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CLINICAL AND HORMONAL FEATURES OF ACROMEGALY IN PATIENTS FROM A UKRAINIAN NEUROENDOCRINOLOGY CENTRE*

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Acromegaly (ACRO) is a disease of an excessive somatic growth and distorted proportions arising from hypersecretion of growth hormone (GH) and insulin-like growth factor I (IGF-I). ACRO, is mostly caused by a GH-producing pituitary micro- or macroadenoma (96–98%). The resulting excess of the GH secretion affects multiple organ systems, and the disease biochemical control is essential to reduce the mortality in population [1–5]. The severity and complexity of the disease demand a lifelong follow-up at highly specialized centres. Such follow-up should be offered to all patients with this pathology [6].

Insidious clinical manifestation of the GH excess, resulting from a GH-secreting pituitary adenoma, renders ACRO as the disease with a delayed diagnosis, which is made approximately 10 years from the symptoms onset. Despite the increasing availability of modern diagnostic methods, the timely diagnosis is still a problem nowadays, and it directly influences the further prognosis. Owing to this reasons, it is important to establish national registers of patients with hormonally active pituitary adenomas, including registers of patients with ACRO. The information on basic demographic parameters, clinical findings, biochemical assays, the date of radiological, histopathological, treatment and outcome in patients with pituitary tumors has been collected in the national registers of many European countries [7–10]. The data are registered at diagnosis, in connection with primary treatment (surgery and/or radiotherapy) and in the dynamic monitoring [11–13]. Unfortunately, not all countries have the possibility to create such registries at the state level. In the countries of Eastern Europe, the research of this kind is carried out in the specialized national medical centers.

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The aim of this study is to investigate basic demographic parameters such as the age and gender related features, the age at making of diagnosis, clinical manifestations, biochemical control and structure of complications in Ukrainian patients with acromegaly in a separate neuroendocrinology centre.

MATERIAL AND METHODS

Subjects, inclusion criteria: Patients with ACRO, including somatotropinoma (ST) and somatomammotropinoma (SMT): the data was collected in the Neuroendocrinologicaly Centre, based in V. Danilevsky' Institute for Endocrine Pathology Problems NAMS of Ukraine (n = 133 [including 47 *de novo*]: female — 88, male — 45) and the retrospective study of 133 patients (female — 91, male — 42) who had neurosurgical treatment (according to database of Romonadov' Neurosurgery Institute of NAMS of Ukraine, Kiev). The control group includes healthy individuals of the corresponding age (n=34). The division of groups is presented in Table 1.

In order to estimate the impact of age on manifestation of ACRO, patients (n=133) were divided into three groups: young (18–39 yrs) (group 1), middle aged (40–59 yrs) (group 2) and elderly (over 60 yrs) (group 3). Group 1 consisted of 33 patients (19 female/14 male), group 2 — of 79 patients (48 female/31 male), and group 3 included 21 patients (15 female/6 male).

Methods: Diagnosis of ACRO was based on the Consensus Statement on acromegaly (2014) [12]. Chemiluminescence method was used to determine the levels of GH, prolactin (PRL), IGF-1 using the Biomerica Immunoassay system (USA). The degree of increase IGF-1 level in the blood was estimated as a percentage of the upper normal limit (IGF-$I_{ULN\%}$) for patient age. All patients underwent an enhanced and a plain MRI scan using a Siemens 1.5 T MRI machine (Magnetom; Siemens AG, Munich, Germany). The tumor V was calculated as follows: $V = a \times b \times c \times \pi / 6$ [14].

Statistical analysis: SPSS19.0 statistical software (IBM Corp., Armonk, NY, US) was used for statistical analysis. Comparisons between plasma GH and IGF-I levels of patients in two groups were done by ANOVA in relation to age, gender, and other hormonal and clinical parameters. Normal distribution of variables was determined using the Shapiro-Wilk test. The Kruskal-Wallis criterion (H) was used to compare several groups with abnormal distribution of variables. The criterion of «chi-squared» ($\chi 2$) with the Yates correction was used for the statistical evaluation of the differences between the empirical and theoretical frequency variation. The obtained results are presented in the tables in the following manner: M ± m; M ± SD; Me; where the M is arithmetic mean, SD is standard deviation, m is mean deviation, Me is median, Min is minimum value; Max is maximum value.

Table 1

Gender and age-related features of patients with acromegaly

Age	Male		Female		Total	
	n	%	n	%	n	%
≤ 20	4	1,49	3	1,12	7	2,61
21–30	14	5,22	24	8,96	38	14,18
31–40	26	9,70	34	12,69	60	22,39
41–50	21	7,84	48	17,91	69	25,75
51–60	24	8,96	47	17,54	71	26,49
61–70	3	1,12	16	5,97	19	7,09
> 70	2	0,75	2	0,75	4	1,49
Total	94	35,07	174	64,94	268	100

RESULTS AND THEIR DISCUSSION

Gender analysis of all patients with ACRO has shown the preponderance of women: the male/female ratio is 1 : 1.9, which is also preserved in the group of patients with ST and SMT (1.0 vs 1.4 and 1.0 vs 2.2, respectively). The revealed gender differentiation takes place rather due to a low compliance and survival of men than to the disease prevalence in women. At the time of observation, the age range of men was 18–71 years (Me 41.5, [33.0–51.0]), mean (41.9 ± 12.5) years, the age range of women — 15–75 years (Me 46. 0 [36.0–54.0]), mean, (45.1 ± 12.4) years. Patients in the ST and SMT groups matched in age: (44.0 ± 12.6) and (44.0 ± 12.0).

