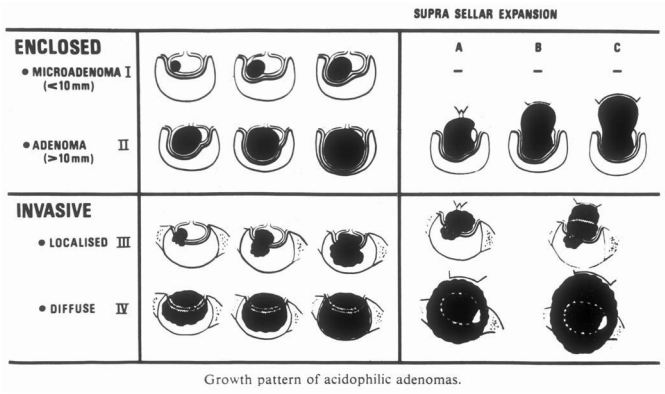

Figure 2. Hardy-Wilson classification of pituitary tumors

Pituitary tumors are staged according to the tumor classification by Hardy and modified by Wilson, based on the grade of sella turcica enlargement and invasion (0 – IV) and suprasellar and parasellar extension (A – E), see Fig. 2. Most microadenomas can be cured be surgery, while larger tumors with some suprasellar extension have a reasonable chance to be cured by surgery. Tumors invading the sellar floor or those with parasellar extension have a low chance to be cured by surgery.

Most pituitary tumors in acromegaly produce only GH, while mixed GH and prolactin production is present in ~30% of cases. A minority of GH producing adenomas also produces TSH or α-subunits.

Clinical Features, Morbidity and Mortality

The incidence of acromegaly is 3 – 4 per one million inhabitants and the prevalence is 60 to 70 per one million as was found in the UK, Spain and Sweden in 1970 – 1980 (12 – 15). There are no known geographical and/or sex differences. The disease is likely underdiagnosed and it is possible that incidence and prevalence rates are higher than reported. As the physical changes appear slowly and symptoms are usually vague and non-specific, mean delay in diagnosis from the onset of clinical disease is 6 to 9 years (12, 16, 17).

Symptoms associated with acromegaly can be subdivided in symptoms related to GH hypersecretion, those related to either hyperprolactinemia or pituitary hormone deficiencies and local, tumor size related, effects (16, 18, 19).

Facial features of acromegaly include growth of enchondral bone especially of the nose and ears and periosteal bone formation leading to prognathism, malocclusion and frontal bossing. The mouth is characterized by diasthemata and macroglossia. Hand and feet enlarge by soft tissue swelling and by periosteal bone formation leading to the characteristic increased ring and shoe size. The stature of the patient with active acromegaly is characterized by kyphosis, and weight and length are increased (20). Organomegaly of liver, heart, kidneys, colon, spleen and thyroid is also frequently present. Symptoms associated with GH

hypersecretion are perspiration, tiredness, a low hoarse voice, paraesthesias, carpal tunnel syndrome, arthropathy, sleep apnea syndrome, hirsutism, snoring, and a thick moist skin. Metabolic diseases associated with acromegaly include hypertension, cardiovascular disease, diabetes mellitus and impaired glucose tolerance (16, 18, 19). Assessment of body composition in active acromegaly shows increased body weight and height, increased total body water and extracellular water and reduced body fat (20).

Due to hyperprolactinemia and/or pituitary hormone deficiencies patients may have galactorrhea, amenorrhea, hirsutism, impotence, infertility and symptoms related to hypothyroidism and hypocortisolism. Local tumoral effects include headache, visual field defects with typical hemianopsia, and sporadically cerebral nerves dysfunction, especially of the trigeminal, trochlear or abducens nerve.

Acromegaly is associated with increased incidence of vascular disease, cardiomyopathy and an increased prevalence of valvular abnormalities and malignancies especially of the gastrointestinal tract (21 – 26). Patients with active acromegaly have a two- to three-fold increased mortality risk due to cardiovascular and respiratory diseases and cancer (12 – 15; 17; 27 – 31).

II. GH PHYSIOLOGY

Regulation of GH and IGF-I

Growth hormone is a single chain polypeptide hormone that is synthesized, stored and secreted by somatotrope cells in the pituitary gland. The 22 kDa GH isoform represents 90% of plasma GH (32). In plasma, GH circulates freely or is bound to GH- binding protein (GHBP). This protein may enhance or limit tissue actions of GH, and significantly reduces the GH clearance rate from 2 – 12 minutes (free GH) to 19 minutes (total GH). GH is cleared via renal and hepatic mechanisms.

Control of GH secretion is effectuated at the hypothalamic and the pituitary level by stimulatory and inhibitory hormones resulting in a diurnal pulsatile secretion pattern by which the majority of GH is released during sleep as is shown in Fig. 3, for review see ref. (33, 34). The hypothalamic stimulatory growth hormone releasing hormone (GHRH) stimulates GH gene transcription, GH cell proliferation and GH release. The hypothalamic inhibitory hormone somatostatin acts via binding to somatostatin receptors and inhibits GH release from the secretory granules in the somatotropes and also inhibits GHRH release. Other negative feedback systems regulating GH secretion are GH at the hypothalamic level, and insulin-like growth factor-I (IGF-I) at the hypothalamic and pituitary level. The physiological role of another stimulatory hormone Ghrelin, the native substrate for the GH- releasing peptide (GHRP) receptor, is not fully elucidated, but high GH responses are induced by GHRP or Ghrelin infusion and these act synergistically to GHRH stimuli (33, 35 – 38).

