

Prevalence of Acromegaly in the Republic of Uzbekistan

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Abstract Acromegaly is a rare disease requiring extensive examination of population to get reliable epidemiological data which are of high value for adverse outcomes of the disease to be reduced, as well as for improvement of early diagnosis and results of treatment. The assessment of acromegaly prevalence in the Republic of Uzbekistan as per the National Registry has been performed. The data on 442 patients with the pituitary somatotrophic adenomas entered the Registry database from January 1, 2007 to January 2018. All patients were examined at the local level for the Registry Card to be filled in. The patients' age varied from 18 to 75 years, mean age was 41 ± 21 years. The findings from the study demonstrated that acromegaly prevalence in the Republic of Uzbekistan is 1.4 cases per 100 000 of population with uneven distribution in the regions of the Republic. High prevalence of the pituitary somatotrophic adenomas was registered in Tashkent-city (2.5) and Namangan region (2.2) with the predominance among women. Late diagnosis of the disease delayed by 6-10 years with the peak at 40-49 years of age for men and at 50-59 years of age for women. Analysis of provoking factors demonstrated that manifestation of the disease was preceded by neuroviral infection (14.6%), psychological traumas and stresses (18.6%), pregnancy (10.1%) and craniocerebral injuries (15.4%). First health-seeking was found delayed corresponding to the height of the disease to be evidenced by the analysis of clinical signs of the disease's manifestation. The vast majority of the patients were found to seek for help with specialists of other profiles, such as, neuropathologists, therapists and cardiologists; while 43.2% of patients visited endocrinologists, and this is thought to cause high prevalence of the disease and its early complications.

Keywords Acromegaly, Epidemiology, Risk factors, Clinical features

1. Introduction

Acromegaly is a rare disease characterized with growth hormone (GH) excess and increased insulin-like growth factor 1 (IGF-1) mostly associated with a pituitary adenoma. The disease results in early invalidization and higher mortality among the acromegalics which is 2-4 times higher than the one in the general population [1,2]. 60% and 25% of patients die due to cardiovascular and respiratory disorders, 15% because of malignancies [1,3,4,5]. GH levels $< 5\text{mU/l}$ ($< 2.5\text{ }\mu\text{g/l}$) facilitate rapid improvement of acromegaly [4,6]. Maintaining GH and/or IGF-1 normal for the age was found to associate with the reduction in mortality rates regardless of concurrent complications [1,7,8].

In 1980-2001 acromegaly incidence was reported to range from 3.8 to 6.9 cases per 100 000 of population; the prevalence was from 0.28 to 0.4 cases per 100 000 of population [9-14]. Recently, in a number of reports from various geographical regions with various levels of public

health care systems information on acromegaly incidence and prevalence (0.2-1.1 and 2.8-13.7 cases per 100 000 of population/year, respectively) was provided [15,16]. The epidemiological worldwide data vary. Thus, according to Daly et al., acromegaly prevalence in Belgium is 12.5 cases per 100 000 of population [17]; Tjörnstrand et al. report on 3.3 cases per 100 000 population in Sweden [18]. There are 3.4 cases per 100 000 population in Spain [19], 13.7 in Iceland [20], 12.4 in Malta [21], 7.8 in the USA [9] and 2.8 in the South Korea [10].

In epidemiology of acromegaly, it is necessary to elucidate possible geographic variance and effects of environmental factors, ethnicity, sex, level of public health care system and accessibility of medical service, as well as to get information on early onset of the disease, familial susceptibility and mixed GH-PRL secreting adenomas [22].

Delay in the diagnosis is still considerable; presence of the disease is usually confirmed in the 5th decade affecting condition of persons of working age, in its turn to result in the decreased working capacity, social and financial consequences, as well as in prolonged burden for the public health care system confirming necessity of higher awareness of medical professionals [23,24].

Acromegaly is a rare disease requiring extensive studies aiming at acquiring valid and reliable epidemiological data

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extremely necessary for reduction of adverse outcomes of the disease, improvement of early diagnosis and patient outcomes, for description of the disease patterns and hypotheses relevant to cause factors, for evaluation of the role the disease plays in the lives of patients, their families and society, as well as for assessment of acromegaly burden for the public health care system [25].

For ascertainment of early acromegaly forms and formulation of a strategy for management of the patients with somatotrophic pituitary adenomas the acromegaly registries making it possible to keep tracking of cases, to assess the factors determining manifestation, course and outcomes of the disease, are of great significance. Our work was initiated to analyze data of the National Uzbekistan Acromegaly Registry, which gives the opportunity to impartially assess a situation with diagnosis and efficiency of therapeutic interventions, and to develop the scientifically grounded strategy for prevention of complications and lethal outcomes, and for improvement of the acromegalics' late-term quality of life.

