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Goiter, cardiovascular and metabolic disorders in patients with acromegaly

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Objective. This study evaluated the relationship between selected acromegaly complications such as IGF-1 serum concentrations at diagnosis as well as of controlled and uncontrolled disease.

Methods. A total of 113 acromegaly patients were enrolled to the study and the duration of active and uncontrolled disease was evaluated as a crucial cause of selected complications.

Results. Goiter, diabetes, hypercholesterolemia, hypertriglycerydemia, hypertension and ischemic heart disease were diagnosed in 85(75.2 %), 23(20.3 %), 48(51.0 %), 15(13.3 %), 65(57.5 %) and 18(15.9%) patients, respectively. Prevalence of goiter and diabetes was significantly related to the duration of uncontrolled acromegaly ($p<0.01$) as well as to the prevalence of hypertension and ischaemic heart disease ($p<0.05$), while no significant relation was found with the prevalence of hypercholesterolemia and hypertriglycerydemia ($p>0.05$). After three years, there was a significant risk of an acromegaly patient being diagnosed at least with one of the above mentioned diseases ($p<0.05$) and such risk became more significant after four years ($p<0.01$). At the time of acromegaly diagnosis, either basal or after 75g glucose intake the level of GH and IGF1 was not significantly ($p>0.05$) related to the prevalence of the already mentioned complications.

Conclusion. The treatment of acromegaly patients should be geared towards fulfilling all criteria for controlled disease, thereby alleviating potential complications and decreasing mortality.

Key words: acromegaly, pituitary, IGF-1, growth hormone, hypertension, goiter, diabetes

Acromegaly is a rare and chronic disease caused by excess growth hormone (GH) secretion which, in the majority of cases, arises from a GH-secreting pituitary adenoma and occurs with an annual incidence of approximately five cases per million individuals as reported by Melmed (2009). Such increased GH secretion further stimulates the liver (predominantly) and some extrahepatic tissues for insulin-like growth factor-1 (IGF-1) excessive production which mediates several of the peripheral somatic effects of GH. The clinical course of this disease, beyond its typical signs and symptoms, is related to several systemic complications, particularly to those affecting the cardiovascular, respiratory, gastrointestinal, endocrine, and skeletal systems as previously reported by several authors (Rajasoorya et al. 1994; Ozbey et al. 1997; Kauppinen-Mäkelin et al. 2005; van Thiel et al. 2005).

It was found that increased mortality associated with acromegaly can be reduced by successful treatment reducing GH secretion as observed by some authors (Orme et al. 1998; Ayuk et al. 2004; Holdaway et al. 2008). Compared to the healthy general population, patients with acromegaly also appear to have a higher prevalence of certain benign or malignant neoplasms as found by Terzolo et al. (2004) and Kurimoto et al. (2008). However, the true incidence rate of cancer in patients with acromegaly remains controversial, as some

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authors have not found any increase in risk (Mustacchi and Shimkin 1957; Orme et al. 1998).

The treatment of acromegaly is multimodal, usually starting with somatostatin analogs (octreotide, lanreotide) administrated intramuscularly over 3-12 months, followed by neurosurgery (dependently on the pituitary tumor size) as proposed by Kumar et al. (2009). After such treatment, the patient is reevaluated to answer whether he/she is completely cured (criteria: IGF-1 normal serum concentration, basal serum concentration of GH<2.5 μg/l, GH ≤1.0 μg/l at 120 min of OGGT) or still suffering from active acromegaly as frequently reported (Krzentowska-Korek et al. 2010). Such patients, constituting up to 50 % of operated cases of pituitary macroadenoma, should be treated either with somatostatin analogs (Feelders et al. 2009; Baldys-Waligorska et al. 2009; Wuster et al. 2010), GH receptor antagonist pegvisomant (Ghigo et al. 2009; Buhk et al. 2010) or by stereotactic radiotherapy as suggested by Roug et al. (2010) in order to fulfill cure criteria and have their disease be classified as under control. The period of active and uncontrolled acromegaly appears to be crucial in the development of complications, be they mild or life-threatening.

The aim of this study was to assess the relationship between selected acromegaly complications, GH and IGF-1 serum concentrations, and duration of controlled and uncontrolled disease.