Our study has established that 82.3 % (n = 219) of all patients were 31 to 60 years old: 32.4 % (n = 71) of men and 67.6 % (n = 148) of women belong to the aforesaid age range (χ^2 = 15.47; P = 0.0001). The analysis of the age structure has also shown that the percentage of women in the reproductive age is significantly higher than that of men (40.7 % and 22.8 %, respectively) (χ^2 = 6.64; P = 0.01). Our attention has been attracted by a small number of men (n = 5) and women (n = 18) over 61 years. There were 9.0 % (n = 24) patients aged less than 30 years old. Age-related features of the kind can be explained by the development of the ACRO chronic complications in elderly patients, which cause premature mortality, as well as by low survival capability of men in the population and a more aggressive course of the disease in men [7].

In 13.4 % of patients ACRO manifests at the age of 50 years, which is connected with an age-related increase in the number of point mutations in somatotrophs. By the age of 40–50 yrs some involutional changes happen in the endocrine system, able to induce the development of multiple organ dystrophic and neoplastic processes.

The average duration of an active phase in all patients was 139.2 months. (Me = 93.6 month) and it varied from 6 to 38 years. The active phase duration was twice longer than then the one of pre-nosological period (period before primary diagnosis) that can be explained by the use of ineffective methods of the disease treatment (medical therapy, radiotherapy).

Pre-nosological period in all patients ranged from 1 to 360 months, (61.33 ± 6.36) months on the average, and indicated, as a whole, the late diagnostics of ACRO. Pre-nosological period fluctuations, revealed in the general group, occur, apparently, due to the individual features of the ACRO clinical course and reflect current problems in the diagnosing of this disease in the separate medical institutions. The early diagnosis of ACRO (within a year from the first complaint) was made only in 20.6 % of patients. A significant pre-nosological period can be explained by the variety of patient's complaints at the time of manifestation. During that period, patients were usually examined and treated by physicians connecting the related pathologies, including osteo-articular and cardiovascular systems, glucose intolerance, menstrual cycle disorders and galactorrhea (female), and sexual function disturbances (male), etc. The presence of some diagnostic errors testifies that of neurologists, cardiologists, gynecologists, andrologists, optometrists and orthopaedic-traumatologists lack information concerning symptoms and clinical features of ACRO.

Analysis of the complaints structure in patients with ACRO at the time of its manifestation has shown that the severity of the common complaints (fatigue (45.5 %), asthenia (43.9 %), headache (43.9 %), and excessive sweating (42.3 %)) contributes to the blurring of the disease clinical features, which is one of the reasons for the late diagnosis. Complaints about the changes of the appearance (increased sizes of hands and feet (60.2 %) coarse facial features (42.3 %)), which are specific morphological markers of ACRO, are more considered as age-related by more than 50 % of patients, so they do not cause special discomfort.

It is well known that persistent effect of hypersomatotropinemia on all organs and systems of the human body varies clinical symptoms of ACRO, which is reflected in the structure of complaints. The complaints, caused by the development of chronic ACRO complications dominate in the general group.

The study has revealed an increased frequency of such complaints as facial changes (42.3 vs 75.6 %; (χ^2 = 22.51; P = 0.00001)), an increased sizes of hands and feet (60.2 and

74.8 %; (χ^2 = 4,47; P = 0.03)), headache (43.9 vs 70.7 %; (χ^2 = 13.83; P = 0.0002)) and vision disorders (11.4 vs 52.8 %; (χ^2 = 38.63; P = 0.00001)), which are characteristic of the disease development in men and women. As at the time of the disease manifestation, the most common (according to questioning) are complaints, associated with the changes of the appearance.

The second place according to the frequency of complains belongs to the headache (70.7 %), which is associated with the development of the liquor hypertension and pituitary adenoma. We pay special attention to headache, as it is considered to be the one of the first signs of the *sella turcica* tumour [15]. Thus, according to the statistics, 10 % of all ambulatory visits of patients with various pathologies take place due to their complaints about headaches of different location, duration and intensity.

In the complaints collection we have considered in detail the incidence of headache and its location, the presence of concomitant symptoms such as nausea, loss of consciousness, seizures, discharge from the nose, vision disorders (visual acuity, restriction of visual fields, etc.). 78.7 % of patients have complaints on headache, accompanied by visual disorders. Headache in patients with ACRO is mostly localized in the frontal part and in orbital area, it occurs predominantly during sleep. Headache, accompanied by nausea, is localized in the occipital region, partly in the eyes area, and it occurs in the day-time.

