J. Endocrinol. Invest. 30: 497-506, 2007

A retrospective analysis on biochemical parameters, cardiovascular risk and cardiomyopathy in elderly acromegalic patients

A. Colao[1], R. Pivonello[1], L. Spinelli[2], M. Galderisi[3], R.S. Auriemma[1], M. Galdiero[1], G. Vitale[1,4], M. De Leo[1], and G. Lombardi[1]

[1]Section of Endocrinology, Department of Molecular and Clinical Endocrinology and Oncology; [2]Section of Cardiology, Department of Internal Medicine; [3]Section of Cardioangiology, Department of Clinical and Experimental Medicine, University of Naples "Federico II", Naples; [4]Section of Endocrinology, University of Milan, San Luca Hospital, Italian Auxologic Institute, Milan, Italy

ABSTRACT. This analytical, observational, retrospective, case-control study was designed to describe clinical presentation, biochemical disease severity, presence, and severity of metabolic and cardiovascular complications in patients diagnosed as having acromegaly at 60 yr or older (no.=57) as compared to sex- and age-matched healthy controls. Patients and controls underwent a complete endocrine, metabolic, and cardiovascular check-up. The age at diagnosis was equally distributed between 60 to 75 yr while only a minority of the patients (5.3%) was diagnosed after 75 yr. Median GH and IGF-I levels were 15 µg/l and 557 µg/l. The prevalence of microadenomas, enclosed macroadenomas, and extrasellar/invasive macroadenomas was 30%, 49%, and 21%, respectively. All patients had joint complaints and goiter (euthyroid in 65% and pre-toxic/toxic in 35%), 82% had hypertension, 58% diabetes and 54% had both. As compared to controls, a higher number of patients were receiving treatment with anti-arrhythmiacs (*p*=0.033), anti-aggregants (*p*=0.013), levothyroxine (*p*=0.015), and metformin (*p*=0.022). Nevertheless, the patients had higher systolic and diastolic blood pressure, heart rate, left ventricular mass index, lipids, glucose and insulin levels as well as percent function of β cells than controls. In conclusion, the high prevalence of systemic complications makes elderly acromegalics more susceptible than controls to cardiovascular events. We suggest that an accurate clinical check-up and, possibly, a more aggressive treatment of hypertension and diabetes are required in elderly acromegalics.
(J. Endocrinol. Invest. 30: 497-506, 2007)
©2007, Editrice Kurtis

INTRODUCTION

Acromegaly is considered a rare disease, with an incidence of 3-4 cases per million population per yr and a prevalence of 50-80 cases per million population. It is caused by a GH-secreting pituitary tumor in more than 98% of cases (1). Pituitary tumors are generally benign; mean age at diagnosis ranges between 40-50 yr (2). Long-lasting uncontrolled GH and IGF-I excess is associated with increased mortality due to cardiovascular, cerebrovascular, and respiratory diseases (3-10). Patients diagnosed at an older age are likely to present more severe cardiovascular and respiratory complications due to the generally long period of uncontrolled disease but a complete description of acromegaly in the elderly is not currently available (11).

In general, pituitary adenomas in the elderly, commonly defined as people aged from 65 yr and older, are fewer than 10% (12). As reported in a recent review by Minniti et al. (12), changes related to ageing and associated diseases may significantly delay the diagnosis of pituitary tumors in this age range. Visual-field defects might be missed in patients suffering from common age-related ocular diseases; cardiovascular and/or respiratory disease, articular problems, hypertension, and diabetes, which are

Key-words: Acromegaly, GH, IGF-I, surgery, somatostatin, octreotide, lanreotide, cardiomyopathy.

Correspondence: A. Colao, MD, PhD, Department of Molecular & Clinical Endocrinology and Oncology, "Federico II" University of Naples, via S. Pansini 5, 80131 Naples, Italy.

E-mail: colao@unina.it

Accepted January 10, 2007.

frequent in the non-acromegalic elderly population, might confound the clinical picture of acromegaly in elderly subjects.

Nowadays, life expectancy is significantly longer than 20 yr ago in the general population: it is thus expected that a higher proportion of patients will be diagnosed for acromegaly in the near future. Nevertheless, GH-secreting pituitary adenomas represent a minority of the tumors removed in the elderly patients in different series (12). Very few data are currently available in the cohort of elderly patients with acromegaly (12) and no data are available on the severity of cardiovascular risk and cardiomyopathy in this age group.

The current study aims at reporting on clinical presentation, biochemical disease severity, presence, and severity of metabolic complications and cardiovascular risk in a consecutive series of 57 patients diagnosed as having acromegaly at 60 yr or older. The patients were compared to controls matched for age and gender and undergoing a complete endocrine, metabolic, and cardiovascular check-up.

MATERIALS AND METHODS

Patients

Inclusion criteria: Patients with active acromegaly coming to the Endocrinology Unit of the "Federico II" University of Naples from Jan 1st 1995 to December 31st 2004 aged 60 yr or more never before treated for acromegaly.

Exclusion criteria: Patients aged <60 yr, or already treated for acromegaly with surgery, medical therapy (dopamine agonists, somatostatin analogues or GH-receptor antagonist) or radiotherapy.

Patients: Of 275 patients diagnosed with acromegaly in our department, 57 patients (27 women, 30 men) were included in this study. All patients had newly diagnosed acromegaly, defined as previously reported (1), by high serum GH levels during a 6-h time course, not suppressible <1 μg/l after glucose load (in non-diabetic patients) and high plasma IGF-I levels for age (expressed as the upper limit value of normal range) (Table 1). The presumed duration of acromegaly was assessed by comparing photographs taken over a period of 10-40 yr and by interviewing the patients as to the date of onset of acral enlargement and facial disfigurement. The interval between assumed clinical onset and the time of diagnosis ranged from 12-480 months (median duration of 204 months). All patients signed an informed consent form at entry to the clinic to approve diagnostic testing, treatment decision, follow-up, and treatment of the data for scientific purposes. This study was conducted in accordance with the Helsinki II Declaration on human experimentation.