Table 1

The prevalence of acromegaly complications in the studied group

Acromegaly complication	n	%
Hypertension	65	57.5
Ischemic heart disease	18	15.9
Diabetes	23	20.3
Glucose intolerance	15	13.3
Impaired fasting glucose	12	10.5
Goiter	85	75.2
Hypercholesterolemia	48	42.5
Hypertrigliceridemia	15	13.3

Patients and methods

A group of 113 acromegaly patients (83 females, 30 males) were diagnosed and treated at the Department of Endocrinology, Jagiellonian University Hospital (Krakow, Poland). Pituitary macroadenoma and microadenoma were confirmed in 77% and 23% of these patients, respectively. The mean duration of follow-up was 6.8 yrs. Mean age at diagnosis was 46.5±14.9 yrs. Serum concentrations of GH and IGF-1 were measured using IRMA (DiaSorin) and RIA (Biosource) methods, respectively. Thyroid volume and structure were evaluated using Aloka SD 100 and General Electric Voluson 700 machines equipped with a 7.5 MHz head. Patients were qualified as having one or more complications (i.e., goiter, glucose intolerance, impaired fasting glucose and diabetes, hypertension, ischemic heart disease, hyperlipidemia) in strict accordance with established clinical practice and current diagnostic criteria.

Statistical evaluation was completed using Shapiro-Wilk, U Mann-Whitney, chi-square and Wilcoxon tests included in the Statistica v.8.0 package.

Results

The prevalence of selected acromegaly complications in studied group is shown in Table 1. Goiter was diagnosed in 85 (75.2 %) patients, being more frequent in females (65.78 %) than in males (20.67 %). Thyroid volume was 26.9±21.8 ml and 36.3±30.7 ml in females and males, respectively. Its prevalence was significantly ($p<0.01$) related to the duration of active acromegaly (Fig. 1).

Diabetes was diagnosed in 23 (20.3 %) patients and its prevalence was significantly ($p<0.01$) related to the duration of active acromegaly (Fig. 2). Glucose intolerance and impaired fasting glucose (IFG) were diagnosed in 13.3 % females and 10.5 % males.

Hypercholesterolemia was diagnosed in 48 (42.5 %) and hypertrigliceridemia in 15 (13.3 %) patients, though prevalence was not related to the duration of uncontrolled acromegaly ($p>0.05$). Hypertension was found in 65 (57.5 %) patients and its prevalence was significantly ($p<0.05$) related to the duration of uncontrolled acromegaly (Fig. 3). Ischemic heart disease was diagnosed in 18 patients (15.9 %) and its prevalence was significantly ($p<0.05$) related to the duration of uncontrolled acromegaly (Fig. 4).

Table 2 shows the relationship between the duration of uncontrolled acromegaly and the prevalence of its

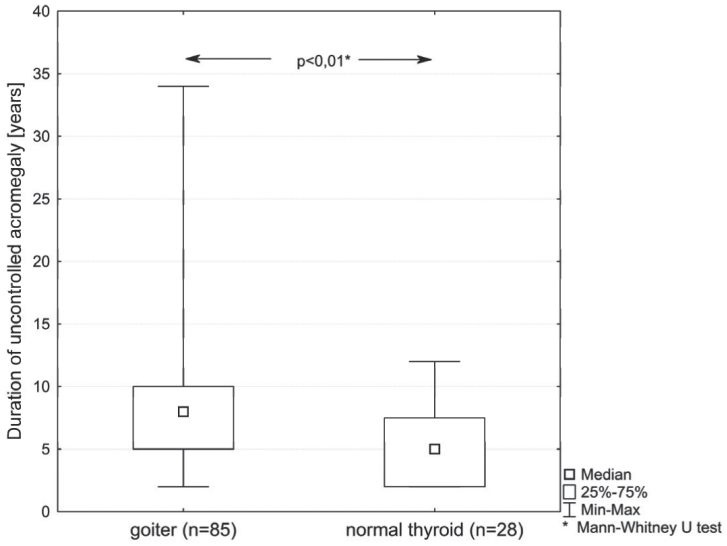

Fig. 1. The relationship between goiter prevalence and duration of uncontrolled acromegaly