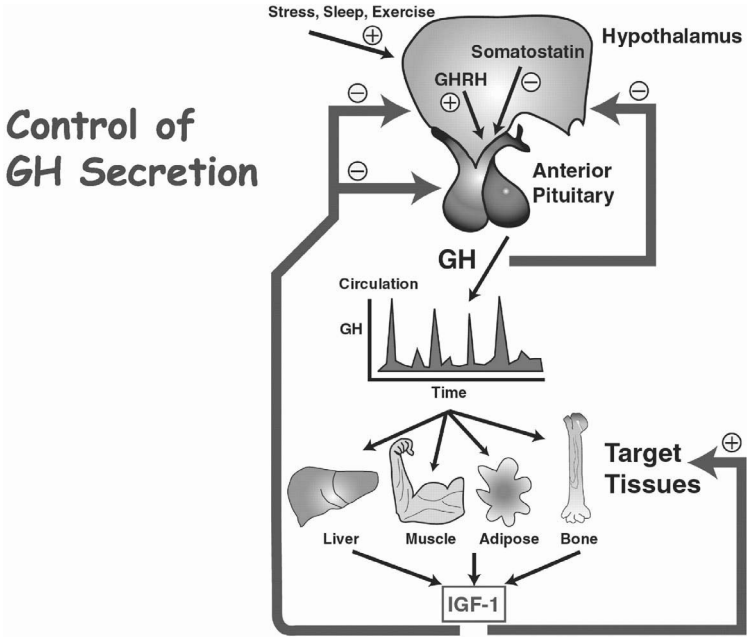

Figure 3. GH regulation (adapted from Kopchick, reference 34)

Physiological stimuli enhancing GH secretion are sleep, hypoglycemia and exercise. Thyroxin, sex steroids, (physiological) glucocorticoids, amino acids and fasting also enhance GH secretion. Inhibition of GH is effectuated among others by meals, glucose, free fatty acids, glucocorticoid excess states and (visceral) adiposity. GH secretion is maximal in the late puberty and thereafter gradually decreases. Females have a higher GH production than males (33;39).

GH stimulates the production of IGF-I in many organs. IGF-I is a polypeptide belonging to the same family of growth factors as insulin (and IGF-II). Most circulating IGF-I is bound to one of the 6 IGF-binding proteins (IGFBPs), mainly to IGF-BP3. The serum IGF-I concentration reflects the GH concentrations over 24 hours and is increased and decreased, when GH production is elevated or decreased, respectively. An important determinant for IGF-I concentrations is age. Increasing age is associated with a decreasing GH production and IGF-I concentrations. Sex steroids, especially estrogens inhibit GH-mediated IGF-I production. Another important determinant of plasma IGF-I is the nutritional status (39). Malnutrition and anorexia (nervosa) are associated with high GH levels in combination with low serum IGF-I concentrations. Obesity, especially visceral obesity, is associated with low serum GH concentrations, together with normal serum IGF-I concentrations (40).

Clinical effects of GH and IGF-I

The primary and most obvious role of GH is the promotion of longitudinal growth. Most, but not all, effects of GH are mediated via IGF-I (see for review ref. 39). The anabolic actions of GH (and IGF-I) involve many organ systems throughout life. These actions include stimulation of protein synthesis, increased lipolysis and inhibition of protein catabolism. GH is involved in bone remodeling, muscle growth and immunomodulation. GH stimulates IGF-I and IGFBP-3 production, acid-labile subunit (ALS) and many other growth factors at a local level. GH directly antagonizes the actions of insulin leading to glucose intolerance and hyperinsulinemia. In contrast, IGF-I has an insulin-like effect by enhancing peripheral glucose uptake.

III. TREATMENT OF ACROMEGALY

Surgery

In most centers, pituitary tumor surgery is performed by the transsphenoidal route. An incision is made in the vestibulum nasi. After insertion of a speculum, the mostly thickened sphenoid sinus and thereafter the sellar floor and the basal dura is opened. The tumor is selectively removed using curettes and forceps under vision of a microscope. The anterior wall of the sella is sealed with muscle fascia and fibrin glue. External lumbar drainage is placed in the case of cerebrospinal fluid leakage. There is a very low mortality and a low incidence of morbidity postoperatively, including meningitis and cerebrospinal fluid leaks (< 1%), transient diabetes insipidus and (partial) hypopituitarism (< 10%). After selective and complete adenoma removal, GH secretion is reported to normalize completely (41). Microadenoma removal is successful in most cases, but with increasing size and expansion of the adenoma total tumor removal is more difficult. Second surgical procedures are generally safe, but less successful than primary surgery (42). The experience of the neurosurgeon is crucial for the success rate (43).