Of 235 non-acromegalic control subjects recruited among the medical and paramedical personnel of our department and their relatives plus clerks and their relatives, 57 (27 women and 30 men) were matched with the patients for age (±2 yr), and gender. Results of 174 out of 235 controls (92 women, 82 men aged 18-80 yr) (13), selected on the basis of the absence of complications were previously reported. In contrast with the previous study (13), the controls included in the current study were unselected for the presence of hypertension, diabetes or obesity in order to have information on the prevalence, severity, and treatment of these complications, if any, between the patients with acromegaly and their controls.

The protocol of the study was approved by the Ethical Committee of the "Federico II" University of Naples and all subjects gave their informed consent to the study. The comparison between patients and controls at study entry is shown in Table 1.

Study design and protocol: This is an analytical, observational, retrospective, case-control study to investigate the cardiovascular risk of elderly patients with acromegaly. After an overnight fasting in all patients and controls the following were performed:

1) Measurement of serum IGF-I levels twice in a single sample at time 0 of the GH profile; GH levels calculated as the mean value of at least 6 samples drawn every 30 min over a period of 3 h; the average value was considered for statistical analysis. Hypogonadism in males was diagnosed by FSH and/or LH <3 mU/l and testosterone levels <2.9 μg/l; in women deficit of FSH and LH was considered when levels were inappropriately low (<10 mU/l) for the post-menopausal age. Deficiency of FSH and LH (<3 mU/l) was considered separately. Pituitary ACTH deficiency was diagnosed when serum 08:00 h cortisol levels were low (<3.6 μg/dl; 100 nmol/l) or cortisol peaked below 21 μg/dl (600 nmol/l) in response to synthetic ACTH stimulation (250 μg, iv) together with an increase from basal of less than 8 μg/dl (220 nmol/l). TSH deficiency was diagnosed when a subnormal serum free T_4 (FT_4) level (<9 pmol/l) was associated with a low or normal TSH (0.3-5 mU/l) level.
2) Measurement of total cholesterol, HDL cholesterol, and triglycerides levels; the total/HDL-cholesterol ratio, index of cardiovascular risk, was calculated (14). Hypertriglyceridemia was diagnosed when triglycerides levels were >1.7 mmol/l (150 mg/dl) (15), hypercholesterolemia was diagnosed when LDL-cholesterol levels were >2.6 mmol/l (100 mg/dl) (15). In line with the modern guidelines (15), the LDL/HDL-cholesterol ratio was also calculated.
3) Measurement of glucose and insulin levels at fasting and every 30 min for 2 h after the oral administration of 75 g of glucose diluted in 250 ml of saline solution. In 10 patients and in 8 controls the glucose load was not performed because of overt diabetes. Diabetes mellitus was diagnosed when fasting glucose was above 7 mmol/l (125 mg/dl) at two consecutive measurements or when 2 h after the oral glucose tolerance test (oGTT) glucose was >11 mmol/l (200 mg/dl) (16). Impaired glucose tolerance (IGT) was diagnosed when glucose level was between ≥7.8 mmol/l and <11 mmol/l 2 h after the oGTT while impaired fasting glucose (IFG) was diagnosed when glucose level was between 5.6 and 6.9 mmol/l at fasting (16). Normal glucose level was considered when below 5.6 mmol/l at fasting. To predict insulin resistance and β-cell function the HOMA (homeostatic model assessment) [HOMA-R (%), and HOMA-β (%), respectively] was used according to Matthews et al. (17). By assuming that normal-weight healthy subjects aged <35 yr have a HOMA-β of 100% and a HOMA-R of 1, the values for individual patients can be assessed from the insulin and glucose concentrations by the formulae: HOMA-R = [insulin (mU/l)*fasting glucose (mmol/l)] / 22.5; HOMA-β (%) = [20*insulin (mU/l)] / [glucose (mmol/l)-3.5].
4) Measurement of blood pressure, as previously reported (18) and heart rate. The average of 6 measurements (3 taken by each of the two examiners) was used in all analysis. In accordance with

Table 1 - *Clinical and endocrine parameters in patients and controls.*

	Patients		Controls		*p*
	(Mean±SD)	(95% CI)	(Mean±SD)	(95% CI)	
No.	57		57		
W/M	27/30		27/30		
Age (yr)	70±6	68-71	70±6	68-71	1
Body mass index (kg/m^2)	24.6±2.3	24.0-25.2	25.3±2.2	24.7-25.8	0.011
GH levels (μg/l)	30.8±62.9	14.1-47.5	0.3±0.3	0.3-0.4	0.0006
Nadir GH levels after oGTT (μg/l)*	12.9±29.7	4.2-21.7	0.03±0.03	0.02-0.03	0.0045
IGF-I levels (μg/l)	598±218	540-656	150±40	139-160	<0.0001
IGF-I levels (ULN)	2.83±1.02	2.56-3.10	0.70±0.17	0.65-0.76	<0.0001
Systolic blood pressure levels (mmHg)	163±20	158-161	148±13	144-152	<0.0001
Diastolic blood pressure levels (mmHg)	96±11	93-99	84±7	82-85	<0.0001
Heart rate (bpm)**	81±5	80-83	79±6	78-81	0.01
Left ventricular mass index (g/m^2)	182.3±63.5	165.4-199.1	102.5±16.8	98.1-107.0	<0.0001
Early to atrial mitral flow velocity (msec)	0.83±0.17	0.78-0.87	1.13±0.08	1.11-1.15	<0.0001
Left ventricular ejection fraction (%)	50.0±5.8	48.6-51.4	58.9±5.8	57.3-60.4	<0.0001
Total cholesterol levels (mmol/l)	5.7±1.3	5.3-6.0	5.2±0.8	5.0-5.4	0.037
HDL-cholesterol levels (mmol/l)	1.1±0.1	1.0-1.1	1.4±0.1	1.4-1.5	<0.0001
Total/HDL-cholesterol ratio	5.3±1.6	4.9-5.8	3.7±0.8	3.5-3.9	<0.0001
LDL-cholesterol levels (mmol/l)	4.2±1.3	3.9-4.6	3.5±0.8	3.3-3.7	<0.0001
LDL/HDL-cholesterol ratio	4.0±1.6	3.6-4.4	2.5±0.8	2.3-2.7	<0.0001
Triglycerides levels (mmol/l)	1.9±0.5	1.7-2.0	1.3±0.3	1.3-1.4	<0.0001
Fibrinogen levels (mg/dl)	380±33	371-388	253±46	241-265	<0.0001
Glucose levels (mmol/l)	6.2±1.5	5.8-6.6	5.4±1.0	5.2-5.7	0.0005
Insulin levels (mU/l)	26.4±14.4	22.4-30.5	10.3±6.2	8.6-11.9	<0.0001
HOMA-R index (%)	2.3±1.1	1.9-2.6	2.7±2.1	2.1-3.2	0.73
HOMA-β index (%)	277±187	188-290	114±49	101-127	<0.0001

