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Prevalence of neoplasms in patients with acromegaly – the need for a national registry

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Abstract

Introduction. Acromegaly is an endocrine disorder caused predominantly by pituitary adenoma leading to autonomic oversecretion of growth hormone and secondary elevation of insulin-like growth factor 1 (IGF-1). Consequently, there are both theoretical and experimental grounds for establishing a correlation between this disorder and the higher incidence of neoplasms.

Objective. The aim of the study is to evaluate the incidence and types of neoplasms among patients with acromegaly.

Materials and method. The study included 67 patients with acromegaly, aged between 24 and 75±18.8 years, 46 women (68.7%) and 21 men (31.3%), BMI: 30.7±5.7 kg/m2, age at diagnosis 49.1±12.5 years, with the medians of GH and IGF-1 levels at diagnosis of 11.3 ng/ml and 663.8 ng/ml, respectively. A retrospective analysis of medical records with particular regard to physical examination, medical history, laboratory and imaging tests was performed.

Results. Fifty-one patients (76.1%) suffered from at least one neoplasm, among whom 48 patients (71.6%) had benign proliferations, whereas malignant neoplasms (larynx, endometrial and colon cancers) were found in only three patients (4.5%).

Conclusions. Benign neoplasms were found in majority of patients with acromegaly (71.6%) most notably: nodular goiter and colon polyps; malignant lesions were rare (4.5%). Only every fifth patient suffered from no neoplastic proliferations. No correlations between the studied parameters and the incidence of neoplasms were found, most likely due to the small number of patients. This is the reason for proposing the creating of the first national register of incidences of neoplasms among acromegalic patients.

Key words

cancer, acromegaly, registry, IGF-1, GH, neoplasms

INTRODUCTION

Acromegaly is an endocrine disorder, predominantly caused by pituitary adenoma, leading to autonomic oversecretion of growth hormone (GH) and secondary elevation of insulin-like growth factor 1 (IGF-1). This disease was first described in 1886 and named acromegaly by a French neurologist Pierre Marie. Only a year later, a German scientist, Oskar Minkowski, linked its symptoms to enlarged pituitary [1, 2].

This endocrinopathy is rare with a population prevalence of 50–70 cases per million people and an incidence of 3–4 cases per million population per year [3]. Such data allows for assessing the number of acromegalic patients in Poland at about 2,660 with 114–152 newly- diagnosed patients each year; however, in Poland there are no reliable epidemiological data on the subject [4].

Observations over the years have indicated that the mortality of patients with acromegaly is significantly higher than in the unaffected population mainly due to cardiovascular and pulmonary diseases. Cancer is another cause of death in this disorder. Acromegaly has been associated with colon as well as – but to a lesser extent – breast, prostate and other forms of cancers [5, 6, 7]. The main role in the carcinogenesis is said to be exerted by IGF-1 and enhanced expression of its receptors, which promotes cell cycle progression through mitogen-activated protein kinases (MAP), which in turn increases the number of cell cycles per unit time, anti-apoptotic activity of the phosphoinositide-3 kinase (PI-3 kinase) and angiogenic effect, thus affecting the capacity of neoplasms to form remote metastases. Current studies indicate the potential role of IGF-1 in the development of resistance to chemotherapy [8, 9].

Oncogenic potential of human GH and IGF-1 has been corroborated in animal models. Transgenic mice with human GH and IGF-1 receptors, after the implantation of cancer cells, showed a higher incidence of breast cancer in comparison mice deficient in GH-releasing hormone (GHRH) receptors (i.e. with decreased levels of GH and IGF-1) exhibiting almost complete inhibition of growth of the implanted cancer tissue. In the animal model, the reduced plasma IGF-1 concentrations were associated with delayed initiation of oncogenesis in response to environmental carcinogens and genetic manipulation [8, 10, 11, 12, 13].

Despite the fact that there are both theoretical and experimental grounds validating the correlation between cancer and acromegaly, Poland lacks coherent epidemiological data. Polish investigators, e.g. Bałdys-Waligórska et al.,

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have already pointed out the need to conduct large-scale prospective studies witch would allow for sounder statistical inference analysis [14].

OBJECTIVES

The aim of the study was to evaluate both the prevalence and the types of neoplasms seen in patients with acromegaly, as well as to establish cooperation between respective Polish health centres in order to create the first national registry of neoplasms prevalence among acromegalic patients.

MATERIALS AND METHOD

A retrospective analysis of medical records was performed with particular regard to physical examination, medical history, laboratory and imaging tests, and surgical as well as pharmacological treatment in order to evaluate neoplastic complications of acromegaly. Cancer screening was implemented in accordance with guidelines of the Polish Society of Endocrinology [15].