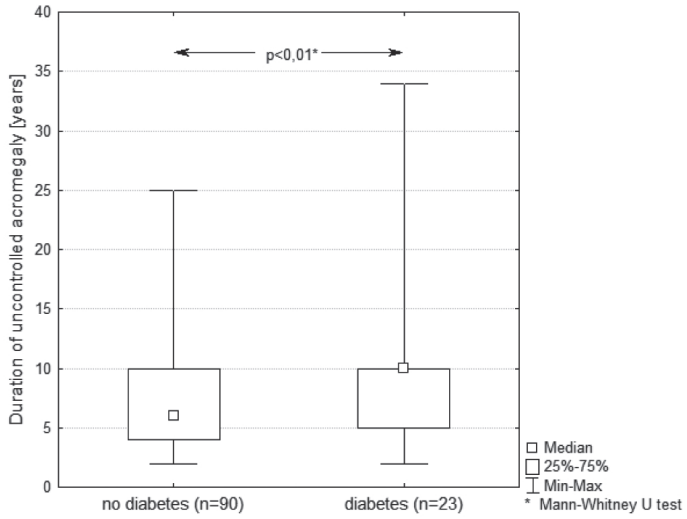

Fig. 2. The relationship between diabetes prevalence and duration of uncontrolled acromegaly

complications known to occur frequently such as hypertension, diabetes and goiter. After three years, there was a significant risk of acromegaly in those patients who were diagnosed at least with one of the above mentioned diseases ($p<0.05$). After four years, however, this risk became much more significant ($p<0.01$). We found no statistically significant relationship between gender and the prevalence of goiter, carbohydrate metabolism disturbances, arterial hypertension, and ischemic heart disease (Table 2). Basal GH as well as GH level following 75 g of glucose intake (OGTT) and IGF-1 levels obtained at the time of acromegaly diagnosis (e.g. 35.26±40.7 μg/l; 37.7±52.6 μg/l and 953.6±707.7 ng/ml respectively), were not significantly ($p>0.05$) related to the prevalence of the already mentioned complications.

Discussion

Acromegaly is a chronic disease with complications restricted not only to typical and outwardly visible skeletal changes, but also seriously affecting other organs and bodily systems. These complications, particularly concerning the cardiovascular system, contribute to the excess morbidity and mortality rates observed in acrome-

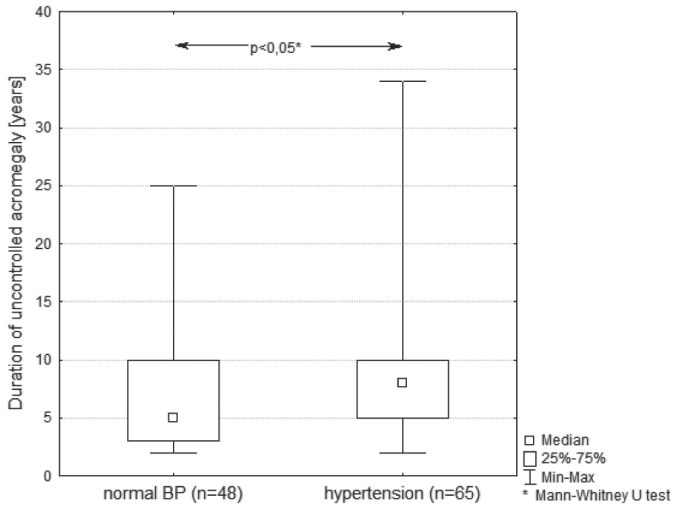

Fig. 3. The relationship between hypertension prevalence and duration of uncontrolled acromegaly.

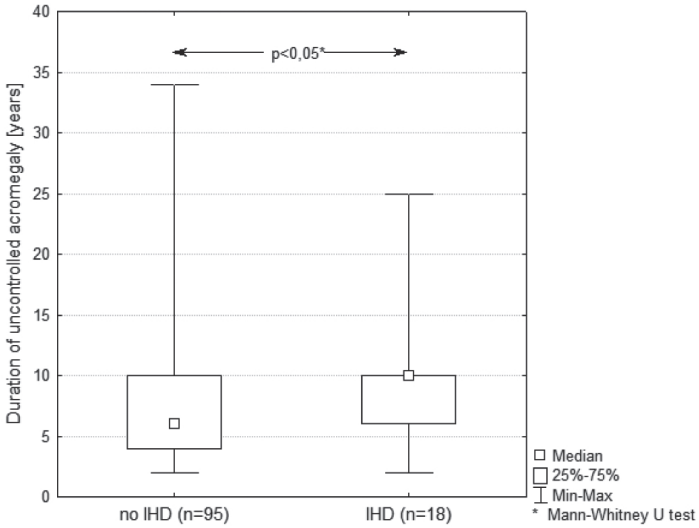

Fig. 4. The relationship between ischemic heart disease (IHD) prevalence and duration of uncontrolled acromegaly.