* Comparison was performed between 47 patients and 49 controls. ** Comparison was performed between 39 patients and 57 controls. The other 18 patients had different arrhythmias.
W: women; M: men; oGTT: oral glucose tolerance test; ULN: upper limit of normal range; HOMA-R: insulin resistance homeostasis model assessment; HOMA-β: β-cell function homeostasis model assessment

the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (19) the severity of hypertension was classified as mild (Stage 1) when the systolic blood pressure (SBP) or diastolic blood pressure (DBP) were between 140 and 159 mmHg and between 90 and 99 mmHg, respectively; severe (Stage 2) when the SBP or DBP were >160 and >100 mmHg respectively; prehypertension was defined as SBP >120 - <140 and DBP >80 - <90 mmHg.

5) Echocardiography by M-mode, 2-dimensional and pulsed Doppler for 3-5 consecutive cardiac cycles as previously reported (20-22) and according to the recommendations of the American Society of Echocardiography (ASE) (23). The following measurements were determined on M-mode tracing: inter-ventricular septum thickness (IVST), left ventricular internal end-diastolic diameter (LVID), and posterior wall thickness (PWT), left ventricular mass (LVM) calculation by Devereux's formula (24): LVM= 1.04[(IVST+LVID+PWT)3-(LVID)3]-14 g. LVM indexed for body surface area (LVMi) was ≥135 g/m^2 in men and ≥110 g/m^2 in women and were considered as cut-off points for LVH. Diastolic function was evaluated by pulsed Doppler mitral inflow as early (E) and atrial (A) peak velocity ratio (E/A), indicating the normal pattern of ventricular diastolic filling when ≥1. Left ventricular systolic function was evaluated by ejection fraction normal (LVEF) when >50%.
6) Only in the patients, magnetic resonance imaging (MRI) of the sellar region performed on clinical 1T and 1.5T scanners

as previously reported (25-26). The sagittal, axial, and coronal diameters at their maximal value were measured to calculate tumor volume by the De Chiro and Nelson formula [(volume= sagittal*coronal*axial diameters)*π/6].

Assays

Serum GH levels were measured by immunoradiometric method: from Jan 1st 1995 to Dec 31st 2001, the sensitivity of the assay was 0.2 µg/l and the intra- and inter-assay variation coefficients (CV) were respectively 4.5 and 7.9%; from Jan 1st 2002, the sensitivity of the assay was 0.02 µg/l and the intra- and inter-assay CV were 4.3 and 8.5%, respectively. Serum IGF-I was measured by immunoradiometric assay (IRMA) after ethanol extraction. The normal range in 51-60, 61-70 and >70 yr old men was 95-270, 88-250, 78-200 µg/l, respectively; in women it was 90-250, 82-200, 68-188 µg/l, respectively. The sensitivity of the assay was 0.8 µg/l. The intra-assay CV were 3.4, 3.0, and 1.5% for low, medium, and high points of the standard curve, respectively. The inter-assay CV were 8.2, 1.5, and 3.7% for low, medium, and high points of the standard curve. IGF-I data are shown as the upper limit of normal range [(ULN) normal=≤1].

Statistical analysis

The data were analyzed using MedCalc Software for Windows (MedCalc, Mariakerke, Belgium). Data are reported as mean±SD unless otherwise specified. The comparison between patients and controls was made by the Student's t-test for paired data. The comparisons between patients and controls when subgrouped according with the presence or absence of hypertension or diabetes was made by the Mann-Whitney test, due to the limited number of cases included in this analysis. Categorical variables were compared using the Pearson's chi-square test.

RESULTS

Disease onset and clinical presentation

As shown in Figure 1, the age at diagnosis was equally distributed between 60 to 75 yr while only a minority of the patients (5.3%) was diagnosed after 75 yr. The estimated age of disease onset (calculated as the difference between the age at diagnosis and the estimated disease duration) was in the 5th decade of life in 28%, in the 6th decade in 40%, and in the 7th decade in 30%.

Of all patients, 33 (57.9%) were referred to our Unit with a diagnosis of acromegaly or suspected acromegaly performed by family doctors or neurosurgeons. The remaining 24 patients (42.1%) were referred to our Unit because of the presence of euthyroid goiter (no.=8, 33.3%), subclinical toxic or toxic goiter (no.=9, 37.5%) or severe cardiac problems in patients with goiter and diabetes (no.=7, 29.2%).