We can conclude that the complaints, associated with chronic complications of ACRO (cardiovascular and osteoarticular pathologies, and glucose intolerance), prevail in patients with ACRO, regardless of the hormonal activity of a pituitary adenoma. The structure of complaints in patients at the time of observation in the groups, depending on the hormonal activity of the pituitary adenoma, is shown in Fig. 2 and 3.

Thus, on the time of primary diagnostics, in the group of patients with ST complaints of headache (χ^2 = 1.62; P = 0.2), increasing sizes of extremities P=0.075), cardialgia (χ^2 = 4.78; P = 0.03), arthralgia (c = 8.11, P = 0.004), asthenia (χ^2 = 20.39; P = 0.0001) and fatigability (χ^2 = 11.30; P = 0.0008) occur more often in women. In patients with SMT complaints about increased size of hands and feet (χ^2 = 2.17; P = 0.14), dyspnoea (χ^2 = 1.67; P = 0.19), vertigo (χ^2 = 0.53; P = 0.46), headache (χ^2 = 0.02; P = 0.87), hyperglycemia (χ^2 = 2.36; P = 0.12), cardialgia (χ^2 = 2.64; P = 0.10) and rapid fatigability (χ^2 = 0.13; P = 0.72) occur with equal frequency in men and women. Women of the studied groups complain of facial changes (χ^2 = 7.97; P = 0.005), fatigability (χ^2 = 11.73; P = 0.0006), arthralgia (χ^2 = 5.19; P = 0.023), arterial hypertension (χ^2 = 4.34; P = 0.037), and blurred vision (χ^2 = 4.34; P = 0.037) more frequently.

Intergroup differences of the basal GH and PRL levels as well as the IGF-1 concentrations have not been registered. At the same time, attention is drawn to a significantly higher GH – OGTT level in the SMT group (Me 34.6 [9.3–223.09]) as compared with the ST group (Me 8.84 [1.9–38.2]) (P = 0.001), confirming a more expressive autonomy of the GH-secreting pituitary adenomas.

Estimation of the clinical and hormonal control of ACRO in the general group has shown that in 3.8 % of patients it is adequate (complete remission), in 27.8 % it is inadequate (partial remission), and in 68.4 % it is poor (active form) [12]. An adequate clinical and hormonal control of ACRO has been attained in 5 patients after neurosurgical treatment, in the other 6 patients it was achieved by the treatment with prolonged somatostatin analogues.

The clinical characteristics, data on the volume of the pituitary gland, secretory and proliferative activity of the GH-secreting adenomas in patients with ACRO in the selected age groups are shown in Table II.

According to the ST/SMT ratio, the correlation in the different age groups was the following: 2.2 : 1, 2.5 : 1 and 3 : 1, respectively. The percentage of patients with an active ACRO was 90.6 % in group 1; 67.6 % in group 2; and 50 % in group 3. Our attention was attracted by a smaller number of women in group 3, as compared with groups 1 and 2 (the male / female ratio was 1 : 1.36; 1 : 1.55 and 1 : 2.5; respectively), related with a lower average lifespan of men.

The diagnostics of patients in group 1 has revealed a pituitary macroadenoma in 84.4 % of subjects, and the percentage of patients

Table 2

Characters of patients with acromegaly in different age groups, (M ± m; Me; Min-Max)

Parameter	Group 1 (n = 33)	Group 2 (n = 79)	Group 3 (n = 21)	H	P
Age, years	32.0 ± 5.31 33.0 18.0–39.0	50.8 ± 5.65 52.0 40.0–59.0	65.2 ± 4.5 63.5 60.0–75.0	95.9	0.0001
Age of manifestation, years	29.1 ± 7.3 30.0 12.0–39.0	43.1 ± 9.1 41.5 23.0–59.0	54.0 ± 10.1 53.5 27.0–71.0	55.9	0.0001
Pre-nosological period, month	40.6 ± 32.8 36.0 1.0–117.0	76.4 ± 75.1 54.0 1.0–360.0	70.6 ± 62.1 48.0 1.0–232.0	5.07	0.08
Total disease period, month	75.7 ± 52.9 60.0 11.0–228.0	163.0 ± 102.7 132.0 22.0–420.0	186.3 ± 117.2 168.0 36.0–456.0	19.7	0.0005
Pituitary volume, cm3	9.76 ± 11.58 4.41 0.15–37.84	5.68 ± 8.66 2.97 0.21–49.58	2.29 ± 1.96 2.11 0.54–4.39	4.82	0.09
GH, ng/ml	68.4 ± 155.2 31.9 5.6–837.0	23.04 ± 22.3 14.0 2.73–95.8	20.39 ± 17.3 9.3 3.9–50.0	10.2	0.006
IGF-I, ng/ml	696.5 ± 356.8 791.5 159.0–1271.0	581.1 ± 402.4 520.5 101.0–1780.0	363.0 ± 285.9 255.0 101.0–1165.0	8.4	0.02
IGF-I%UNL	126.1 ± 100.9 157.5 – 45.3–283.0	133.9 ± 167.1 100.1 – 59.9–570.7	74.6 ± 134.4 20.3 – 52.4–449.5	1.96	0.37

Table 3

Gender features in the clinical course of the disease in patients with acromegaly, (Me, [Min-Max])

