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# Primary Symptoms of Inactive Pituitary Adenoma in Patients at the Time of Diagnosis

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**Annotation:** Early diagnostics of IPA is an actual problem, not only for the modern health care, including neuroendocrinology, but also is a medico-social problem. The analysis of primary symptoms of the disease in 325 patients at the time of diagnosis is carried out in this article. Proceeding from data provided in this article it is possible to note with confidence that the complex of the revealed signs can be an object of the diagnostic differentiated screening and monitoring in patients with IPA.

**Keywords:** inactive pituitary adenoma, symptoms, prevalence, incidence.

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As has been repeatedly noted, with IPA there are no typical clinical symptoms of hypersecretion of anterior pituitary hormones, such as hypercortisolism, acromegaly, thyrotoxicosis, but as clinical experience and numerous studies show, galactorrhea-amenorrhea and a decrease in libido and potency against the background of a moderate increase in the level of PRL in the blood serum, which in the presence of macroadenoma leads to overdiagnosis of prolactinomas [3,6]. An increase in the concentration of PRL in the blood in such cases is explained by the so-called “effect of the crossed pituitary stalk” [7]. It is assumed that the growing tumor compresses or damages the hypothalamus or pituitary stalk, thereby suppressing the synthesis, release or adenohipophyseal transport of dopamine, which is considered the main hypothalamic factor that inhibits PRL secretion. IPA are defined by various authors as clinically non-functioning tumors, which are characterized by the absence of hypersecretory endocrine signs and symptoms. At the same time, it is indicated that they may be accompanied by sexual disorders, hyperprolactinemia, but in the future, no source specifies the formulation of the diagnosis of IPA in the presence of hyperprolactinemia with its characteristic symptoms [1,4,7].

The aim of this study was to study the frequency of occurrence of certain symptoms and clinical manifestations of IPA at the time of diagnosis.

**Materials and methods.** Between 2020 and 2022 325 patients aged 18 to 70 years ( $44.5 \pm 3.85$  years) with IPA were identified in the Republican specialized scientific and practical Endocrinology Medical Center during the clinical examination. Verification of the diagnosis was assessed on the basis of clinical manifestations, the results of magnetic resonance imaging (MRI) and / or computed tomography (CT), ELISA - blood serum tests to determine the level of tropic and peripheral hormones. Exclusion criteria from the survey were patients with IPA with prolactinomas, somatotropinomas, gonadotropinomas, Cushing's disease, thyrotropinomas, hypogonadism and acromegaly, patients after radiation therapy and concomitant diseases of the endocrine system, including diabetes mellitus.

According to the goal of the study, patients with IPA were divided into 3 alternative groups: group 1 - 137 (42.2%) patients (men - 63 and women - 74) with pituitary microadenoma

(adenoma size up to 10 mm), group 2 group - 108 (33.2%) patients (54 men and 54 women) with pituitary macroadenoma (adenoma size up to 20 mm) and group 3 - 80 (24.6%) patients with giant pituitary adenomas (adenoma size more than 20 mm) (men-63 and women-17). According to the size of the pituitary tumor in group 1, women slightly prevailed - 54%, men - 46.0%, in group 2 the ratio of men and women was 50.0% to 50.0%, while patients in group 3 were mostly men - 78.8%, and women were in 21.2% of cases (Table 1).

The assessment of the clinical picture in patients with IPA was carried out by analyzing the main complaints at the time of establishing the disease. At the same time, we adhered to the proposed scheme-questionnaire, which includes information about the assessment of visual, sexual, neurological and general disorders. It should be noted that patients with IPA had symptoms and a clinical picture that required the participation of various specialists. In this regard, in order to clarify the diagnosis of IPA, in addition to a neuroendocrinologist, the participation of narrow specialists was required: an internist, a neuropathologist, an ophthalmologist, a urologist, a gynecologist, an oncologist, an MRI/CT specialist, a radiologist, end so on.