At diagnosis, all patients had joint complaints and goiter (euthyroid in 65% and subclinical toxic/toxic in 35%), the majority had hypertension (82%) and/or diabetes (58%); 54% of patients had both hypertension and diabetes (Fig. 2). In controls prevalence of

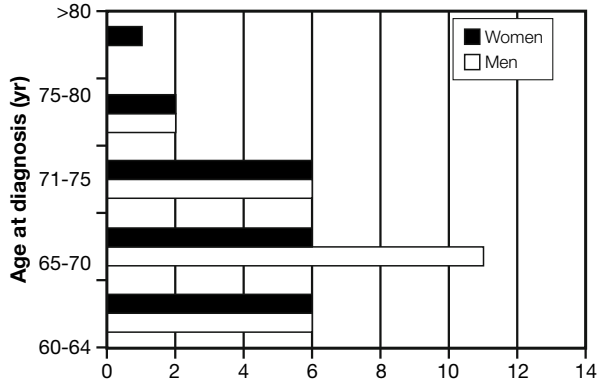
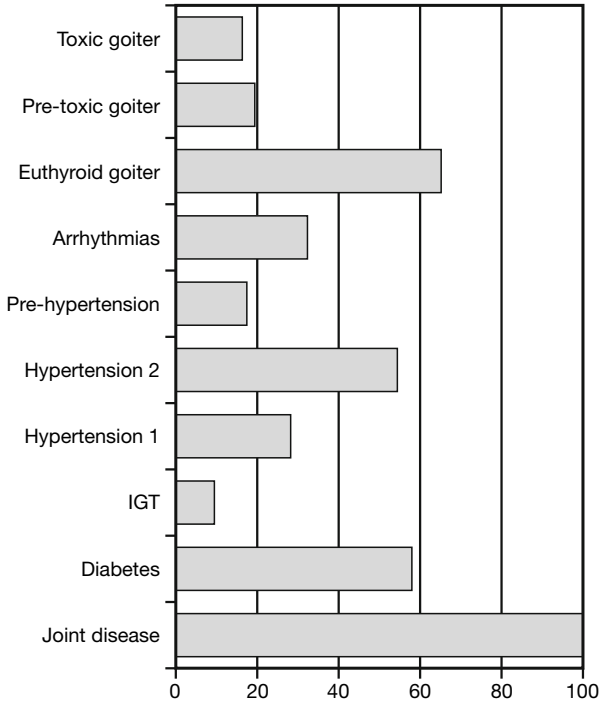


Fig. 1 - *Age at diagnosis (top) and estimated age of onset of acromegaly (bottom) in the 57 patients aged above 60 yr included in the study.*

hypertension, diabetes, and euthyroid goiter was 67%, 28%, and 42%, respectively.

GH and IGF-I levels and tumor size

Fasting mean GH levels were 15 µg/l (median), 9.5 µg/l in women and 16 µg/l in men (p=0.47), while



Hypertension was classified according to the 7th report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (21). IGT= Impaired glucose tolerance.

Fig. 2 - *Prevalence of clinical symptoms on diagnosis of acromegaly over 60 yr.*

IGF-I levels were 557 µg/l (median), 454 µg/l in women and 630 µg/l in men (p=0.13). The prevalence of microadenomas, enclosed macroadenomas, and extrasellar/invasive macroadenomas was 30%, 49%, and 21%, respectively, similarly distributed in women and men (Table 2). Tumor volume was 1360±1102 mm^3 in women and 1484±2069 mm^3 in men (p=0.28): individual tumor volume distribution is shown in Figure 3. Patients with microadenomas and enclosed macroadenomas had a longer disease duration (and thus a younger age at disease onset) than those with extrasellar/invasive macroadenomas (Table 3). Seven patients (12%), all women, had associated hyperprolactinemia (range 31-355 µg/l).
Normal pituitary function was found in 5 patients with microadenomas (29%), 11 patients with enclosed macroadenomas (39%), and two patients with extrasellar/invasive macroadenomas (16.7%; p=0.36). The prevalence of one or two pituitary hormone deficiencies was also similar in the three groups: 71%, 54%, and 82%, respectively. Only two male patients with enclosed macroadenomas (7%) had three hormone deficiencies, namely FSH, LH, and TSH. Fourteen patients had hypoprolactinemia (PRL levels below 5 µg/l).
None of the patients with microadenoma or with enclosed macroadenoma had visual field defects; 6 of the 12 patients with extrasellar/invasive macroadenomas (50%) showed impinging of the optic chiasm by the tumor but only two of them showed minor visual field defects such as monolateral quadrantopsy. The prevalence of hypertension (88%, 86%,

Table 2 - *Clinical and endocrine parameters in the patients according to tumor size.*

	Microadenomas	Macroadenomas enclosed	Macroadenomas extrasellar/invasive	*p*
No.	17	28	12	0.003
W/M	8/9	12/16	7/5	
Tumor volume (mm^3)	162±86	1121±509	4204±3168	<0.0001
Age (yr)	70±6	71±6	68±5	0.32
Estimated disease duration (months)	260±86	178±117	6±33	<0.0001
Estimated age at onset of acromegaly (yr)	48±9	56±8	63±5	<0.0001
GH levels (µg/liter)	18.3±19.6	22.6±17.2	67.9±130.3	0.068
Nadir GH levels after oGTT (µg/l)*	5.2±2.7	10.4±12.4	29.3±60.9	0.13
IGF-I levels (µg/l)	582±294	615±209	583±199	0.55
IGF-I levels (ULN)	2.73±1.12	2.92±1.01	2.91±1.0	0.35
Systolic blood pressure levels (mmHg)	161±18	163±19	166±24	0.58
Diastolic blood pressure levels (mmHg)	98±13	96±9	93±13	0.6
Heart rate (bpm)	79±3	81±6	84±4	0.072
Left ventricular mass index (g/m^2)	180.7±53.4	188.5±76.2	170.1±42.7	0.98
Early to late mitral flow velocity (msec)	0.83±0.18	0.83±0.18	0.83±0.15	0.96
Left ventricular ejection fraction (%)	49.4±4.9	49.7±4.3	51.1±8.1	0.61
Total/HDL-cholesterol ratio	5.7±2.2	5.4±1.3	4.7±1.3	0.26
LDL/HDL-cholesterol ratio	4.3±2.1	4.0±1.3	3.4±1.2	0.61
Glucose levels (mmol/l)	6.4±1.6	6.5±1.5	5.5±1.2	0.14
Insulin levels (mU/l)	29.2±10.0	29.0±14.7	26.4±7.6	0.16
HOMA-R index (%)	2.4±1.1	2.4±1.3	1.9±0.5	0.13
HOMA-β index (%)	264±87	222±100	421±327	0.005

*Comparison was performed among 13, 24 and 10 patients undergoing the glucose tolerance test at diagnosis.
W: women; M: men; oGTT: oral glucose tolerance test; ULN: upper limit of normal range; HOMA-R: insulin resistance homeostasis model assessment; HOMA-β: β-cell function homeostasis model assessment.