Parameter	Male (n = 51)	Female (n = 82)	P
Age, years	48.0 [18.0–71.0]	52.0 [25.0–75.0]	0.09
Age of manifestation, years	39.0 [12.0–71.0]	41.0 [16.0–71.0]	0.13
Total desease period, month	132.0 [11.0–420.0]	108.0 [12.0–456.0]	0.18
Pre-nosological period, month	60.0 [11.0–360.0]	36.0 [1.0–232.0]	0.017
Active period, month	120.0 [11.0–204.0]	60.0 [12.0–432.0]	0.02
Pituitary volume, cm^3	4.32 [0.21–49.58]	3.15 [0.15–37.84]	0.41
GH, ng/ml	45.30 [0.5–837.0]	24.17 [0.7–144.88]	0.01
IGF-1, ng/ml	548.2 [101.0–1780.0]	326.0 [101.0–1271.0]	0.03
$IGF\text{-}1_{\%ULN}$	124.89 [– 57.30–570.67]	23.02 [– 59.92–340.55]	0.009
GH/IGF-1, c.u.	0.04 [0.003–4.65]	0.03 [0.004–0.70]	0.009
PRL, mU/l	309.65 [8.15–7767.86]	383.92 [18.85–3558.0]	0.93

with an active form of ACRO, irrespective of the treatment, comes to 90.6%, also indicating a high secretory and proliferative activity of a GH-secreting adenoma in young patients. It has also been established that the volume of macroadenoma in patients of group 1 is significantly higher than that in groups 2 and 3 (Me 4.49 [1.73–37.84], Me 3.19 [0.77–49.58] and Me 3.52 [0.69–4.39] cm^3; respectively) ($P < 0.05$).

A tendency to extension of pre-nosological period in the age groups 2 and 3 has been found as compared with the group 1 (Table 2). With regard to this finding, the prevalence of macroadenomas in groups 1 and 2 with a relatively short pre-nosological period testifies to the fact that the main factor of an increased pituitary volume is a high level of GH.

It has been established that pre-nosological period has a linear proportional increase, related with age in patients with ACRO: $R^2 = 3.4$ %; $P = 0.041$), and is also associated with the age of first manifestation ($R = 0.24$; $R^2 = 5.96$ %; $P = 0.007$). Table I data suggests a conclusion that the course of ACRO in the age group 3 can be characterized as a slowly progressive one, which is confirmed by a significantly longer, pre-nosological period as well as lower serum levels of GH and IGF-I, as compared with group 1. Instead, a significantly shorter pre-nosological period, as compared to group 3, higher serum level of GH and IGF-I in patients of group 1 suggests a rapidly progressing course of ACRO.

The analysis results are given in Table III. It has been established that the clinical course in men is characterized by an early manifestation of the disease, a long-term pre-nosological period and the presence of an active phase (which can indicate resistance to the treatment).

DISCUSSION

Over the last 20 years some changes have been observed in the paradigm of diagnosis and treatment of ACRO and assessment of its effectiveness, which has been reflected in a number of international consensuses [12, 16–19]. According to the current requirements, the main criteria of the treatment efficiency are to increase the duration and improve the quality of life of the patient with ACRO, which cannot be achieved without an appropriate clinical and hormonal control of the disease. Changes in the opinions on diagnosis and treatment have caused the need to review the effectiveness of the existing methods for the diagnosis and treatment of ACRO in the terms of new criteria for assessing the state of clinical and hormonal control.

Ukraine has not yet reviewed the strategy for the treatment of ACRO that is related with an advanced level of neuroendocrine assistance at present. Some modifications in the approaches to the diagnosis and treatment of this rare disease took place in the «V. Danilevsky Institute for Endocrine Pathology Problems of the NAMS of Ukraine» in parallel with opening in 2009 of the Acromegaly Treatment Centre (the Neuroendocrine Centre since January 2013). The register of patients with ACRO (n = 168) has also been approved, making it possible to solve a number of methodological, diagnostic, medical and social tasks, including considerations on the National consensus for the diagnosis and treatment of ACRO, introduction into the clinical practice of algorithms for the diagnosis and treatment of the disease, as well as its complications.

The organizational structure of a new methodological approach is the national register on ACRO, which makes it possible to perform the monitoring of the epidemiological situation and an efficient analysis of the clinical data (duration of the pre-nosological period, total duration of the disease, the size of the pituitary adenoma, its hormonal activity, the structure of chronic complications, methods of the provided treatment, and the state of the disease clinical and hormonal control). Today, national registers of patients with ACRO have been established and they are actively supported in all countries of the European Union, North and South America, Russian Federation, Japan, some countries of Central Asia and Middle East [20–24, 26].The methodological basis for creating the register is, first of all, the development of the integrated diagnostic and prognostic criteria that allow the experts to

predict the clinical course of ACRO and define an individual optimal treatment tactic [26].

According to the available sources of special literature, the epidemiological situation regarding ACRO differs significantly in various countries, which can be explained, on the one hand, by different levels of their economic development, organization of medical care and health centres supervision, on the other hand, by the availability of qualified physicians and the accessibility of a thorough medical examination [25–29]. Since Ukraine has not yet introduced a register on ACRO, it is certainly not possible to assess the real prevalence of this endocrine disease. One can only hypothetically predict that the number of patients with this pathology in Ukraine is assumed to be 1840–3220 people, taking into account the average incidence of acromegaly (40–70 cases per million) in the world.