It should be noted that at the time of the initial visit to the doctor, patients with IPA had numerous complaints that manifested themselves in one or another combination, as well as monosymptoms were noted: sexual disorders, decreased and / or limitation of visual fields, headaches, double vision, olfactory disorders, vegetative crises, discharge of fluid and/or milk from the breasts, dizziness, infertility, end so on.

As a result of the analysis of the data obtained, it was found that in patients with IPA, individual symptoms rarely occur, they are more often combined and/or the multisymptomatic nature of the disease is detected to a greater extent - 3-5 symptoms at a time. Undoubtedly, the incidence of clinical signs of IPA disease was influenced by the size of the tumor.

The combination of 2-3 symptoms of the disease in the 1st group of patients (n=137) was detected in 62 (45.3%) patients, multisymptomaticity in 27 (19.7%) and monosymptomaticity in 48 (35.0%).

In group 2 (n=108), a combination of 2-3 symptoms was detected in 45 (41.7%) patients, multiple symptoms in 45 (41.7%) and monosymptoms in 18 (16.4%) patients.

**Table №1 Composition of patients, n=325**

	microadenomas		macroadenomas		Giant adenomas	
	abs	%	abs	%	abs	%
Total number	137	42.2%	108	33.2%	80	24.6%
Men,	63	46.0%	54	50.0%	63	78.8%
including men up to 55 years	57	41.6%	50	45.4%	62	77.5%
Women,	74	54.0%	54	50.0%	17	21.2%
including women up to 50 years	63	46.0%	49	45.8%	14	17.6%

In the 3rd group (n=80), a combination of 2-3 symptoms of the disease was detected in 21 (26.25%), multiple symptoms in 58 (72.5%) and monosymptoms in 1 (1.25%).

Both in the 2nd and 3rd groups of patients with IPA, important clinical manifestations were sexual disorders in 78.7 and 95.0%, decreased vision in 76.9 and 100.0%, headaches in 100

0% in both groups of patients. Also in these groups, an otoneurological syndrome was diagnosed, which was detected in 64.7% and 77.5% of patients, respectively, which was manifested by stem vestibular disorders caused by the influence of the process on the subcortical and/or diencephalic-stem parts of the brain, as well as a violation of the cranial cerebral nerves (CN) (mainly III, V pairs), asymmetric influence on the brain stem in the region of the posterior cranial fossa.

And in group 1, complaints of headache prevailed - in 55.5%, menstrual irregularities - in 50.1% of women under the age of 50, dizziness - in 24.1%, discharge from the breasts - in 41.2% sick. At the same time, this group did not reveal such complaints as limited visual fields, lack of vision, diplopia, burning eyes and lacrimation, olfactory disorders, liquorrhea. When analyzing the frequency of complaints of sexual disorders in patients with IPA, depending on the size of the tumor, the same trend can be traced as in previous studies - with an increase in the size of the tumor, the frequency of complaints increases. So, in patients with 1-gr. with a tumor size of up to 10 mm among women under 50 years of age, 15.9% had complaints of amenorrhea, 50.1% of menstrual disorders, and in men under 55 years of age, 26.3% had a decrease in libido or impotence; in patients with tumor size up to 20 mm, i.e. 2-gr. - 26.9% of patients complained about the development of amenorrhea, 36.1% - about menstrual irregularities, and 70.0% - among men about sexual dysfunction.

**Table №2 Symptoms of the disease in patients with IPA in the study groups in a comparative aspect**

Symptoms	1-gr. n=137		2-gr. n=108		3-gr. n=80	
	abs	%	abs	%	abs	%
Sexual disorders	57	56.2	85	78.7	76	95.0
Decreased vision	20	14.6	83	76.9	80	100.0
Headache	76	55.5	108	100.0	80	100.0
Dizziness	33	24.1	83	76.9	78	97.5
Restriction of fields of view	-	-	84	77.8	80	100.0
Double vision	17	12.4	56	51.9	80	100.0
Lacrimation	14	10.2	37	34.3	49	61.3
Visual discomfort	19	13.9	91	84.3	80	100.0
Olfactory disorders	-	-	35	32.4	47	58.8
Vegetative crises	33	24.1	54	50.0	53	66.3
Excessive hair growth (W)	17	23.0	21	38.9	15	88.2
Liquorrhea	-	-	35	32.4	43	53.8
Lactorrhea (+, ++, +++)	57	41.2	54	50.0	35	43.8
For women under 50						
A) menstrual disorders cycle	32	23.4	30	36.1	-	-
B) lack of menstruation	10	7.3	11	10.2	14	17.6
For men under 55						
sexual dysfunction	15	26.3	35	70.0	62	77.5