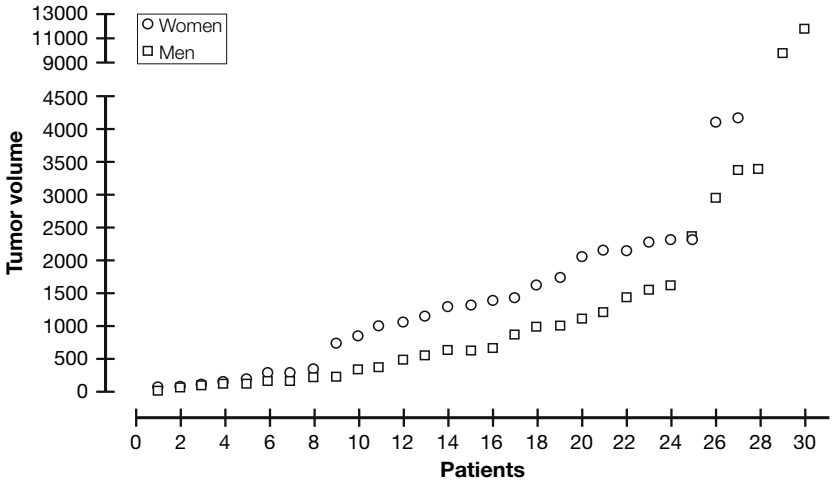


Fig. 3 - *Distribution of tumor volume according to gender in patients with acromegaly over 60 yr.*

83%; *p*=0.93) and of abnormalities of glucose tolerance (71%, 71%, 50%; *p*=0.39) was similar in the three groups.

Cardiovascular risk and cardiac parameters

As for the classical cardiovascular risk factors, 24 patients (42.1%) and 29 controls (50.9%) were non-smokers, 7 (12.3%) and 10 (17.5%) were ex-smokers while 26 (45.6%) and 18 (31.6%) were smokers. Normal weight (<25 kg/m^2) was found in 31 patients (54%) and 22 controls (39%; *p*=0.13); overweight (25-30 kg/m^2) in 25 (44%) and 34 (59%, *p*=0.13) while obesity (>30 kg/m^2) was found in one subject in each group (2%). Mean body mass index was slightly lower in the patients than in controls (Table 1). As compared to controls (Fig. 4), a higher number of patients were receiving treatment with anti-arrhythmics, anti-aggregants levothyroxin and metformin.
The patients had higher SBP and DBP, heart rate, LVMi, lipids, glucose, and insulin levels as well as the percent function of β cells than controls (Table 1). Only 6 of the 57 patients (10%) did not have hypertension or were not receiving treatment for hypertension, thus a subanalysis of normotensive subjects was not performed. Pre-hypertension was found in all these 6 patients and in 17 controls (30%, *p*=0.02). Left ventricular hypertrophy was found in all but 2 patients (96%) and in 9 controls (16%, *p*<0.0001). Diastolic and systolic dysfunction was significantly more prevalent in the patients than in controls (82% *vs* 2% and 51% *vs* 2%; *p*<0.0001).
Patients and controls were grouped according to the presence of normal glucose tolerance or diabetes (Table 3). Impaired glucose tolerance and/or impaired fasting glucose was found in 13% of patients and in 30% of controls (*p*=0.0006). Patients with normal glucose tolerance were younger, had a shorter disease duration (131±100 *vs* 207±123 months, *p*=0.026), lower SBP, triglycerides levels, total/HDL cholesterol, and LDL/HDL-cholesterol ratios and higher HDL-cholesterol levels than those with diabetes. Similarly, controls with normal glucose tolerance were younger, slimmer, had a lower DBP, better cardiac function, and lipid profile than those with diabetes.
Of all subjects with normal glucose tolerance, fasting glucose levels were higher in the patients than in the controls (5.1±0.4 *vs* 4.5±0.3 mmol/l, *p*=0.0002). The HOMA-R index in the patients with normal or abnormal glucose tolerance was unexpectedly similar (2.2±0.9 *vs* 2.4±1.4, *p*=0.59) while it was expectedly higher in the controls with abnormal glucose tolerance than in those with normal tolerance (1.4±0.7 *vs* 2.2±0.7, *p*<0.0001). The patients with acromegaly and normal glucose tolerance had a HOMA-β index approximately 3 times higher than controls (409±235 *vs* 138±59%, *p*<0.0001).

DISCUSSION

Only very few studies have characterized the clinical and hormonal features of acromegaly in elderly patients. This analytical, observational, retrospective, case-control study shows that acromegaly diagnosed after the age of 60 yr has no gender difference; it has a distribution of age of onset similar for each 5-yr period up to 70 yr and is rarer afterwards; it is caused less frequently by extrasellar or invasive macroadenomas, is characterized by goiter and left ventricular hypertrophy, and has a higher prevalence of hypertension, diabetes, diastolic and systolic dysfunction than sex- and age-matched non acromegalic controls.