It has been established that one of the organizational shortcomings of ACRO register implemented by us is just passive registration of patients, who sought medical advice in our clinic. It is obvious that the number of the registered patients reflects not so much the actual epidemiological situation on the disease in Ukraine as the inefficiency of the treatment applied. The experience of other countries with an appropriate medical examination of the population and realization of the program, concerning an active search for patients, has shown that the prevalence of ACRO is much higher. According to the new Consensus statement on acromegaly therapeutic outcomes [18] this necessitates to organize the unified methodological centres, specialized diagnostic and medical bases, the expert councils, to design educational and information programs, and to introduce a quality control system for the treatment of patients. Therefore, the most effective method for estimating the morbidity and prevalence of any disease, and especially such a rare one as ACRO, is a population-based screening for patients of high-risk groups, but in Ukraine it requires the development of methodological approaches and economic grounds. Germany has a great experience in this regard: ACRO has been diagnosed in 1034 people per million according to the data of a population-based screening of IGF-1 blood concentration, whereas according to official statistics this rate is 70 people per million [24].

We have found that ACRO occurs more often in women than in men (1.9 : 1). In addition, 88.8 % of the examined patients belong to the age group of 31–60 years. It has been established that the peak of the disease manifestation is at the most productive age ((41.3 ± 12.0) years). The data obtained regarding the demographic characteristics of the examined patients with ACRO are comparable to these of the Russian and Spanish registries of ACRO [27, 28]. Although for the diagnosis of ACRO only the morphological signs of the disease, as a rule, are sufficient for an experienced specialist, duration of the pre-nosological period (Me 41.0 months) in the studied patients reflects certain diagnostic problems.

The problem of the late diagnosis of ACRO is also urgent for the countries with a high level of rendering neuroendocrine assistance to the population. Thus, according to the data obtained by R. Knutzen and S. Ezzat, duration of the pre-nosological period in 54% of patients with ACRO is more than 10 years, and in 37 % it lasts more than 15 years [30]. Hence, the problem of the late diagnosis of ACRO should not be considered only as an inadequate qualification of doctors and inaccessibility of current diagnostic methods, although these factors should also been taken into account. The solution of the problem needs to be considered in all its aspects: as the search for the best understanding of the individual features of the disease clinical course as well as revealing the risk factors. Formation of the risk groups for an active revealing of genetic and sporadic forms of ACRO should take place with consideration of all the above-mentioned factors, including a thorough examination of the patient's close relatives with the use of current genetic research. Gender characteristics, revealed in the clinical course of ACRO, should be paid attention as well. It has been defined that the clinical course in men is characterized by an early debut of the disease, the duration of the pre-nosological period, caused by a variety of clinical symptoms of the disease and the resistance to treatment. It is suggested, that the clinical course of ACRO in men is more aggressive than that in women. The results obtained

are consistent with the data of some other authors, who also note a more aggressive course of ACRO in men than in women. So, according to R. Knutzen et al., men differ from women in an earlier age of manifestation (41.0 vs. 47.0 years) ($P < 0.001$) and significantly higher levels of GH and IGF-1 concentrations [30]. Early manifestation of ACRO in men at higher levels of GH and IGF-1 concentrations has been established also by S. Petersenn et al. [24, 31]. According to the results of the analysis of the Sweden register on ACRO, male gender is recognized as an independent predictor of premature death, along with the age of manifestation and the GH basal level [32]. In addition, according to epidemiological studies, a significantly higher risk of premature death from cardiovascular, cerebrovascular complications and malignant neoplasms has been revealed in men with ACRO [33]. This allows concluding that the activity of ACRO is influenced, first of all, by the age and gender of the patient. The male sex is an additional independent predictor of the «aggressive» course of ACRO, which substantiates the expedience of applying a more aggressive treatment strategy in men.

The information on the influence of the age factor on the clinical course of ACRO is still insufficient. The data concerning the age-related features of the ACRO course, presented in the literature, are, as a rule, descriptive, impeding the systemic comprehension of the clinical material. The cause of an improper systematization of the clinical material is the insignificant prevalence of ACRO and the absence of the present-day methods for examination in a number of medical institutions due to some objective reasons. The results obtained indicate that the features of the disease clinical course are confined not only to the presence of morphological, hormonal-metabolic and organic disorders, as the patient's age puts some adjustments in the peculiarities of the disease, clinical symptoms and its course.

The age of the patient is usually analyzed in the clinical study at the time of the disease diagnosis and registration of the passport age, while the age of manifestation is not given a proper attention. However, this measure is fundamentally important since it reflects the secretory and proliferative activity of the pituitary GH-secreting adenoma and is associated with the severity of chronic complications and determines the prognosis.