2. Materials and Methods

442 patients with the somatotrophic pituitary adenomas whose data were entered into Uzbekistan Acromegaly Registry database from January 1, 2007 to January 1, 2018, were the object of the study. All the patients were examined at the local level for the personal registry card to be filled up. The patients' age varied from 18 to 75 years, mean age was 41 ± 21 years.

All patients underwent

- the clinical examination,
- RIA of hormones, such as LH, FSH, TSH, GH, IGF-1, IGFBP-3, cortisol, testosterone, estradiol, free T_4 , prolactin/
- X-ray study including the sella spot filming, CT and/or MRI of the hypothalamo-pituitary region,
- US study of inner organs and the thyroid,
- Neuro-ophthalmological evaluation of vision acuity, fundus of the eye and fields of vision.

To characterize complications we categorized them as cardio-vascular, endocrine-metabolic, respiratory, osteoarticular and neuromuscular, and neoplasms, such as tumors of large intestine, breast, thyroid or prostate) [1,26].

3. Results and Discussion

Of 442 acromegalics, there were 277 (62/6%) women and 165 (37.4%) men. The highest prevalence of the disease was found in patients aged from 30 to 44 years (43.4%), the lowest one could be seen in persons of age group of 75 years and older (2.1%); as a whole the trend persisted for both sexes. Mean prevalence of acromegaly in the Republic of Uzbekistan is 1.4 cases per 100 000 population (Table 1), varying from 0.5 cases in Djizak and Kashkadarya regions to

2.7 per 100 000 population in Tashkent-city. Due to varying acromegaly prevalence, we arbitrarily categorized the regions into those with low, intermediate and high frequency.

Table 1. Cases of acromegaly per 100 000 population in the Republic of Uzbekistan as per the Acromegaly Registry

Regions	Population (thousand people)	Total number of cases of acromegaly	Cases of acromegaly per 100 000 population
Republic of Uzbekistan	32387.2	442	1.4
Karakalpakstan	1829.9	17	0.9
Andijan	2987.1	19	0.6
Bukhara	1856.7	27	1.4
Jizzakh	1312.9	7	0.5
Kashkadarya	3118.5	17	0.5
Navoiy	950.3	17	1.8
Namangan	2675.7	49	1.8
Samarkand	3685.7	33	0.9
Surkhondarya	2487.7	16	0.6
Sirdarya	809.4	12	1.5
Tashkent	2845.3	74	2.6
Fergana	3592.4	32	0.9
Khorezm	1790.7	23	1.3
Tashkent-city	2444.9	67	2.7

Thus, Tashkent-city and Tashkent region turned out to be the regions of high prevalence (2.7 and 2.2 cases per 100 000 population, respectively). Bukhara (1.4), Namangan (1.8), Khorezm (1.3) and Navoyi (1.0) regions were among those with intermediate prevalence. Regions of low prevalence included Andijan (0.6), Djizak (0.5), Kashkadarya (0.5), Syrdarya (0.6), Samarkand (0.9) regions and Republic of Karakalpastan (0.9 cases of acromegaly per 100 000 population).

Growth hormone secretion is known to have sex and age peculiarities [27], so we studied the frequency of acromegaly cases by the factors (Fig.1).

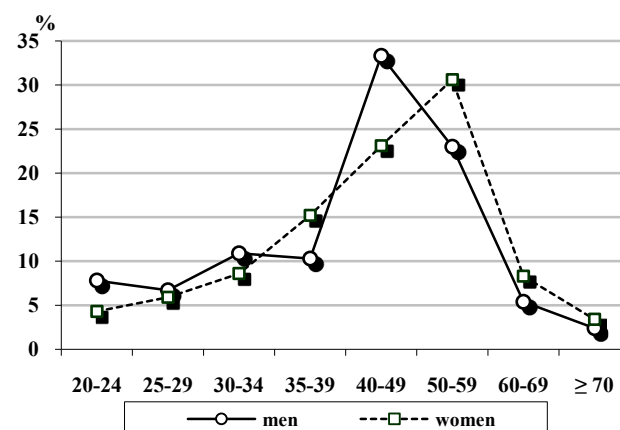


Figure 1. Frequency of acromegaly cases by sex and age

Our findings demonstrated that the acromegaly prevalence is higher in females, but the incidence rate turned out to be sex-specific. Thus, incidence in females starts increasing from the 4th decade of life (23.1%), peaking at 50-59 years of age (30.7%) and lowering to the value found in the age group of 30-34 years (8.6%). In men the disease peaks at 40-49 years of age.

