ORIGINAL ARTICLE

A follow-up of 130 patients with acromegaly in a single centre

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Abstract

OBJECTIVES: Acromegaly is a rare disease with increased mortality rate. The aim was to present our centre experience in the diagnosis and treatment of a series of patients suffering from acromegaly.

METHODS: 130 patients (55 men, 75 women) aged 19–84 years presenting with clinical and hormonal features of acromegaly, attending Department of Endocrinology and Out-patient Clinic between 1990 and 2004 were studied. They were analyzed their GH and IGF-1 levels, CT and MRI scans, and they were administered medical therapy, neurosurgery and radiotherapy.

RESULTS: We have observed 106 macro-, 16 microadenomas and 1 case of ectopic GHRH. 115 patients were operated, as cured were recognized 74 of them. Pituitary irradiation was applied to 11 patients, in 4 of them it did not cure the disease. Medical therapy was efficacious in 12% patients treated with bromocriptine, 73% with long-acting lanreotide and 58% with long-acting octreotide. In 7 patients other malignant neoplasm were detected. 11 patients died during the follow-up.

CONCLUSIONS: There is possible underdiagnosis of acromegaly in our region, especially in males. We have observed better diagnostic opportunities in recent years when MRI was available. It was accompanied by better outcome of surgical and pharmacological treatment and better control of the complications of the disease.

Abbreviations

BR	- bromocriptine
CNS	- central nervous system
CT	- computed tomography
GH	- growth hormone
IGF-1	- insulin-like growth factor-1
MRI	- magnetic resonance imaging
PET	- positron emission tomography
SSA	- somatostatin analog
TCS	- transcranial surgery
TSS	- transsphenoidal surgery
US	- ultrasound

Introduction

Acromegaly is an uncommon disease caused by GH hypersecretion usually from benign anterior pituitary adenoma. In extremely rare cases GH excess is due to ectopic GHRH or GH production. The prevalence of the disease is 50–70 cases per million, annual incidence about 3–4 cases per million, and equal distribution between sexes. Acromegaly, when not cured, is associated with increased death rate from cerebrovascular, cardiovascular diseases, respiratory dysfunction and some cancers [3,4,23,24,26]. Clinical picture of acromegaly presents typical acral and facial changes, menstrual disturbances in women, impotence in men, excessive perspiration, carpal tunnel syndrome, hypertension and arthropathy. In some patients glucose intolerance or diabetes mellitus, goiter, colonic polyps and hyperlipidemia may occur. The effect of tumor mass may cause headaches, visual field deficit and visual deterioration, hyperprolactinemia and/or secondary pituitary hormones deficits and diabetes insipidus [6,22,24,26,29].

Diagnostic criteria for active acromegaly are fulfilled by failure to suppress GH during the oral glucose tolerance test below 1 μg/L, and elevated age and sex matched IGF-1 level [20,21,27]. The treatment of choice is surgical adenomectomy by transsphenoidal (TSS) approach. Other treatment options include transcranial (TCS) neurosurgery, somatostatin analogs (SSA) or dopamine agonists (bromocriptine – BR) in medical therapy, radiotherapy and GH receptor antagonist application in SAA resistant patients [1,2,13,19,30].

Aim of the study

The aim of our study is to present the results of a follow-up of 130 patients with acromegaly from southwestern part of Poland during preceding 15 years.

Material and methods

Between years 1990 and 2004 a series of 130 patients with acromegaly was diagnosed and treated in Department of Endocrinology, and Out-patient Clinic. They were diagnosed acromegaly upon high, and not suppressed by oral glucose load GH level, high IGF-1 level and/or presence of pituitary tumor in MRI/CT scan with association of typical clinical features of the disease. They were 75 women and 55 men, in mean age at the diagnosis of 52.6 yr and 51.6 yr, and estimated mean age of the initial presentation of symptoms and signs of the disease 42.1 yr and 39.6 yr for women and men, respectively. In all patients hormonal analyses of GH, IGF-1 and other hormones by RIA and IRMA methods were carried out. Their pituitary images were studied by CT (until 1993) and MRI (since 1994) scans. The basal clinical and laboratory data of the patients are shown in Table 1.