Table 2

Duration of uncontrolled acromegaly and significant increases in the prevalence of complications known to occur frequently

Duration of uncontrolled acromegaly	> 2 yrs. vs. ≤ 2 yrs.	>3 yrs. vs. ≤ 3 yrs.	> 4 yrs. vs. ≤ 4 yrs.	>5 yrs. vs. ≤ 5 yrs.	> 6 yrs. vs. ≤ 6 yrs.	> 7 yrs. vs. ≤ 7 yrs.
Hypertension	NS	p<0.05	p<0.005	p<0.005	p<0.005	p<0.001
Diabetes	NS	NS	NS	p<0,05	p<0.005	p<0.005
Goiter	NS	NS	p<0.05	<0.05	p<0.05	p<0.01

NS – statistically insignificant (p>0.05)

galy patients by Dekker's et al. (2008) and Holdaway et al. (2008). In this study, goiter was found in 75.3 % of patients which appears consistent with other published reports by several authors (Gasperi et al. 2002; Hermann et al. 2004; Kasagi et al. 1999). In the studied population, twenty-six (23.0 %) patients were diagnosed with diabetes. Glucose intolerance and impaired fasting glucose (IFG) were found in 13.3 % and 10.5 %, respectively. Data

previously published allowed to find a very wide range of diabetes prevalence among acromegaly patients such as 19.0-40.5 % (Biering et al. 2000; Kreze et al. 2001; Colao et al. 2009). Cardiovascular complications belong to well known causes of excess mortality in acromegaly as found by Herrmann et al. (2009). In our group, sixty four (56.6 %) patients presented with hypertension. According to Colao et al. (2008) this may partly result from hyperinsulinism in acromegaly. Vitale et al. (2005) reported hypertension in 46 % of 200 investigated acromegaly patients vs. 25 % of control patients. Ischemic heart disease was found in eighteen (15.9 %) patients involved in this study. German authors (Hermann et al. 2009) reported degree of coronary calcifications as correlated with acromegaly duration.

Our study found a direct relationship between the duration of active and uncontrolled acromegaly and occurrence of complications. Other variables, namely GH (i.e., basal and following 75 g of consumed glucose, OGGT) and IGF-1 serum concentrations at the moment of diagnosis as well as total (i.e., controlled and uncontrolled) disease duration did not significantly influence the prevalence of complications. Similar conclusions have been published by other authors. For instance, nationwide Finland study revealed that an increased basal GH serum concentration (i.e., >2.5 μg/l, considered a criterion of uncontrolled disease) leads to excess mortality (Kauppinen-Mäkelin et al. 2005). Rajasoorya et al. (1995) posited the significance of GH serum concentration resulting from therapy. Holdaway et al. (2008) in meta-analysis suggested that mortality rates may decrease among acromegaly patients when their GH serum concentration falls bellow 2.5 μg/l. Several reports have also presented the role of increased serum concentration of IFG-1, the second marker used to measure the control of the disease, as a factor leading to excess mortality (Swearingen et al. 1998; Holdaway et al. 2004). However, the results of two large studies published by Ayuk et al. (2004) and Kauppinen-Mäkelin et al. (2005) did confirm such relationship. This discrepancy between GH and IGF-1 may be explained as follows: IGF-1 is not the only growth factor regulated by GH and not all actions of GH are mediated by IGF-1. Among the acromegaly complications investigated in our study, only hypercholesterolemia and hypertriglyceridemia were not significantly related to the duration of uncontrolled disease. Tan et al. (1997) suggested that increased LDL cholesterol fractions may be related to elevated cholesterol ester transfer protein (CEPT) serum concentration.

Different association of ischemic heart disease and dyslipidemia with the duration of uncontrolled acromegaly indicates other possible mechanisms of heart muscle ischemia in acromegaly. Some recent studies have been aimed at determining the newer indicators (as cathepsin B) of acromegaly activity and prognosis (Daroszewski and Bolanowski 2010). Comparing the results of published studies which examined acromegaly complications is difficult due to different evaluation criteria. Our findings confirm the need for acromegaly treatment options intensive enough to fulfill the criteria for controlled disease.

In conclusion, it was observed that the prevalence of goiter, hypertension, ischemic heart disease and diabetes, contrary to hypercholesterolemia and hypertriglyceridemia, significantly depended on the duration of active and uncontrolled acromegaly. These complications were not significantly related to basal GH, GH following 75 g of glucose intake (OGTT), and IGF-1 serum concentrations at the time of diagnosis (i.e. prior to the treatment). The treatment of acromegaly patients should be geared towards fulfilling all criteria for controlled disease, thereby alleviating possible complications and decreasing mortality.

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