As a whole, the data seems to be true, but according to the literature data, due to slow progression of acromegaly, its diagnosis lags behind its onset, and 5-15 years can pass between the symptoms onset and diagnosis of the disease [28]. In our study this period varied from 2 to 26 years; the diagnosis delayed in 19.5% by 3 years, in 24.7% by 3-5 years, in 45.6% by 6-10 years and in 10.2% by 10 years. Thus, in one fifth of patients the disease was diagnosed within a short time, while the diagnosis was found to delay in 80% of the acromegalics predisposing to complications.

Pathogenesis of pituitary adenomas is known to be multi-step one with chromosomal mutations within a cell [29,30]. But there are factors likely to accelerate the process; some authors report that nearly 15.1% of patients associate onset of the disease with a craniocerebral injury, ~ 6% of women attribute it to abortions or deliveries, while 20% of patients link their disease with chronic sinusitis and otitis [26].

Most patients (n=164) in our cohort have associated onset of their disease with no event in particular; no data in medical history indicated either causes or factors facilitating adenoma growth. This indicates that formation of a tumor in the pituitary gland is genetically determined; the process starts subtly. Prior psychoinjuries and stresses were pointed out as the possible causes by 18.6% (n=82) (Fig.2).

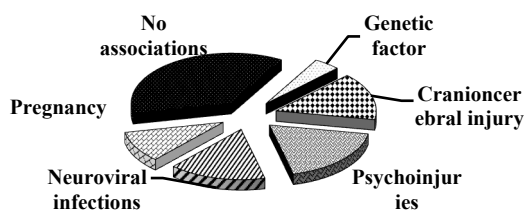


Figure 2. Risk factors in medical histories of patients in the period prior to acromegaly manifestation

Acute respiratory viral infection and inflammatory conditions in the brain preceded manifestation of acromegaly in 14.6% (n=70). 10.1% (n=28) female patients associated the disease onset with pregnancy.

Moreover, craniocerebral injuries (n=68, 15.4%) and hereditary burden (n=19, 4.3%) turned out to be significant factors.

As to the symptoms that caused patients to seek medical advice, headache was the most frequent complaint (72%), followed by changes in appearance, such as enlargement of the nose, earflaps, hands and feet (71%), hyperhidrosis (61%), swelling of the face and extremities (66%). In addition, 70% of women complained of menstrual disorders (Table 2).

Table 2. Acromegaly symptoms as per The National Acromegaly Registry (n=442)

Complaints	Frequency (%)
Enlargement of the hands and feet	64
Changes in appearance	71
Headache	72
Hyperhidrosis	61
Swelling of the face and extremities	66
Parestesias	78
General weakness and work decrement	80
Menstrual disorders	70
Joint and back pain	65
Low libido and sexual potency	45
Vision disorders	40
High arterial pressure	30
Dryness of the mouth, thirst	32

Next, we analyzed frequency of clinical features typical of acromegaly to establish that at the moment of visiting a physician most patients had the dramatic ones (Table 3). Thus, changes in face features, enlarged hands and feet, swelling of the face and hands could be seen in all patients. 98% of patients had thickened skin folds, 87% complained of hyperhidrosis and 70% of women of menstrual disorders, such as oligomenorrhea or amenorrhea; lactorrhea was found in 40%. 53% of male patients had low libido and sexual potency. High arterial pressure could be seen in 30%.

Table 3. Clinical features of acromegaly as per cards of the Registry

Clinical features	Frequency, %
Enlarged hands and feet	100
Changes in face features	100
Diastema	82
Progenia	21
Hyperostosis frontalis interna	25
Swelling of the face and hands	100
Thickened skin folds	98
Hyperhidrosis	87
Menstrual disorders	70
Enlarged thyroid	70
Seborrhea	56
Proximal myopathy	55
Low libido and sexual potency	53
Kyphoscoliosis	45
High arterial pressure	48
Acne	44
Skin tags	43
Carpal tunnel syndrome	41
Coarse voice	41
Lactorrhea	40
Tunneling of vision	40
Apnea	8
Hirsutism	33

Our findings demonstrated that most acromegalics sought medical advice of professionals from other than endocrinology area of expertise; only 27.4% visited an endocrinologist (Table 4).