Making estimation of the age impact on the peculiarities of the disease clinical course it is necessary to take into account the diseases, associated with physiological aging, which substantially modify the clinical manifestations of the disease. The problem of the late diagnosis of acromegaly in the elderly people is an increase of cardiovascular and surgical risks and shortening of the life-span of the patients. This problem is widely discussed in the literature. Improving the quality of medical assistance to the elderly people is an urgent problem of the health care system, considering the tendency to the gradual aging of the population in Ukraine.

CONCLUSION

Secretory and proliferative activity of the GH secretive pituitary adenoma is associated with the age of the patient at the time of the manifestation of acromegaly. Sexual dimorphism of the clinical course of acromegaly is manifested at a young age and is characterized by a higher secretory activity of GH-secreting adenoma and is greater in men. High total secretory activity of GH-secreting pituitary adenoma, tumor growth rate, which are associated with the young age, determine the «fast-moving» course of acromegaly in young people. In elderly patients, the domination of the secretory over the proliferative activity of the GH-secreting pituitary adenoma and the satisfactory sensitivity to the treatment determine the «slowly progressive» clinical course of disease.

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CLINICAL AND HORMONAL FEATURES OF ACROMEGALY IN PATIERNTS FROM A UKRAINIAN NEUROENDOCRINOLOGY CENTRE

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Acromegaly (ACRO) is a rare disease of an excessive somatic growth and distorted proportions arising from hypersecretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Insidious clinical manifestation of the GH excess, resulting from a GH-secreting pituitary adenoma, renders ACRO as the disease with a typically delayed diagnosis, approximately 10 years from the symptoms onset. Despite the increasing availability of modern diagnostic methods, the timely diagnosis of ACRO at present is still a problem which is directly connected with the further prognosis. Owing to this reasons, it is important to establish national registers of patients with hormonally active pituitary adenomas, including registers of patients with ACRO. But not all countries have the possibility to create such registries at the state level. In the countries of Eastern Europe, the research of the kind is carried out in the specialized national medical centers.

The aim of this study is to investigate basic demographic parameters such as the age and gender related features, age at diagnosis of the disease, its clinical manifestations, biochemical control and structure of complications in Ukrainian patients with ACRO in a single neuroendocrinological centre.

Material and methods. Patients with acromegaly, including somatotropinoma (ST) and somatomammotropinoma (SMT): the data collected within the Neuroendocrinological Centre, based in V. Danilevsky' Institute for Endocrine Pathology Problems (n = 133 [including 47 *de novo*]: female — 88, male — 45) and retrospective study 133 patients (female — 91, male — 42) who had neurosurgical treatment (according to database of Romonadov' Neurosurgery Institute). Diagnosis of ACRO was based on the Consensus Statement on acromegaly (2014). The levels of PRL, GH and IGF-1 were measured. All patients underwent an enhanced and a plain MRI scan using a Siemens 1.5 T MRI.

Statistical analysis: SPSS 19.0 statistical software (IBM Corp., Armonk, NY, US) was used for statistical analysis. Comparisons between plasma GH and IGF-1 levels of patients in two groups were done by ANOVA for age, gender, and other hormonal and clinical parameters.

Results. Our study has established that 88.8% (n = 238) of the overall sample consist of patients aged 31 to 60 years: 26.5 % (n = 71) of men and 55.2 % (n = 148) of women belong to the aforesaid age range ($\chi^2 = 15.47$; P = 0.0001). Peak of the ACRO manifestation in the overall sample falls on the age of working efficiency (41.3 ± 12.0) years: (39.0 ± 13.2) years for men and (42.8 ± 11.0) for women. Analysis of the complaints structure in patients with acromegaly at the time of its manifestation has shown that the severity of the common complaints (fatigability (45.5 %), asthenia (43.9 %), headache (43.9 %), and excessive sweating (42.3 %)) contributes to the blurring of the disease clinical features, which is one of the purposes for its late diagnosis. Complaints about the changes in their appearance (increasing sizes of hands and feet (60.2 %) and in facial features (42.3 %)), which are specific morphological markers of ACRO, more than 50 % of patients consider as age-related, so they do not cause special uneasiness. The average duration of an active phase in the overall sample is 139.2 months. (Me = 93.6 month) and it varies from 6 to 38 years. The active phase duration is more than twice of pre-nosological period that can be explained by the use of no effective methods and outlines of the disease treatment (medical therapy, radiotherapy). It has been established that pre-nosological period has a linear proportional increase, related with age in patients with ACRO: $R^2 = 3.4$ %; P = 0.041) and is also associated with the age of manifestation (R = 0.24; $R^2 = 5.96$ %; P = 0.007).

Conclusion. Sexual dimorphism of the clinical course of acromegaly is manifested at a young age at the time of manifestation of the disease and is characterized by a higher secretory activity of GH-secreting adenoma and a it greater mass effect in men. Secretory and proliferative activity of the GH secretive pituitary adenoma is associated with the age of the patient at the time of the manifestation of ACRO. High total secretory activity of GH-secreting pituitary adenoma, tumor growth rate, resistance to treatment and predisposition to relapse, which are associated with the young patient at the time of the manifestation of the disease, determine the «fast-moving» flow of ACRO. In elderly patients, the domination of the secretory over the proliferative activity of the GH-secreting pituitary adenoma gland and the satisfactory sensitivity to the treatment determine the «slowly progressive» clinical course of disease.