Table 3 - *Clinical and endocrine parameters in patients and controls according to their glucose tolerance status.*

	Normal glucose tolerance			Diabetes mellitus		
	Patients	Controls	*p*	Patients	Controls	*p*
No.*	19	23		33	17	
Age (yr)	68±4[A]	66±5[B]	0.28	71±7	73±7	0.68
Body mass index (kg/m^2)	24.6±2.2	24.6±2.1[B]	0.86	24.6±2.5	26.4±2.3	0.012
GH levels (μg/liter)	18.7±16.2	0.4±0.3[B]	<0.001	26.8±29.6	0.2±0.3	<0.001
IGF-I levels (μg/liter)	573±232	167±37	<0.001	607±221	137±45	<0.001
IGF-I levels (ULN)	2.61±1.01	0.76±0.15	<0.001	2.94±1.07	0.67±0.21	<0.001
Systolic blood pressure levels (mmHg)	156±20[A]	140±12	0.01	167±19	156±15	0.057
Diastolic blood pressure levels (mmHg)	95±10	80±7[B]	<0.001	98±12	87±6	0.002
Heart rate (bpm)	81±3	79±7	0.13	81±6	80±4	0.47
Left ventricular mass index (g/m^2)	170.5±48.5	90.7±10.2[B]	<0.001	192.1±73.7	113.2±13.7	<0.001
Early to Atrial mitral flow velocity (msec)	0.87±0.17	1.17±0.7[B]	<0.001	0.80±0.18	1.10±0.08	<0.001
Left ventricular ejection fraction (%)	52.2±6.8	62.7±5.9[B]	<0.001	48.6±4.2	54.8±3.4	<0.001
Total cholesterol levels (mmol/l)	5.3±1.1	4.8±0.6[B]	0.18	5.9±1.5	5.6±0.9	0.37
LDL-cholesterol levels (mmol/l)	3.8±1.1	3.1±0.6[B]	0.034	4.5±1.5	3.9±0.9	0.15
HDL-cholesterol levels (mmol/l)	1.1±0.1[B]	1.5±0.1[B]	<0.001	1.0±0.1	1.3±0.1	<0.001
Triglycerides levels (mmol/l)	1.7±0.3[A]	1.1±0.2[B]	<0.001	2.0±0.5	1.5±0.2	0.003
Total/HDL-cholesterol ratio	4.7±1.2[B]	3.2±0.6[B]	<0.001	5.8±1.8	4.2±0.9	0.001
LDL/HDL-cholesterol ratio	3.4±1.2[B]	2.1±0.6[B]	<0.001	4.4±1.7	3.0±0.9	0.001

*: Prevalence in the two cohorts, p=0.56. Superscript letters indicate the statistical significance of patients and controls with diabetes. A=p<0.05; B=p<0.01. Significance was established by the Mann-Whitney U test. ULN: upper limit of normal range.

Disease onset and clinical presentation

The prevalence of acromegaly in different series of pituitary adenomas of elderly patients has been reported to be lower than that of other tumor histotypes such as clinically non-functioning adenomas (12, 27-29). This clinical finding is confirmed by the rarity of positive GH immunostaining in pituitaries obtained at unselected autopsies of 152 subjects over 80 yr of age (30). In the period of one decade, we diagnosed pituitary tumors in 170 patients of elderly age: the majority (no.=88; 52%) had a clinically non-functioning adenoma, 14% had a macroprolactinoma (no.=24), only one had an ACTH-secreting adenoma (0.6%), while 57 had acromegaly (33.5%). Thus, at least in our series of elderly patients with pituitary adenomas, the GH-secreting is the second most frequent histotype, while in the general population of pituitary tumors it is less frequent than prolactinomas and clinically non-functioning adenomas.

As reported by other authors, visual impairment due to chiasmatic compression is rare in GH-secreting tumors, affecting fewer than 20% of cases (28, 31, 32). In our series, which is by far the largest reported series of patients with acromegaly aged above 60 yr at diagnosis, visual field defects were indeed uncommon (3.5%), even in the small groups of patients bearing extrasellar or invasive macroadenomas (17%). Acromegaly is generally recognized by typical clinical features even if the clinical picture is reported to be milder than in younger patients (28). In the current study we did not perform a comparison between young and elderly patients: however, all patients presented with arthropathy and skeletal abnormalities which were more severe and more frequent than previously reported (11). Besides, all the 57 patients with acromegaly presented with goiter that was pre-toxic or toxic in 35% of cases, confirming a previous report in a larger series of patients unselected for age of disease diagnosis (33). Associated hypopituitarism is reported to be uncommon (31, 32). Our findings are in partial disagreement with the previous ones since one or two pituitary hormone deficiencies were found in 71% of patients with microadenomas, 54% of patients with enclosed macroadenomas, and 82% of those with extrasellar or invasive macroadenomas. However,

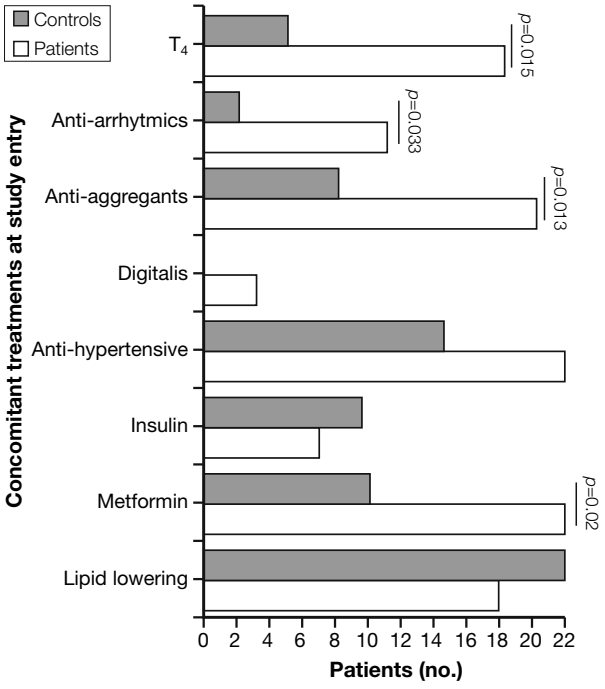


Fig. 4 - *Treatment of complications in patients with acromegaly and controls over 60 yr. Data are expressed as percentage prevalence.*

these were mainly referred to FSH and LH. It should be considered, however, that some degree of testicular dysfunction in the elderly is not rare (34, 35) and that other complications such as diabetes and obesity might play a role in determining hypogonadism. Though obesity is not common in acromegaly, poor control of diabetes may be responsible (at least partly) for such high prevalence of hypogonadism in this cohort.

In contrast, systemic complications, such as diabetes mellitus and hypertension, are known to be more frequent in this age group and increase cardiovascular risk (11, 12, 36). In our series, the vast majority of the patients were hypertensive (82%) or diabetic (58%) or both (54%). The remaining 18% of the patients had the newly classified pre-hypertension so that none of the patients has normal blood pressure levels. Strikingly, most hypertensive and diabetic patients were already receiving treatment addressing these complications (49% and 51%) with unsatisfactory therapeutic effects.