Results

Hormonal analyses

Mean serum GH concentration at the diagnosis was 26.7 μg/L (7.0–213.2). Mean GH after tumor surgery and/or radiotherapy was 8.7 μg/L (0.6–37.6). Mean IGF-1 concentration at the diagnosis was 893 ng/ml (173–2 542). Mean IGF-1 after above-mentioned therapy was 500 ng/ml (112–1 363).

Other hormones: hyperprolactinemia was present in 24 patients (10 men, 14 women). Hypopituitarism at the time of diagnosis of acromegaly was shown in 4 patients (2 men, 2 women) harboring macroadenomas. In 2 cases acromegaly contributed to MEN-1 syndrome. There were 2 cases of acromegaly together with primary hyperparathyroidism (1 male 53 yr, 1 female 53 yr old). Both patients underwent parathyroid adenoma surgery. Goiter was shown in 26 patients (19 women, 7 men). Euthyroid goiter was operated in 2 cases, before the diagnosis of acromegaly. Hyperthyroidism was present in 6 female patients, in 4 of them it was in course of toxic nodular goiter, in 2 other due to Graves' disease. Radioiodine was applied to 2 women with toxic nodular goiter. Thyrostatic medical therapy was given to 4 patients with following normalization of thyroid function, 2 of them were operated. In 1 case acromegaly (33 yr) followed Turner Syndrome diagnosed earlier.

Visualization

Using MRI, microadenoma was shown in 13 cases, macroadenoma in 64 patients, and postoperative tumor fragments in 6 other (they were included into macroadenoma patients). There was 1 case of hyperplastic pituitary with no evidence of adenoma (case of ectopic GHRH secretion). CT scans revealed 3 microadenomas, 36 macroadenomas and no changes in other 16 cases. All but 11 of patients had pituitary adenoma shown by CT scans. Out of them, in 5 cases the pituitary surgery was carried out followed by normalization or reduction of GH secretion confirming presence of adenoma not shown by CT. In the remaining 3 subjects adenoma was documented by MRI scans performed some time later. In 2 male patients (51 and 70 yr old) necrotic or destructed foci within anterior pituitary were shown, suggesting self cure of the disease. They both presented with typical clinical features of acromegaly, and normal GH secretion. In 1 case ectopic, extra pituitary source of GHRH production by bronchial carcinoid was documented

Table 1. Clinical and laboratory data of 130 patients with acromegaly at the diagnosis of the disease.

	total	men	women
Number	130	55	75
Age at diagnosis (yr)	52.2	51.6	52.6
Estimated age at the onset (yr)	41.0	39.6	42.1
Mean basal GH (μg/L)	26.7	32.7	22.7
Mean basal IGF-1 (ng/ml)	893	1015	879
Macroadenoma	106	45	61
Microadcenoma	16	6	10
Necrotic foci	2	2	0
Pituitary hyperplasia	1	0	1

(61 yr old woman). Moreover, in our series intracranial meningioma was shown on MRI scans in 2 patients (woman 61 yr with ectopic GHRH, man 35 yr). Cerebral artery aneurysm was observed in 1 patient (man 58 yr). The results of visual studies by CT and MRI scans are shown in Table 1.

Neoplasms

Among patients with acromegaly other intracranial CNS tumor was diagnosed in 47 yr old man, he died before neurosurgery. Three premenopausal women underwent breast cancer surgery (37, 40 and 41 yr). In 1 woman (58 yr) thyroid carcinoma was operated. Male patient presented with two non-related neoplasms: embryonal carcinoma of left testis with metastases (45 yr) requiring orchidectomy, chemo- and radiotherapy and renal tumor 5 cm in size visualized recently by US at the age 66 yr. Gastric carcinoma was operated with subsequent radio- and chemotherapy in 1 woman (59 yr). In another woman (49 yr) 2 metastatic (adenocarcinoma of unknown origin) lymph nodes were resected without known primary focus, even whole body PET examination did not show pathological origin. Colonic polyps were shown in 2 men (both after 3 operations of pituitary adenoma, 1 of them was finally cured – 51 yr, another did not – 35 yr) [9]. Left adrenal incidentaloma 1 cm in size was visualized by US in a 33 yr old male patient.

Therapy: Surgery

115 patients were submitted to neurosurgical procedure and surgery was carried out once in 89 of them, twice in 21 and three times in 5. TSS was carried out in 94 patients, with complete success in 61 out of them. TCS was performed in 21 patients, in 6 cases when TSS failed, or as a primary surgery in 15 cases of large tumors. Surgical treatment was abandoned in 15 cases because of either advanced age (3), coexisting diseases (2) or patients' disagreement for the surgery (10). In 1 case negative decision was based on religious reasons. As the cured by surgery were recognized 74 out of 115 operated patients.