Radiotherapy

Conventional radiotherapy is administered by a linear accelerator (4 – 8 MeV) in a total dose of 40 Gray (Gy) fractionated in at least 20 sessions. A rotational field, laterally opposed fields or 3 fields irradiation techniques have been used. A decline of about 50% in serum GH levels is observed in the first 2 years after radiotherapy and after 5 years a 75% decline (44 – 46). Whether GH and IGF-I levels normalize in the follow-up, is mainly dependent on the pre-irradiation serum GH concentration. Remission rates of radiotherapy are thus affected by surgical intervention (debulking) prior to radiotherapy. The incidence of hypopituitarism increases with the follow-up duration after radiotherapy. A lower incidence of hypopituitarism is potentially observed when a smaller dose of 20 Gy, in stead of 40 Gy, is used (47). Optic nerve damage is directly related to the radiation dose and is not observed when the radiation dose

does not exceed 45 Gy and the fractional dose is less than 2.5 Gy. Secondary carcinogenesis is very rare, in the range of less than 2% in 20 years (48).

Other irradiation techniques are proton beam irradiation and stereotactic radiosurgery (gamma knife) (49). With radiosurgery, a high single dose is administered at the stereotactically mapped region so that the tumor is precisely ablated while the surrounding tissue receives a low radiation dose. GH decline is faster than with conventional techniques with a possible lower incidence of hypopituitarism, but long-term studies are not available (50, 51).

Medical therapy

Somatostatin analogs

Somatostatin analog treatment has been the most important medical therapy for more than a decade (52). The currently used analogs, octreotide, lanreotide and vapreotide inhibit GH secretion via the somatostatin receptor subtypes 2 and 5 (53). Their half-life is longer than that of the native somatostatin. They were first used subcutaneously in a three-daily regimen or continuously administered by pump infusion. The introduction of long-acting release forms using monthly intramuscularly injectable depots with microspheres (octreotide-LAR) or subcutaneously injectable water solutions (Lanreotide Autogel) has improved the treatment results and facilitated the use of these agents (54). Few side effects are observed with these drugs, the most important being explained by the physiological action of somatostatin. These include bile stone formation, inhibition of insulin secretion and therefore a slight deterioration in glucose tolerance in a minority of patients, and (mostly transient) abdominal pain, diarrhea and nausea.

Reduction in GH and IGF-I levels during treatment with somatostatin analogs is observed in many patients, but control of disease depends on octreotide sensitivity (determined by somatostatin subtype status of the adenoma) and baseline serum GH concentrations. Tumor volume reduction of GH adenomas has been reported to occur in 20 – 50% of acromegalic patients during somatostatin analog treatment (54). Medical pretreatment before surgery of especially macroadenomas, however, does not clearly improve outcome (55).

Potential improvements in the number of patients controlled by medication and a more effective GH suppression may be achieved by use of the new selective (e.g. BIM-23244) and universal somatostatin analogs (e.g. SOM230), of which clinical trials are upcoming (56).

No significant tachyphylaxis does occur in acromegalic patients treated by long-acting somatostatin analogs. There is no contraindication for long-term (life-long) use. Somatostatin analog treatment costs in the range of 10,000 – 26,000 euro per patient per year.

GH receptor antagonists

Pegvisomant is a genetically engineered GH analog that antagonizes GH at the GH receptor site, and thus blocks GH at its receptor (34, 57, 58). Although it increases GH concentration,

serum IGF-I is effectively reduced in almost all patients. Likewise complaints and metabolic consequences associated with GH excess in acromegaly are ameliorated. Thus, the treatment results in terms of normalization of IGF-I are excellent compared to other available treatment regimens. A major concern with Pegvisomant treatment is growth of the pituitary adenoma due to disrupted feedback systems, in concordance with the development of Nelson's syndrome in patients with Cushing's disease treated by bilateral adrenalectomy. With the short-term use of this drug, tumor growth has been observed in only a very small number of patients, and might be prevented by the combined used of GH antagonist and somatostatin analogs. Another side effect is the development of liver function test abnormalities. The long-term safety of this treatment requires further investigation.

Mean cost of Pegvisomant is 28,000 – 115,000 euro per patient year.

Dopamine agonists

Dopamine agonists reduce GH secretion in a minority of GH adenomas (44) and are used in some patients with a mixed GH/prolactin producing adenoma. Addition of a dopamine agonist to chronic somatostatin analog treatment in octreotide-resistant patients with acromegaly may be able to normalize serum IGF-I concentrations in 30 to 40% of patients irrespective of the prolactin concentration (59).

Aims of treatment, criteria for diagnosis and remission and recurrence of disease

Aims

The aim of treatment of acromegaly is first to relief the symptoms of GH excess and mass effects of the pituitary tumor. Additional aims are the restoration of the metabolic changes and reduction of the increased mortality risk associated with active acromegaly. The most convenient treatment with the lowest incidence of side effects and the safest procedure are preferred, but also the financial aspects should be considered. In addition, the risk for recurrent disease should be low. Ideally, the aim should be directed towards restoration of physiological GH secretion, which is achieved when responses to dynamic stimuli have normalized, and a normal 24-hr GH production and other secretory characteristics such as diurnal rhythm and secretory regularity are restored.