Table 4. First symptoms of acromegaly (according to the patients) and professionals referred

	Professionals referred	Number of patients	
		n	%
Changes in face features, enlarged hands, feet, high arterial pressure, headache	Therapist	154	34.6
Vision disorder	Ophthalmologist	56	12.6
Menstrual disorders. Breast discharge	Gynecologist	70	15.8
Dryness of the mouth Polydipsia, polyuria	Endocrinologist	122	27.4
Voice changes, snoring	Otorhinolaryngologist	4	0.9
Low libido and sexual potency Swelling of the face and hands	Urologist, nephrologist	36	8.1
Pain in the mandible, changes in occlusion	Dentist	3	0.6

Due to slow progression of the disease, paucisymptomatic clinical picture misled both the patients and physicians preconditioning delayed diagnosis and complicated course of the disease.

Among the complications, in Uzbekistan endocrine (96.1%), cardiovascular (54.2%) and osteoarticular and neuromuscular (65.6%) were the most frequent (Fig.3).

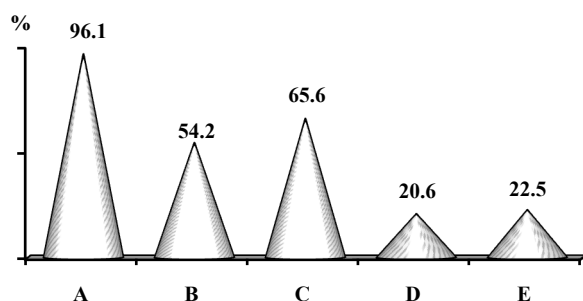


Figure 3. Complications in the acromegalics. A – endocrine, B – cardiovascular, C – osteoarticular and neuromuscular, D – respiratory, E – neoplasms

Next, computed tomography (CT) and magnetic resonance imaging (MRI) were used to study the sizes of pituitary tumors (Table 5). Microadenomas were registered in 9 patients (3%), 68 patients (22.7%) had the adenoma with endosellar growth. Macroadenomas with extrasellar growth were found in 192 patients (64%), and those with suprasellar growth were registered in 102 patients (34%). 25 patients (8.3%) had gigantic pituitary adenomas. According to CT/MRI findings 32 patients (10.3%) had partially empty

sella with the pituitary hypoplasia (Table 5).

According to our findings, large sizes and extrasellar growth are typical of somatotrophic pituitary adenomas (71.7%). In addition, in 32.1% of patients the tumor's invasive growth was found. Merely by the character of an adenoma's growth it is evident that more than 80% of patients should have got operated, 32.1% needed radiotherapy.

Table 5. CT/MRI findings

Pituitary CT/MRI		Number of patients	
		n	%
Microadenoma		10	2.3
Endosellar adenoma		23	5.2
Extrasellar adenoma	Suprasellar	130	29.4
	Gigantic	45	10.2
	Invasive	142	32.1
Empty sella syndrome, pituitary hypoplasia		92	20.8
Total		442	100

The evaluation of GH secretion, that is, single measurement of basal GH, which varied in our study from 2.3 to 115.4 mU/l (mean value 47.4 ± 21.6 mU/l), was principal in the laboratory diagnosis. Herewith, "harmless" GH level < 5 mU/l was registered in 54 (12.2%) patients only. In other words, though most patients (87.8%) needed an intensive therapy they received some drug treatment or another. Thus, of 442 patients 44.5% received dopamine agonists, 28.4% underwent radiotherapy and only 27.1% got operated.

4. Conclusions

To sum up, acromegaly prevalence in the Republic of Uzbekistan is 1.4 cases per 100 000 population with non-uniform regional distribution. The highest frequency of the somatotrophic pituitary adenomas was found in Tashkent-city (2.5) and Namangan region (2.2). The female predominance could be clearly seen. The delayed diagnosis by 6-10 years with peaking at 40-49 years among men and at 50-59 years among women was found. As to potential triggering factors, neuroviral infections were found to precede the disease onset in 14.6% of the patients, psychoinjuries and stresses in 18.6%; 101% of women associated the disease onset with pregnancy, 15.4% of patients linked it with the craniocerebral injuries.

As the results from analysis of clinical presentation period demonstrated, the patients first sought medical attention late and at the height of the disease. Herewith, most acromegalics sought medical advice of professionals from other than endocrinology area of expertise, that is, of a neuropathologist, a therapist or a cardiologist, while only 27.4% of acromegalics visited an endocrinologist; of all others, this determined high frequency and early onset of complications. The point to be emphasized is that high frequency of

complications with affection of endocrine, cardiovascular, and osteoarticular and neuromuscular systems caused by the delayed diagnosis and nonspecific manifestations of the disease which could be confused with arterial hypertension, cephalgia, menstrual disorders and infertility, hypothyroidism and diabetes mellitus.

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