Complications of surgery

Diabetes insipidus is present after transcranial surgery of macroadenoma in 1 patient (woman 43 yr); in other it was transient, only. Epilepsy is observed is 49 yr old female patient, following 2 TCSs and radiotherapy of macroadenoma. Hypopituitarism is present in 8 patients (4 men, 4 women). 1 woman (49 yr) died due to pulmonary embolism a day following TSS. Vision loss occurred in 49 yr old man after TCS followed by radiotherapy.

Radiotherapy

Radiotherapy was applied to 11 patients, in 9 of them following failed surgery, 2 were irradiated without former surgery. GH normalization is present in 7 cases (after mean of 15 yrs). Two patients from this subgroup died in a course of CNS complications and diabetes mellitus without clinical and laboratory improvement following irradiation, another lost vision. In the remaining subjects the decrease of GH from baseline values and clinical improvement is observed.

Medical treatment

Initially, BR (Parlodel, Parlodel LAR, Sandoz, and Bromergon, Polfa) therapy was administered in 66 patients (oral Parlodel, Bromergon 5–30 mg daily, or intramuscular Parlodel LAR 50–100 mg monthly, mostly in 1990–1996). Normalization of GH secretion was shown in 8 patients, decrease more than 50% from baseline in 32 other. In general, BR therapy was good tolerated, no serious adverse effects were noted [6]. Lanreotide (Somatuline, Ipsen) 30 mg intramuscular every 2 weeks was given to 22 patients. In 16 of them GH concentration had normalized, in remaining 6 it was suppressed more than 50% from the baseline. In most of the patients the tolerance of therapy was good, in 1 female patient diarrhea and pancreas irritation was observed, only [7]. Octreotide (Sandostatin, Sandoz) at a dose of 100 μg 3 times daily was administered shortly to 14 patients with normalization of GH in 10 of them. In the remaining subjects marked decrease from the baseline GH was observed. It was good tolerated, but acute pancreatitis in 1 man was observed. Long-acting octreotide (Sandostatin LAR, Novartis) was administered to 50 patients. Out of them 24 required 30 mg every 4 weeks, 25 other 20 mg every 4 weeks, and 1 woman 10 mg only due to diarrhea and dyselectrolytemia when higher dose was given [8]. 47 of the patients were administered Sandostatin LAR as a pretreatment before a surgery, 22 out of them requires further long-term therapy because of failed, non-radical surgery and 3 as a primary therapy because no agreement (woman 48 yr) or contraindications (women 77 and 79 yr) to neurosurgery. Hormonal normalization was achieved in 29 patients (58%).

Deaths

11 patients died during this 15 yr period of time. 3 of them for CNS complications associated with coexisting diabetes mellitus: 2 men (60 and 70 yr) with highest initial GH values, 70 yr old woman. Other 4 patients died

for cardiac insufficiency: 2 men (47 and 74 yr), 2 women (55 and 60 yr). 1 woman (49 yr) died from pulmonary embolism a day following neurosurgery, 1 men (47 yr) due to other intracranial neoplasm and 2 women older than 80 yr without known cause of death.

Conceptions

Two female patients (27 and 31 yr) conceived and delivered a child 2 and 3 years following successful TSS. In one case it was despite post surgical failure of TSH and gonadotrophins secretion was observed together with clinical symptoms of secondary hypothyroidism and menstrual disorders. Another patient conceived and delivered a child 2 years after radiotherapy (29 yr) following 2 failed TSSs. She presents now with secondary thyroid and adrenal insufficiency and requires hormonal (thyroid and adrenal) replacement.

Discussion

We present a follow-up of a series of 130 patients with diagnosed acromegaly who attended Department of Endocrinology, Wroclaw Medical University and Outpatients Clinic between 1990 and 2004. Our center gathered the medical care of vast majority of patients from Lower Silesia region (south-western part of Poland) with a population of approximately 4 million. It seems that the number of diagnosed cases should be higher, as compared with epidemiological data, but subsequent patients had been diagnosed after year 2004 [4,22,23,24].