The mean duration of active acromegaly before diagnosis is still 6 to 9 years. As many metabolic effects induced by the GH excess are related to the duration of active disease and may not be fully reversible, another important aim is the early identification of patients with acromegaly.

Criteria for diagnosis and remission

Biochemical criteria are largely dependent on the GH assay used. Therefore, reference values should be determined in each laboratory for all biochemical parameters used in the diagnosis and follow-up of patients with acromegaly.

The glucose tolerance test (GTT) is the gold standard for the diagnosis of GH excess. In healthy controls, after oral glucose load of 75 grams, the serum GH is suppressed to low levels. In contrast, in active acromegaly, the serum GH concentration is insufficiently suppressed after glucose loading. The glucose tolerance test (GTT) provides a reproducible standardized test, although there are interpretative difficulties in overt diabetes mellitus, renal and hepatic disease and anorexia nervosa. In addition, the test has not been validated for evaluation of the GH suppression during medical therapy (60, 61). In our center, controls suppressed to below 2.5 mU/L (1.25 µg/L) when measured by RIA (Biolab, Serona, Coissins, Switzerland) and below 1 mU/L (0.38 µg/L) when measured by the presently used IFMA (Wallac, Turku, Finland). The latter is highly sensitive for the 22 kDa GH protein exclusively. Male controls may suppress even lower than 1 mU/L (0.38 µg/L). No data are available on the relation between glucose- suppressed GH concentrations and morbidity and mortality.

A random (or mean) serum GH concentration is also frequently used in the literature to evaluate disease activity in treated acromegaly. Due to the pulsatile nature of GH secretion, a single high GH concentration does not always indicate active disease. However, in active acromegaly a fairly good correlation is present between random and mean serum GH concentrations. As British studies found a relation between the cut-off level of 5 mU/L and mortality, a serum GH below 5 mU/L is regarded as a 'safe GH concentration'. At present, this goal of treatment is used in many therapeutic trials (28).

Serum IGF-I, a marker that reflects the mean serum GH concentration, is elevated in most patients with active acromegaly (62) and may be decreased in the GH deficient state (63). As IGF-I decreases with age, values should be interpreted after adjustment for age. In addition, gender, sex hormone status and body mass index may influence the serum IGF-I (and GH) concentrations. Also, the IGF-I assay methodology is important for interpretation of the results. The IGF-I molecule has to be removed from its binding protein by an extraction process or equivalent blocking procedure, as binding proteins compete with the used antibodies (61). Assays differ largely in their quality of removal of binding proteins and have variable (high) intra- and inter-assay variation coefficients. Normative values for IGF-I are not always well characterized. Therefore a good knowledge of used assays and its limitations is required. Only one study found a relation between normalized mortality and serum IGF-I values in surgically treated patients (27).

Serum IGF-BP3 is stimulated by IGF-I and thus elevated in many patients with acromegaly. Its use in the diagnosis and follow-up of patients with acromegaly is not established, but probably limited (64).

The "paradoxical" thyrotropin-releasing hormone (TRH)-induced GH response is an unexplained feature occurring in half of patients with acromegaly. This phenomenon disappears following successful surgery. It may therefore serve as a tumor marker in indicating the presence of residual disease in those who exhibit this phenomenon preoperatively. Luteinizing-hormone releasing hormone (LHRH) induces a GH increase in a smaller proportion of patients than TRH and may be of use in selected patients without TRH but with LHRH induced GH release (61, 65).

Detailed studies of GH secretion in acromegaly have been performed to obtain insight in the secretory and regulatory disturbances caused by the disease and in the effects of various treatments on GH regulation. Using GH concentrations measured at 10 minutes intervals, the 24-hour basal and pulsatile GH production can be calculated using mathematical techniques such as deconvolution analysis. Also the diurnal rhythmicity and secretory regularity can be assessed by cosinor and approximate entropy analysis (66 – 70). Active acromegaly is characterized by an increased basal GH production, increased pulse frequency, disturbed diurnal secretion and irregularity (41, 71). Studies on GH regulation are not routinely used, but may be of value in case of diagnostic difficulties.

Radiological investigation with MRI is able to identify the adenoma preoperatively in most patients with acromegaly. In postoperative MRI assessments, a residual sellar mass does not always indicate the presence of persistent disease, as interpretation is difficult in postoperatively changed tissue. No evidence is present that tumor growth occurs without accompanying biochemical recurrent evidence of disease(72). Following surgery, irradiation and also during somatostatin analog treatment, MRI assessment does not provide additional value over biochemical assessment of disease status, although some suggest periodical radiological follow-up (60). The necessary frequency of radiological follow-up during Pegvisomant treatment requires further investigation.

Recurrence of disease

The incidence of recurrent acromegaly is largely dependent on the criteria used and the duration of follow-up after intervention. Following surgery recurrences develop in 5 to 15% of patients, usually very slowly in the course of 15 years postoperatively (19, 27). Recurrences may be regrowth of postoperatively non-detectable tumor remnants or new monoclonal cell expansions. Following radiotherapy recurrences are rarely observed. During chronic somatostatin analog treatment, tumor growth is rarely observed. At present, the incidence of tumor growth during long-term treatment with Pegvisomant is not known.