The study included 67 patients with acromegaly treated in the Department of Endocrinology of the Medical University of Lublin and in the outpatient clinic in 2004–2015, i.e. 46 women (68.7%) and 21 men (31.3%), age at diagnosis 49.1±12.5 years where the age of onset of initial symptoms was evaluated at 41±10.2 years; medians of GH and IGF-1 levels – 11.3 ng/ml and 663.8 ng/ml, respectively (Tab. 1).

Table 1. Anthropometric and clinical characteristics of the study group

Patient characteristics			
Gender structure	Women	46 (68.7%)	
	Men	21 (31.3%)	
BMI (kg/m^2)		BMI: 30.7 ±5.7	
Age at diagnosis		49.1±12.5 years	
Age of first symptoms		41±10.2 years	
Median level at diagnosis	GH	11.3 ng/ml [2.00–67.45 ng/ml]	
	IGF-1	663.8 ng/ml [274–1,500 ng/ml]	
Surgical patients	48 (71.6%)	Complete tumor removal	27 (56.3%)
		Incomplete removal	21 (43.7%)
Pharmacotherapy (somatostatin)		19 (28.4%) before surgery or in patients who did not consent to surgery	

RESULTS

Fifty-one patients (76.1%) suffered from at least one neoplasm among whom 48 patients (71.6%) had benign proliferations, whereas malignant neoplasms (larynx, endometrial and colon cancers) were found in only three patients (4.5%). Twelve patients (17.9%) were diagnosed with two concomitant neoplasms, nine (13.4%) with three proliferative lesions, and three (4.5%) had as many as four accompanying neoplasms. Among benign lesions: nodular goiter, colon polyps and uterine myomas were found most often (Tab. 2).

Analysis found no correlations between the studied parameters, such age at diagnosis, mean levels of GH and IGF-1 at diagnosis, whether the patient underwent a complete or incomplete surgery or the incidence rate of neoplasms, which may be attributed to the small patients sample size.

Table 2. Number of benign and malignant neoplasms in patients with acromegaly

Localization	Benign proliferations	Malignant neoplasms
Thyroid	36	-
Colon	14	1
Uterus	8	1
Prostate	6	-
Breast	4	-
Larynx	-	1
Gall bladder polyps	3	-
Meningiomas	2	-
Parathyroid adenomas	2	-
Adrenal glands	1	-
Skin	1	-
Neurofibroma	1	-
Total	**77**	**3**

DISCUSSION

Summing-up the results of the studies to date which assess the prevalence of neoplasms during the course of acromegaly, it can be concluded that this condition contributes to an increased incidence of various neoplasms, more often benign than malignant [16]. In the study group, the patients were predominantly diagnosed with benign tumors (71.6%). Only every fifth patient suffered from no neoplasms. Neoplasms constituted approximately 30% of accompanying diseases, and according to Swedish studies, is the second most concomitant disease following hypertension [17].

Most authors suggest an enhanced number of benign neoplasms, and colon cancer as the most frequent neoplastic comorbidities associated with somatotropinoma [5, 6, 7, 18]. However, data from the current study provided only one case of colon cancer, although 14 patients (27.5%) were diagnosed with benign proliferation in the form of polyps. Similar to authors from the Kraków centre, proliferations – but only the benign – were most frequently located in the thyroid. Two Polish studies showed an increased risk for thyroid cancer in that population, which is partially corroborated in the presented study [14, 19], which, however, were unable to substantiate the postulates of many investigators, e.g. Nabarro, Au et al., Baris et al. and Orme et al., who underlined the higher incidence rate of other neoplastic lesions such as breast, colon cancers and tumours of the central nervous system, such as meningiomas [5, 14, 20].

Conversely, many authors have not confirmed an increased incidence of neoplasms in acromegaly, but they emphasize the need to conduct multicentre studies due to the relatively small number of patients included in their studies which precludes the drawing reliable conclusions [21, 22].

Caution must be exercised when interpreting the data of ths study. The first limitation is the relatively small number of patients which made it difficult to perform a fully reliable statistical analysis. Another issue is the fact that the studied lesions were over-diagnosed since the patients with

acromegaly more often underwent diagnostic tests, such as colonoscopy or ultrasound, than the general population.

Such arguments are often raised with regard to similar studies conducted by other Polish endocrinology centres [14]. This is the reason for proposing the creating of the first national registry of incidence of neoplasms in acromegalic patients. This is especially relevant since such registries have already been successfully introduced in many other European countries, such as Germany, Sweden, Denmark and Italy [22, 23].

Establishing such a registry to include all Polish patients with acromegaly will allow the drawing of reliable conclusions and the performance of analysis with more statistical power. Such steps will translate into finding correlations between acromegaly and promotion of carcinogenesis, such as an already postulated higher incidence of breast cancers, which may serve as a basis for modifying current guidelines with regard to recommended cancer screening tests in acromegalic patients. At the same time, it seems that the optimum solution would be to design a prospective randomized cohort study with larger study groups in order to attain the minimal statistical power accepted in clinical practice.

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