Keywords: Acromegaly; GH-pituitary adenomas; early diagnosis.

КЛИНИКО-ГОРМОНАЛЬНЫЕ ОСОБЕННОСТИ АКРОМЕГИИ У БОЛЬНЫХ ПО ДАННЫМ УКРАИНСКОГО НЕЙРОЭНДОКРИНОЛОГИЧЕСКОГО ЦЕНТРА

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Акромегалия (ACRO) является орфанным тяжелым нейроэндокринным заболеванием, которое обусловлено гиперпродукцией гормона роста (GH) и инсулиноподобного фактора роста-1 (IGF-1) у лиц с закончившимся физиологическим ростом и характеризуется патологическим диспропорциональным ростом костей скелета, мягких тканей и внутренних органов, а также нарушением различных видов обмена веществ. Торпидное клиническое течение позволяет отнести ACRO к группе заболеваний с отсроченным диагнозом, который устанавливается примерно через 10 лет после появления первых симптомов. Долгосрочный прогноз течения заболевания напрямую связан с ранней диагностикой, применяемыми методами лечения и оценки их эффективности. В связи с этим важную роль имеют постоянно обновляемые национальные реестры пациентов с гормонально активными аденомами гипофиза, в том числе реестры пациентов с ACRO. К сожалению, не все страны имеют возможность создавать такие реестры на государственном уровне. В странах Восточной Европы подобные исследования проводятся в специализированных национальных медицинских центрах.

Целью данного исследования является изучение основных демографических параметров, клинических особенностей, возраста на момент постановки диагноза, уровня биохимического контроля и структуры осложнений у пациентов Украины с акромегалией в отдельном нейроэндокринологическом центре.

Материалы и методы. Пациенты с акромегалией, в том числе соматотропиномой (ST) и соматомаммотропиномой (SMT): по данным нейроэндокринологического центра на базе ГУ «Институт проблем эндокринной патологии им. В. Данилевского НАМНУ» (n = 133 [в том числе 47 de novo]: женщины — 88, мужчины — 45) и по данным ретроспективного анализа историй болезни 133 пациентов (женщины — 91, мужчины — 42), которым было проведено нейрохирургическое лечение на базе ГУ «Институт нейрохирургии им. А. П. Ромонадова НАМНУ». Диагностика ACRO проводилась согласно рекомендациям Консенсуса по диагностике и лечению акромегалии Европейского эндокринологического общества (2014). Исследовали уровни пролактина (PRL), GH и IGF-1 в сыворотке крови. Всем пациентам проведено МРТ сканирование головного мозга с использованием аппарата Siemens 1,5T. Статистический анализ проведен с использованием стандартной программы SPSS 19.0 (IBM Corp., Armonk, NY, US).

Результаты. Установлено, что 88,8 % (n = 238) от общей выборки составляют пациенты в возрасте от 31 до 60 лет: из них 26,5 % (n = 71) мужчин и 55,2 % (n = 148) женщин (χ^2 = 15,47; P = 0,0001); пик манифестации ACRO приходится на трудоспособный возраст (41,3 ± 12,0) лет: (39,0 ± 13,2) лет для мужчин и (42,8 ± 11,0) для женщин. Высокая частота неспецифических общесоматических и неврологических жалоб (утомляемость (45,5 %), астения (43,9 %), головная боль (43,9 %) и повышенное потоотделение (42,3 %) является причиной поздней диагностики заболевания. Такие специфические морфологические маркеры ACRO, как изменения внешности (увеличение размеров рук и ног (60,2 %), лица (42,3 %)) более 50 % пациентов считали возрастными изменениями, поэтому они не вызывали у них особого беспокойства. Средняя продолжительность активной фазы ACRO составила 139,2 месяца (Me = 93,6 месяца) и колебалась в диапазоне от 6 до 38 лет. Продолжительность активной фазы более чем вдвое превышала длительность донозологического периода, что можно объяснить использованием неэффективных методов и схем лечения заболевания (медикаментозная терапия, лучевая терапия). Установлено, что длительность донозологического периода пропорционально увеличивается в зависимости от возраста больных: R^2 = 3,4 %; P = 0,041, и также зависит от возраста начала заболевания (R = 0,24; R^2 = 5,96 %; P = 0,007).

Заключение. Половой диморфизм клинического течения акромегалии проявляется в молодом возрасте во время проявления заболевания и характеризуется у мужчин более высокой секреторной активностью GH-аденомы и более выраженным масс-эффектом опухоли. Секреторная и пролиферативная активность GH-аденомы гипофиза зависит от возраста пациента на момент заболевания. Для больных молодого возраста характерно быстро прогрессирующее и рецидивирующее течение акромегалии, что обусловлено высокой суммарной секреторной, пролиферативной активностью GH-аденомы и высокой скоростью роста опухоли. Для пожилых пациентов характерно «медленно прогрессирующее» клиническое течение заболевания, что обусловлено преобладанием секреторной активности GH-аденомы гипофиза над пролиферативной.

Ключевые слова: акромегалия; аденома гипофиза; ранняя диагностика.