IV. OUTLINE OF THE THESIS

Treatment outcome in acromegaly

Acromegaly is a rare disease but associated with significant morbidity and mortality. Most patients will be treated in tertiary referral centers. However, even then it requires many years to build sufficient experience and a large database to evaluate single center treatment results. Therefore, prospective and randomized studies can best be performed in a multi-center setting or using (inter)national disease databases. In the present thesis we evaluated the treatment results of patients with acromegaly who underwent primary pituitary surgery by an experienced neurosurgeon between 1977 and 2002 in a single-center long-term follow-up study. For this evaluation we used currently widely accepted strict criteria for remission, which determined the application of adjuvant treatment already from the start of the study.

Transsphenoidal microsurgery is the treatment of choice when an experienced neurosurgeon is available and there are no contraindications for surgery. We were able to evaluate the results of surgery with detailed and prolonged follow-up in a consecutive patient series. In ***Chapter 2,*** we describe the results of transsphenoidal surgery focusing on the late outcome (more than 10 years follow-up) of this procedure. Direct postoperative remission rates in our and other single surgeon centers are about 60% when strict criteria for cure are used. We investigated also whether the success rates of surgery are maintained in the long-term in initially cured patients and whether multimodality therapy is able to achieve and maintain normalization of GH and IGF-I concentrations in the non-cured or in those with recurrence of disease.

Radiotherapy was mainly used in an adjuvant treatment setting after unsuccessful surgery before the introduction of somatostatin analogs. Since the availability of effective medical therapies its use is now limited to those patients with insufficient response to medication or with adverse reactions. Using yearly follow-up results of our cohort of acromegaly patients who underwent postoperative radiotherapy, we evaluated the rate of decrease in serum GH concentration, the duration to normalization and the fraction of patients with normalization of GH hypersecretion. The results of postoperative radiotherapy are described in ***Chapters 3 and 4,*** focusing on its efficacy using strict criteria for remission of acromegaly, i.e. a normal age-adjusted serum IGF-I concentration, a normal glucose-induced GH suppression (below 1 mU/L) and a GH concentration (mean or random) below 5 mU/L. These criteria are both associated with normalization of the increased mortality risk associated with acromegaly. Furthermore, we assessed the incidence of hypopituitarism in the (late) follow-up after radiotherapy.

Since the introduction of long-acting somatostatin analogs, subcutaneous octreotide and the intramuscularly injected depot preparation octreotide LAR, medical therapy is the preferred adjuvant treatment after unsuccessful surgery. In addition, an increasing number of patients is treated primarily with a somatostatin analog, eventually in anticipation of surgery.

Some studies have suggested an advantage in surgical outcome in octreotide-pretreated patients. In ***Chapter 5****,* we evaluated the surgical results after pretreatment with octreotide in a randomized trial focusing on the surgical outcome.

Octreotide LAR has a characteristic release pattern from the intramuscularly injected microspheres and in dose-finding studies serum octreotide levels remain in a therapeutic range for at least 42 days. We assessed whether cost reduction was achievable in acromegalic patients well controlled on a regular 4-week dose scheme of octreotide LAR by increment of the dosage interval. The results of this prospective cohort study are described in ***Chapter 6*****.**

The results of pharmacotherapy with somatostatin analog, GH receptor antagonist and dopamin agonist treatment for acromegaly are reviewed in ***Chapter 15***. In this chapter a treatment algorithm of primary and secundary treatment of acromegaly is proposed.

Clinical outcome in acromegaly

Untreated acromegaly is associated with significant morbidity and an increased mortality risk. Recent studies have shown that effective treatment of acromegaly to a normal serum GH concentration reduces the increased mortality risk to normal. Less knowledge is present on the co-morbidity, clinical symptoms and quality of life in patients with acromegaly in remission according to strict criteria.

In ***Chapter 7*** we evaluated the mortality risk in our surgically treated cohort and also in the subset that was biochemically cured immediately following surgery. We furthermore aimed to assess which remission criterion and cut-off level for serum GH and IGF-I was associated with survival and which were other predictive factors for survival present at the time of inclusion in the survival analysis.

Quality of life has not yet been assessed in cured acromegalic patients, but this important clinical parameter appeared to be significantly affected in patients with active acromegaly. Recently, Webb *et al.* developed a disease-specific quality of life questionnaire for acromegalic patients (73). We evaluated quality of life in our cohort of well-controlled patients using the disease-specific ACRO-QOL and other quality-of-life questionnaires in order to assess to which extent physical, psychological and other limitations persisted after treatment. The results are detailed in ***Chapter 8.***

In addition, we assessed the prevalence of co-morbidity in the same cohort, which underwent the quality of life assessments. The prevalences of e.g. arthropathy, hypertension, myocardial infarction and diabetes mellitus were investigated using explorative symptom questionnaires and patient records. We furthermore assessed the impact of related co-morbidity on quality of life scores. Results are described in ***Chapter 9*****.**

GH is a well-known anabolic agent for bone and most studies report a normal to increased BMD in active acromegaly. However, the bone status in long-term cured acromegaly is not established. In ***Chapter 10,*** we assessed whether a normal to high bone mineral density (BMD) is maintained in the long-term after normalization of GH hypersecretion. Also other factors,

for example gonadal status, duration of active disease and of remission were explored in relation to BMD.