GH and IGF-I levels and tumor size

The severity of acromegaly was reported to be milder in elderly patients than in young ones as it was associated with lower GH values and smaller tumors at presentation (28, 37, 38). In a previous multicenter study enrolling 45 elderly patients with acromegaly (including 17 of the 57 reported in the current study), we found a median GH level of 7.5 µg/l and IGF-I levels of 622 µg/l, significantly lower than patients aged below 40 yr or aged between 40 to 60 yr (38). In the current series, GH levels, but not IGF-I levels, were higher than previously found (38). This finding could be explained by the larger tumors included in the current series: in fact, the maximal tumor diameter reported in our previous series (38) was of 11 mm (median) while in the current series the median diameters of coronal, anteroposterior, and sagittal were respectively of 12.2, 13.5, and 13.4 mm. The reported smaller tumors in elderly patients is, anyway, confirmed by the evidence of a significantly lower prevalence of extrasellar or invasive tumors in this series (21%) compared to a recently published series of 99 patients unselected for age (62%) which included 25 patients of the present study (39). Additionally, we did not find any gender difference here as for GH and IGF-I levels. In younger patients series, women were reported to have lower IGF-I levels (38) easier to normalize after treatment (40, 41). The gender difference in the GH status is generally explained by the patients' gonadal status and therefore in the elderly patients no gender difference is expected. In a recent study, however, we did not report any gender difference in the response to somatostatin analogues in a series of patients analyzed according to gonadal status and gender (26).

Cardiovascular risk and cardiac parameters

Cardiovascular and cerebrovascular diseases are the most frequent cause of premature death in acromegaly (2-10). Long-lasting GH and IGF-I excess has been shown to induce several changes of the cardiovascular system: GH and IGF-I receptors have been shown on cardiomyocytes, vascular smooth muscle cells, arterial endothelial cells, as expression of the main cell subtypes of this system (11, 42). Left ventricular hypertrophy is the most common cardiac consequence of acromegaly, followed by hypertension, diastolic dysfunction, and cardiac valve disease (11). From a previous analysis, acromegaly in the elderly was shown to be associated with left ventricular hypertrophy in approximately 80% of the patients (11). Few data on the severity of the cardiomyopathy have been reported in other cohorts of elderly patients with acromegaly so far. In a study focusing on the surgical outcome in patients with acromegaly aged above 65 yr, Minniti et al. (32) reported hypertension in 50%, left ventricular hypertrophy in 68%, diabetes or impaired glucose tolerance in 41%: overall the anesthesiological risk was increased in 73% of the patients. To note that in this series, 6 out

of 22 patients received pre-surgical treatment with somatostatin analogues for 2 to 6 months and thus left ventricular mass could have been partly reduced by this treatment (11).

In the current study we included 20 of the patients whose results were previously reported in the analysis of the severity of cardiomyopathy according to patients' age (11). The current larger series of patients demonstrates that left ventricular hypertrophy can be considered a characteristic of elderly acromegaly being found in 96% of the patients. This can be explained both by the high incidence of hypertension and by the long-lasting GH and IGF-I hypersecretion that have clear-cut hypertrophic effect on cardiomyocytes (11). Interestingly, none of our patients showed normal blood pressure levels: a minority of the patients (18%) had the newly classified form of pre-hypertension which was found also in 30% of controls. Despite the fact that treatment of hypertension was given more frequently to the patients, blood pressure levels were higher in the patients than in controls. As a consequence, of the higher prevalence of uncontrolled hypertension and diabetes and the presence of left ventricular hypertrophy, a higher proportion of patients had diastolic and systolic dysfunction. This result was rather expected on the basis of previous findings showing a progressive aggravation of cardiac dysfunction during life-span in acromegalic patients. Similarly, it was not surprising that most patients had diabetes (either newly diagnosed or already receiving specific treatment). It is interesting that compared to controls with normal glucose tolerance, the patients had a significantly higher estimated percent function of β-cells: this is in line with the hypothesis that diabetes in acromegaly appears when β-cells function fails after years of hyperstimulation (42).

CONCLUSION

Only very limited data are presently available in patients with acromegaly aged above 60 yr. The current study indicates that left ventricular hypertrophy and goiter are invariably present in these patients at diagnosis. Hypertension, diabetes, diastolic and systolic dysfunction are also present in most patients at diagnosis. We suggest that an accurate clinical work-up and, possibly, a more efficient treatment of hypertension and diabetes are required in elderly acromegalics.

REFERENCES

1. Colao A, Lombardi G. Growth-hormone and prolactin excess. Lancet 1998, 352: 1455-61.
2. Holdaway IM, Rajasoorya C. Epidemiology of acromegaly. Pituitary 1999, 2: 29-41.
3. Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R. Epidemiology of acromegaly in the Newcastle region. Clin Endocrinol (Oxf) 1980, 12: 71-9.
4. Bengtsson B, Eden S, Ernest I, Oden A, Sjogren B. Epidemiology and long-term survival in acromegaly. A study of 166 cases diagnosed between 1955 and 1984. Acta Med Scand 1988, 223: 327-35.
5. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. The United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab 1998, 83: 2730-4.
6. Swearingen B, Barker FG 2nd, Katznelson L, et al. Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab 1998, 83: 3419-26.
7. Beauregard C, Truong U, Hardy J, Serri O. Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. Clin Endocrinol (Oxf) 2003, 58: 86-91.
8. Holdaway IM, Rajasoorya RC, Gamble GD. Factors influencing mortality in acromegaly. J Clin Endocrinol Metab 2004, 89: 667-74.
9. Ayuk J, Clayton RN, Holder G, Sheppard MC, Stewart PM, Bates AS. Growth Hormone and pituitary radiotherapy, but not serum insulin-like growth factor-I concentrations, predict excess mortality in patients with acromegaly. J Clin Endocrinol Metab 2004, 89: 1613-7.
10. Kauppinen-Makelin R, Sane T, Reunanen A, et al. A nationwide survey of mortality in acromegaly. J Clin Endocrinol Metab 2005, 90: 4081-6.
11. Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. Endocr Rev 2004, 25: 102-52.
12. Minniti G, Esposito V, Piccirilli M, Fratticci A, Santoro A, Jaffrain-Rea ML. Diagnosis and management of pituitary tumours in the elderly: a review based on personal experience and evidence of literature. Eur J Endocrinol 2005, 153: 723-35.
13. Colao A, Spiezia S, Di Somma C, et al. Circulating insulin-like growth factor-I levels are correlated with the atherosclerotic profile in healthy subjects independently of age. J Endocrinol Invest 2005, 28: 440-8.
14. Castelli WP. Lipid, risk factors and ischaemic heart disease. Atherosclerosis 1996, 124 (Suppl): S1-9.
15. Grundy SM, Cleeman JI, Bairey Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 2004, 110: 227-39.
16. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2006, 29: S43-8.
17. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985, 28: 412-9.