КЛІНІКО-ГОРМОНАЛЬНІ ОСОБЛИВОСТІ АКРОМЕГАЛІЇ У ПАЦІЄНТІВ ЗА ДАНИМИ УКРАЇНСЬКОГО НЕЙРОЕНДОКРИНОЛОГІЧНОГО ЦЕНТРУ

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Акромегалія (ACRO) є орфанним важким нейроендокринним захворюванням, яке обумовлено гіперпродукцією гормону росту (GH) і інсуліноподібного фактору росту-1 (IGF-1) у осіб із завершеними фізіологічним ростом і характеризується патологічним диспропорційним зростанням кісток скелета, м'яких тканин і внутрішніх органів, а також порушенням різних видів обміну речовин. Повільний клінічний перебіг дозволяє віднести ACRO до групи захворювань з відстроченим діагнозом, який встановлюється приблизно через 10 років після появи перших симптомів. Довгостроковий прогноз перебігу захворювання безпосередньо пов'язаний з ранньою діагностикою, застосовуваних методів лікування і оцінки їх ефективності. У зв'язку з цим важливу роль мають постійно оновлювані національні реєстри пацієнтів з гормонально активними аденомами гіпофіза, в тому числі реєстри пацієнтів з ACRO. На жаль, не всі країни мають можливість створювати такі реєстри на державному рівні. У країнах Східної Європи подібні дослідження проводяться в спеціалізованих національних медичних центрах.

Метою даного дослідження є вивчення основних демографічних параметрів, клінічних особливостей, віку на момент постановки діагнозу, рівня біохімічного контролю та структури ускладнень у пацієнтів України з акромегалією в окремому нейроендокрінологическом центрі.

Матеріали та методи. Пацієнти з акромегалію, в тому числі із соматотропіномою (ST) і соматомаммотропіномою (SMT): за даними нейроендокрінологического центру на базі ДУ «Інститут проблем ендокринної патології ім. В. Я. Данилевський НАМНУ» (n = 133 [в тому числі 47 de novo]: жінки — 88, чоловіки — 45) і за даними ретроспективного аналізу історій хвороби 133 пацієнтів (жінки — 91, чоловіки — 42), яким було проведено нейрохірургічне лікування на базі ДУ «Інститут нейрохірургії ім. А.П. Ромоданова НАМНУ». Діагностика ACRO проводилася відповідно до рекомендацій Консенсусу з діагностики та лікування акромегалії Європейського ендокринологічного товариства (2014). Досліджували рівні пролактину (PRL), GH і IGF-1 в сироватці крові. Всім пацієнтам проведено МРТ сканування головного мозку з використанням апарату Siemens 1,5T. Статистичний аналіз проведено з використанням стандартної програми SPSS 19.0 (IBM Corp., Armonk, NY, US).

Результати. Встановлено, що 88,8 % (n = 238) від загальної вибірки становлять пацієнти у віці від 31 до 60 років: з них 26,5 % (n = 71) чоловіків і 55,2% (n = 148) жінок (χ^2 = 15,47; P = 0,0001); пік маніфестації ACRO доводиться на працездатний вік (41,3 ± 12,0) років: (39,0 ± 13,2) років для чоловіків і (42,8 ± 11,0) років для жінок. Висока частота неспецифічних загальносоматичних і неврологічних скарг (стомлюваність (45,5 %), астенія (43,9 %), головний біль (43,9 %) і підвищене потовиділення (42,3 %) є причиною пізньої діагностики захворювання. Такі специфічні морфологічні маркери ACRO, як зміни зовнішності (збільшення розмірів рук і ніг (60,2 %), обличчя (42,3 %)) більше 50 % пацієнтів вважали віковими змінами, тому вони не викликали у них особливого занепокоєння. Середня тривалість активної фази ACRO склала 139,2 місяці (Me = 93,6 місяця) і коливалася в діапазоні від 6 до 38 років. Тривалість активної фази більш ніж удвічі перевищувала тривалість донозологіческого періоду, що можна пояснити використанням неефективних методів і схем лікування захворювання (медикаментозна терапія, променева терапія). Встановлено, що тривалість донозологіческого періоду пропорційно збільшується в залежності від віку хворих: R^2 = 3,4 %; P = 0,041, і також залежить від віку початку захворювання (R = 0,24; R^2 = 5,96 %; P = 0,007).

Висновки. Статевий диморфізм клінічного перебігу акромегалії проявляється в молодому віці під час прояви захворювання і характеризується у чоловіків більш високою секреторною активністю GH-аденоми і більш вираженим мас-ефектом пухлини. Секреторна і проліферативна активність GH-аденоми гіпофіза залежить від віку пацієнта на момент захворювання. Для хворих молодого віку характерно швидко прогресуючий і рецидивуючий перебіг акромегалії, що обумовлено високою сумарною секреторною, проліферативною активністю GH-аденоми і високою швидкістю росту пухлини. Для літніх пацієнтів характерно «повільно прогресуючий» клінічний перебіг захворювання, що обумовлено перевагою секреторною активності GH-аденоми гіпофіза над проліферативної.

Ключові слова: акромегалія; аденома гіпофіза; рання діагностика.