Dynamic tests in acromegaly

Heterogeneous responses to pharmacological stimuli underlie differences in genetic background of GH secreting adenomas and therefore may explain variable sensitivity to medical treatment. Only 60 – 70% of patients are effectively suppressed during somatostatin analogs treatment. Using the depot preparations of these drugs, treatment results can only be evaluated after at least three months, when a steady state is reached. In an unselected cohort of patients with active acromegaly we first assessed the response to a single iv dose of octreotide to study the range of responsiveness and the coincident characteristics, i.e. prolactin co-production, size of octreotide- responsive and non-responsive tumors. In a selection of patients, the predictive value of the acute octreotide test for the response to chronic octreotide LAR treatment was evaluated. The results are described in ***Chapter 11.***

A TRH-induced GH response is present in about 50% of patients with GH- secreting adenoma, but not in healthy adults. This paradoxical GH release seems to be a tumor-related phenomenon as it can disappear after successful surgery. In ***Chapter 12,*** we assessed whether the persistence of this pathological response is predictive for the development of recurrence after surgical treatment for acromegaly.

GH regulation during treatment and in rare cases of acromegaly

Detailed studies of 24- hr GH secretion in active and cured acromegaly have been performed in our center by Van den Berg et al. and by others (41, 71, 74, 75). In active acromegaly, GH secretion is characterized by increased pulse frequency, increased basal secretion and pulse amplitude and mass, and increased irregularity. Van den Berg *et al.* reported that all these parameters are restored to normal after successful surgery. In ***Chapter 13*** we assessed to what extent the pathological secretion characteristics are restored during the use of chronic Sandostatin LAR in octreotide- sensitive patients with acromegaly.

In less than 1% of patients, the clinical syndrome of acromegaly is not caused by a pituitary adenoma, but by a GHRH producing tumor. In ***Chapter 14*** we describe the long-term treatment results and our experience with somatostatin analogs in three patients with GHRH-producing tumors. We also studied the characteristics of serum GH and GHRH secretion in two of our patients and in two other patients reported in literature to assess to what extent GH secretion in these patients is different from patients with a GH producing pituitary adenoma.

REFERENCES

1. Marie P 1886 Sur deux cas d'acromegalie: hypertrophie singuliere, non congenitale, des extremites superieures, inferieures et cephalique. Rev Med Liege 6:297-333
2. Massalongo R 1892 Sull'acromegalia. Riforma Med 8:74-77
3. Cushing H 1909 The hypophysis cerebri: clinical aspects of hyperpituitarism and of hypopituitarism. JAMA 53:249-255
4. Cushing H 1909 Partial hypophysectomy for acromegaly: with remarks on the function of the hypophysis. Ann Surg 50:1002-1017
5. Evans HM, Long JA 1921 The effect of anterior lobe of the pituiary administered intra-peritoneally upon growth, maturity and oestrus cycle of the rat. The Anatomical Record 21:62
6. de Herder WW 2004 [Giantism. A historical and medical view]. Ned Tijdschr Geneeskd 148:2585-2590
7. Hardy J 1971 Transsphenoidal hypophysectomy. J Neurosurg 34:582-594
8. Guiot G, Derome P 1972 [Indications for trans-sphenoid approach in neurosurgery. 521 cases]. Ann Med Interne (Paris) 123:703-712
9. Guiot G, Bouche J, Oproiu A 1967 [Indications of the trans-sphenoidal approach to pituitary adenomas. Experience with 165 operations]. Presse Med 75:1563-1568
10. Melmed S, Braunstein GD, Horvath E, Ezrin C, Kovacs K 1983 Pathophysiology of acromegaly. Endocr Rev 4:271-290
11. Melmed S 1990 Acromegaly. N Engl J Med 322:966-977
12. Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R 1980 Epidemiology of acromegaly in the Newcastle region. Clin Endocrinol (Oxf) 12:71-79
13. Bengtsson BA, Eden S, Ernest I, Oden A, Sjogren B 1988 Epidemiology and long-term survival in acromegaly. A study of 166 cases diagnosed between 1955 and 1984. Acta Med Scand 223:327-335
14. Etxabe J, Gaztambide S, Latorre P, Vazquez JA 1993 Acromegaly: an epidemiological study. J Endocrinol Invest 16:181-187
15. Ritchie CM, Atkinson AB, Kennedy AL, et al. 1990 Ascertainment and natural history of treated acromegaly in Northern Ireland. Ulster Med J 59:55-62
16. Nabarro JD 1987 Acromegaly. Clin Endocrinol (Oxf) 26:481-512
17. Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ, Ibbertson HK 1994 Determinants of clinical outcome and survival in acromegaly. Clin Endocrinol (Oxf) 41:95-102
18. Ezzat S, Forster MJ, Berchtold P, Redelmeier DA, Boerlin V, Harris AG 1994 Acromegaly. Clinical and biochemical features in 500 patients. Medicine (Baltimore) 73:233-240
19. Ben Shlomo A, Melmed S 2001 Acromegaly. Endocrinol Metab Clin North Am 30:565-83, vi
20. Bengtsson BA, Brummer RJ, Eden S, Bosaeus I 1989 Body composition in acromegaly. Clin Endocrinol (Oxf) 30:121-130
21. Colao A, Spinelli L, Marzullo P, et al. 2003 High Prevalence of Cardiac Valve Disease in Acromegaly: An Observational, Analytical, Case-Control Study. J Clin Endocrinol Metab 88:3196-3201
22. Pereira AM, Thiel van SW, Lindner JR, et al. 2004 Increased prevalence of regurgitant valvular heart disease in acromegaly. J Clin Endocrinol Metab 89:71-75
23. Ezzat S, Strom C, Melmed S 1991 Colon polyps in acromegaly. Ann Intern Med 114:754-755
24. Jenkins PJ, Fairclough PD, Richards T, et al. 1997 Acromegaly, colonic polyps and carcinoma. Clin Endocrinol (Oxf) 47:17-22
25. Vasen HF, van Erpecum KJ, Roelfsema F, et al. 1994 Increased prevalence of colonic adenomas in patients with acromegaly. Eur J Endocrinol 131:235-237
26. Terzolo M, Boccuzzi A 1996 The prevalence of colonic polyps in acromegaly: a colonoscopic and pathological study in 103 patients. J Clin Endocrinol Metab 81:2406-2407
27. Swearingen B, Barker FG, Katznelson L, et al. 1998 Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab 83:3419-3426
28. Bates AS, Van't Hoff W, Jones JM, Clayton RN 1993 An audit of outcome of treatment in acromegaly. Q J Med 86:293-299
29. Wright AD, Hill DM, Lowy C, Fraser TR 1970 Mortality in acromegaly. Q J Med 39:1-16