18. Vitale G, Pivonello R, Auriemma RS, et al. Hypertension in acromegaly and in the normal population: prevalence and determinants. Clin Endocrinol (Oxf) 2005, 63: 470-6.
19. The seventh report of the joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. JAMA 2003, 289: 2560-1.
20. Colao A, Marzullo P, Ferone D, et al. Cardiovascular effects of depot long-acting somatostatin analog Sandostatin LAR in acromegaly. J Clin Endocrinol Metab 2000, 85: 3132-40.
21. Colao A, Spinelli L, Cuocolo A, et al. Cardiovascular consequences of early-onset growth hormone excess. J Clin Endocrinol Metab 2002, 87: 3097-104.
22. Colao A, Marzullo P, Cuocolo A, et al. Reversal of acromegalic cardiomyopathy in young but not in middle-aged patients after 12 months of treatment with the depot long-acting somatostatin analogue octreotide. Clin Endocrinol (Oxf) 2003, 58: 169-76.
23. Sahn DJ, De Maria A, Kissio J, Weyman A. The committee on M-mode standardization of the American Society of Echocardiography. Recommendations regarding quantification in M-mode echocardiography: results of a survey of echocardiography measurements. Circulation 1978, 58: 1072-83.
24. Devereux RB. Detection of left ventricular hypertrophy by M-mode echocardiography. Anatomic validation, standardization and comparison to the other methods. Hypertension 1987, 9 (Suppl 2): 19-26.
25. Colao A, Ferone D, Marzullo P, et al. Long-term effects of depot long-acting somatostatin analog octreotide on hormone levels and tumor mass in acromegaly. J Clin Endocrinol Metab 2001, 86: 2779-86.
26. Colao A, Pivonello R, Cappabianca P, et al. Effect of gender and gonadal status on the long-term response to somatostatin analogue treatment in acromegaly. Clin Endocrinol (Oxf) 2005, 63: 342-9.
27. Cohen DL, Bevan JS, Adams CBT. The presentation and management of pituitary tumours in the elderly. Age Ageing 1989, 18: 247-52.
28. Turner HE, Adams CB, Wass JA. Pituitary tumors in the elderly: a 20 year experience. Eur J Endocrinol 1999, 140: 383-9.
29. Benbow SJ, Foy P, Jones B, Shaw D, MacFarlane IA. Pituitary tumours presenting in the elderly: management and outcome. Clin Endocrinol (Oxf) 1997, 46: 657-60.
30. Kovacs K, Ryan N, Horvath E, Singer W, Ezrin C. Pituitary adenomas in old age. J Gerontol 1980, 35: 16-22.
31. Puchner MJ, Knappe UJ, Ludecke DK. Pituitary surgery in elderly patients with acromegaly. Neurosurgery 1995, 36: 677-84.
32. Minniti G, Jaffrain-Rea ML, Esposito V, et al. Surgical treatment and clinical outcome of GH-secreting adenomas in elderly patients. Acta Neurochir (Wien) 2001, 143: 1205-11.
33. Gasperi M, Martino E, Manetti L, et al. Prevalence of thyroid diseases in patients with acromegaly: results of an Italian multi-center study. J Endocrinol Invest 2002, 25: 240-5.
34. Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Stud of Aging. J Clin Endocrinol Metab 2001, 86: 724-31.
35. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab 2002, 87: 589-98.
36. Desailloud R, Crépin-Hemon S, Simovic-Corroyer B. Acromegaly in elderly people. Ann Endocrinol (Paris) 2005, 66: 540-4.
37. van der Lely AJ, Harris AG, Lamberts SW. The sensitivity of growth hormone secretion to medical treatment in acromegalic patients: influence of age and sex. Clin Endocrinol (Oxf) 1992, 37: 181-5.
38. Colao A, Amato G, Pedroncelli AM, et al. Gender- and age-related difference in the endocrine parameters of acromegaly. J Endocrinol Invest 2002, 25: 532-8.
39. Colao A, Pivonello R, Auriemma RS, et al. Predictors of tumor shrinkage after primary therapy with somatostatin analogues in acromegaly: a prospective study in 99 patients. J Clin Endocrinol Metab 2006, 91: 2112-8.
40. Parkinson C, Ryder WD, Trainer PJ, Sensus Acromegaly Study Group. The relationship between serum GH and serum IGF-I in acromegaly is gender-specific. J Clin Endocrinol Metab 2001, 86: 5240-4.
41. Edén Engström B, Burman P, Karlsson FA. Men with acromegaly need higher doses of octreotide than women. Clin Endocrinol (Oxf) 2002, 56: 73-7.
42. Bayes-Genis A, Conover CA, Schwartz RS. The Insulin-Like Growth Factor Axis. A review of atherosclerosis and restenosis. Circ Res 2000, 86: 125-30.
43. Luft R, Cerasi E, Hamberger CA. Studies on the pathogenesis of diabetes in acromegaly. Acta Endocrinol (Copenh) 1967, 56: 593-607.