We observed the mean time of diagnosis of the disease similar between men and women, with the earlier age in men, and the time of presentation of the signs and symptoms of the disease was similar between both sexes, as well, but the difference was greater between sexes, it was observed earlier in our male than female patients. This is an observation confirming previous ones, indicating earlier recognition of the disease in male patients since men had more aggressive tumors larger at presentation and diagnosed earlier [17,22]. Unfortunately, our patients were diagnosed acromegaly approximately 10 years later than shown by other studies [4,22,23,29]. This could be due to insufficient awareness of disease both among the patients and health service staff. The mean time in the delay of the diagnosis was 10.5 yrs for women and 12.0 yrs for men. It is similar to reported by other [23,24,29]. The female patients contributed for 57.7% our acromegalics. It might suggest underdiagnosis of the disease in male population, since other reports point the similar gender distribution of the disease [17,22]. But, there exist other data on both females' [4,23] and males' [29] predominance, as well. Our male patients had higher concentrations of GH and IGF-1, suggesting more active disease, they usually needed higher doses of SSA in the medical therapy [8,17,18,22,27].

We have observed in our series relatively high number of neoplasms, similarly as other papers suggesting the harmful influence of GH and/or IGF-1 excess for other tumors promotion, but the number of colonic polyps was not as high as in other studies [9,16,26]. The number of deaths in our patients reflects higher mortality in acromegaly, and their causes (cardiovascular, neoplasms) are typical for the disease [3,17,23,24,29]. We did not analyze in details cardiologic aspects of the disease since they are the subject of other on-going study. An interesting observation was successful pregnancy in 3 women while normalization of GH secretion (following TSS in 2 cases and radiotherapy after 2 failed TSS in another). Very recent study shows normal pregnancies and deliveries in female acromegalics as quite common [16].

We had at our disposal an opportunity for pituitary CT scanning since 1985, and MRI since 1994, only. The accuracy of diagnostic procedure improved since the latter time, and we could visualize even microadenomas which were non-detectable by CT, previously. In several patients we have documented adenoma on MRI scan, despite previous normal pituitary CT scans. Availability of MRI gave us an opportunity to monitoring therapy outcome and early documenting of tumor regrowth following non-radical surgery. We have observed more macro- than microadenomas in our patients, and the outcome of the therapy was better in the latter patients. This reflects conclusions from other studies, since the initial size of the tumor and the level of GH secretion are the important determinants for final outcome of the surgery [15,25,28,32].

We have documented in our series one case of bronchial carcinoid producing GHRH. Its removal by pulmonary surgery was followed by hormonal and biochemical recovery [11]. Another unusual case described was acromegaly in a 33 yr old patient with Turner Syndrome which was diagnosed in the childhood, without GH therapy in any time [10].

The results of surgery are better in cases of micro- than macroadenomas, and in women than in men. It could be explained by the higher initial GH and IGF-1 levels in our male than female patients. In some patients several attempts of surgery was required before complete cure of the disease occurred. The results of surgery are similar to the results published by other. We have observed better outcome of surgery since it was performed in one centre by two experienced surgeons and when it was preceded by SSA administration [1,7,12,14,25].

Medical therapy succeeded in limited group of our patients prior to the surgery, but it was impossible to become a treatment of choice, since poor availability of SSA to our patients in the past [7,8]. Long-acting Lanreotide was reimbursed in Poland in years 1995–1999, and long-acting Octreotide since 1999 till present. Surprisingly, a quite high number of our patients responded to BR, together with good tolerance of this medication [6]. Other dopamine agonists were either unavailable or without reimbursement in Poland (cabergoline), so we could not assess their efficacy. Our data confirm importance of SSA in primary medical therapy of acromegaly, in presurgical preparation and when surgery fails [13,14,19,30].

Positive results of conventional radiotherapy were observed in a group of patients irradiated following failed surgery, but on the other hand, in this group of patients the deaths were relatively common. It suggests as doubtful the indication of routine radiotherapy after non-complete tumor surgery [2,5].

The survey of our patients could be a valuable and significant contribution in the Polish national and European database (Acromegaly Registry) [23,31].

Conclusions

There is possible underdiagnosis of acromegaly in our region, especially in males.

We have observed better diagnostic opportunities in recent years when MRI was available.

It was accompanied by better outcome of surgical and pharmacological treatment and better control of the complications of the disease.

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