30. Orme SM, McNally RJ, Cartwright RA, Belchetz PE 1998 Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab 83:2730-2734
31. Beauregard C, Truong U, Hardy J, Serri O 2003 Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. Clin Endocrinol (Oxf) 58:86-91
32. Baumann G 1991 Growth hormone heterogeneity: genes, isohormones, variants, and binding proteins. Endocr Rev 12:424-449
33. Giustina A, Veldhuis JD 1998 Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. Endocr Rev 19:717-797
34. Kopchick JJ, Parkinson C, Stevens EC, Trainer PJ 2002 Growth hormone receptor antagonists: discovery, development, and use in patients with acromegaly. Endocr Rev 23:623-646
35. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K 1999 Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 402:656-660
36. Gualillo O, Lago F, Gomez-Reino J, Casanueva FF, Dieguez C 2003 Ghrelin, a widespread hormone: insights into molecular and cellular regulation of its expression and mechanism of action. FEBS Lett 552:105-109
37. Petersenn S 2002 Growth hormone secretagogues and ghrelin: an update on physiology and clinical relevance. Horm Res 58 Suppl 3:56-61.:56-61
38. Roelfsema F, Biermasz NR, Veldman RG, et al. 2001 Growth hormone (GH) secretion in patients with an inactivating defect of the GH-releasing hormone (GHRH) receptor is pulsatile: evidence for a role for non-GHRH inputs into the generation of GH pulses. J Clin Endocrinol Metab 86:2459-2464
39. Le Roith D, Bondy C, Yakar S, Liu JL, Butler A 2001 The Somatomedin Hypothesis: 2001. Endocr Rev 22:53-74
40. Buijs MM. Metabolic implications of reduced growth hormone availability in abdominal obesity. 2004. Thesis/Dissertation Leiden University.
41. van den Berg G, Frolich M, Veldhuis JD, Roelfsema F 1994 Growth hormone secretion in recently operated acromegalic patients. J Clin Endocrinol Metab 79:1706-1715
42. Long H, Beauregard H, Somma M, Comtois R, Serri O, Hardy J 1996 Surgical outcome after repeated transsphenoidal surgery in acromegaly. J Neurosurg 85:239-247
43. Ahmed S, Elsheikh M, Stratton IM, Page RC, Adams CB, Wass JA 1999 Outcome of transphenoidal surgery for acromegaly and its relationship to surgical experience. Clin Endocrinol (Oxf) 50:561-567
44. Thorner MO 2003 Controversy: radiotherapy for acromegaly. Clin Endocrinol (Oxf) 58:136-137
45. Barkan AL 2003 Radiotherapy in acromegaly: the argument against. Clin Endocrinol (Oxf) 58:132-135
46. Wass JA 2003 Radiotherapy in acromegaly: a protagonists viewpoint. Clin Endocrinol (Oxf) 58:128-131
47. Littley MD, Shalet SM, Beardwell CG, Robinson EL, Sutton ML 1989 Radiation-induced hypopituitarism is dose-dependent. Clin Endocrinol (Oxf) 31:363-373
48. Brada M, Ford D, Ashley S, et al. 1992 Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma. BMJ 304 1343-1346.
49. Mahmoud-Ahmed AS, Suh JH, Mayberg MR 2001 Gamma knife radiosurgery in the management of patients with acromegaly: a review. Pituitary 4:223-230
50. Landolt AM, Haller D, Lomax N, et al. 1998 Stereotactic radiosurgery for recurrent surgically treated acromegaly: comparison with fractionated radiotherapy. J Neurosurg 88:1002-1008
51. Attanasio R, Epaminonda P, Motti E, et al. 2003 Gamma-Knife Radiosurgery in Acromegaly: A 4-Year Follow-Up Study. J Clin Endocrinol Metab 88:3105-3112
52. Lamberts SW, van der Lely AJ, de Herder WW, Hofland LJ 1996 Octreotide. N Engl J Med 334:246-254
53. Hofland LJ, Lamberts SWJ 2003 The Pathophysiological Consequences of Somatostatin Receptor Internalization and Resistance. Endocr Rev 24:28-47
54. Freda PU 2002 Somatostatin Analogs in Acromegaly. J Clin Endocrinol Metab 87:3013-3018
55. Ben Shlomo A, Melmed S 2003 The Role of Pharmacotherapy in Perioperative Management of Patients with Acromegaly. J Clin Endocrinol Metab 88:963-968

56. Lamberts SW, van der Lely AJ, Hofland LJ 2002 New somatostatin analogs: will they fulfil old promises? Eur J Endocrinol 146:701-705
57. van der Lely AJ, Hutson RK, Trainer PJ, et al. 2001 Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet 358:1754-1759
58. Trainer PJ, Drake WM, Katznelson L, et al. 2000 Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med 342:1171-1177
59. Cozzi R, Attanasio R, Lodrini S, Lasio G 2004 Cabergoline addition to depot somatostatin analogues in resistant acromegalic patients: efficacy and lack of predictive value of prolactin status. Clin Endocrinol (Oxf) 61:209-215
60. Giustina A, Barkan A, Casanueva FF, et al. 2000 Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 85:526-529
61. Freda PU 2003 Current concepts in the biochemical assessment of the patient with acromegaly. Growth Horm IGF Res 13:171-184
62. van der Lely AJ, de Herder WW, Janssen JA, Lamberts SW 1997 Acromegaly: the significance of serum total and free IGF-I and IGF- binding protein-3 in diagnosis. J Endocrinol 155 Suppl 1:S9-13
63. Hoffman DM, O'Sullivan AJ, Baxter RC, Ho KY 2000 Diagnosis of growth-hormone deficiency in adults. Lancet 343:1064-1068
64. de Herder WW, van der Lely AJ, Janssen JA, Uitterlinden P, Hofland LJ, Lamberts SW 1995 IGFBP-3 is a poor parameter for assessment of clinical activity in acromegaly. Clin Endocrinol (Oxf) 43:501-505
65. Pieters GF, Romeijn JE, Smals AG, Kloppenborg PW 1982 Somatostatin sensitivity and growth hormone responses to releasing hormones and bromocryptine in acromegaly. J Clin Endocrinol Metab 54:942-948
66. Veldhuis JD, Pincus SM 1998 Orderliness of hormone release patterns: a complementary measure to conventional pulsatile and circadian analyses. Eur J Endocrinol 138:358-362
67. Veldhuis JD, Moorman J, Johnson ML 1994 Deconvolution analysis of neuroendocrine data: waveform-independent methods and application. Methods in Neurosciences 20:279-325
68. Veldhuis JD, Johnson ML, Veldhuis OL, Straume M, Pincus SM 2001 Impact of pulsatility on the ensemble orderliness (approximate entropy) of neurohormone secretion. Am J Physiol regul Integr Comp Physiol 280: R721-R729
69. Veldhuis JD, Johnson ML 1992 Deconvolution analysis of hormone data. Methods Enzymol 210:539-575
70. Veldhuis JD, Johnson ML 1995 Specific methodological approaches to selected contemporary issues in deconvolution analysis of pulatile neuroendocrine data. Methods in Neurosciences 28:25-92
71. Ho KY, Weissberger AJ 1994 Characterization of 24-hour growth hormone secretion in acromegaly: implications for diagnosis and therapy. Clin Endocrinol (Oxf) 41:75-83
72. Zirkzee EJ, Corssmit EP, Biermasz NR, et al. 2004 Pituitary magnetic resonance imaging is not required in the postoperative follow-up of acromegalic patients with long-term biochemical cure after transsphenoidal surgery. J Clin Endocrinol Metab 89:4320-4324
73. Webb SM, Prieto L, Badia X, et al. 2002 Acromegaly Quality of Life Questionnaire (ACROQOL) a new health-related quality of life questionnaire for patients with acromegaly: development and psychometric properties. Clin Endocrinol (Oxf) 57:251-258
74. van den Berg G, Pincus SM, Frolich M, Veldhuis JD, Roelfsema F 1998 Reduced disorderliness of growth hormone release in biochemically inactive acromegaly after pituitary surgery [see comments]. Eur J Endocrinol 138:164-169
75. Ho PJ, Jaffe CA, Friberg RD, Chandler WF, Barkan AL 1994 Persistence of rapid growth hormone (GH) pulsatility after successful removal of GH-producing pituitary tumors. J Clin Endocrinol Metab 78:1403-1410