When studying the data on the frequency of complaints about general somatic disorders, it was found that in the 1st group with a tumor up to 10 mm, symptoms of weakness, fatigue and drowsiness occurred in 24.1% of cases, memory loss - 10.2%, in the 2nd group in 77.8 and 50.0%, respectively, in the 3rd group in 100% of cases there were symptoms and weakness and memory loss. 12.4% of patients complained of thirst in the 1st group, 51.9% in

the 2nd group, and 68.8% of the patients in the 3rd group. (Table 3)

**Table №3 Comparative data on the frequency of complaints of neurological disorders in patients with IPA, depending on the size of the tumor.**

Violations	Up to 10mm		>10mm		Giant	
	1 gr. n=137		2- gr. n=108		3- gr. n=80	
	abs	%	abs	%	abs	%
Decreased memory	14	10.2	54	50.0	80	100.0
Vegetative crises	17	12.4	48	44.4	80	100.0
Weakness, fatigue, drowsiness	33	24.1	84	77.8	80	100.0

In 1-gr. 14.6% complained of weight gain, 1.5% of patients complained of weight loss, in the 2nd group - 52.8% and 4.6%, respectively, and 3-gr. 87.5% of patients complained of weight gain. There were no complaints about weight loss in this group of patients. In patients with IPA of the 2nd and 3rd groups, there were cases of a decrease in the level of blood pressure. With a tumor size up to 20 mm, i.e. in 2-gr. this indicator was detected in 13.0% of patients, in the 3rd group in 68.8% of cases (Table 4).

Thus, the analysis of the obtained research results showed that patients with IPA of all groups have significant visual, sexual, neurological and general somatic disorders, which can be associated with the development of pituitary insufficiency of varying severity, due to excessive pressure of normal pituitary tissue or pituitary stalk. Patients with a tumor size of up to 20 mm and with giant tumors, according to most researchers [1,2,5], often complain of visual and neurological, as well as sexual and general somatic disorders, which was confirmed by our studies.

It has been established that the pressure of the optic nerve or the optic chiasm leads to a limitation of the visual fields (quadrantopia or hemianopsia, mainly bitemporal). In other cases, diplopia or ophthalmoplegia may be observed. It is assumed that the occurrence of visual disturbances are the first symptoms of IPA disease [6,7]. It should be emphasized that among the important symptoms that are not taken into account by neuroendocrinologists and therapists are frequent and severe headaches, which are due to excessive pressure on the dura mater. Intracranial hypertension with headache, nausea, vomiting occurring suddenly, usually accompanied by a rapid decrease in vision, hypotension, is a typical picture of pituitary apoplexy due to hemorrhagic tumor infarction, and in some cases the first manifestation of IPA. It can be assumed that the increase in the frequency of complaints with the progression of tumor growth, the difference in the symptoms of the disease correspond to the degree of compression or invasion of neighboring structures.

**Table №4 Comparative data on the frequency of complaints about general somatic disorders in patients with IPA depending on the size of the tumor**

Violations	Up to 10mm		>10mm		Giant	
	1 gr. n=137		2- gr. n=108		3- gr. n=80	
	abs	%	abs	%	abs	%
Weight gain	20	14.6	57	52.8	70	87.5
Weight loss	2	1.5	5	4.6	-	-
Thirst	17	12.4	56	51.9	55	68.8

Decreased blood pressure	-	-	14	13.0	55	68.8
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In this regard, as a rule, the diagnosis was made by doctors when the size of the tumor was already large, causing visual impairment, headache and / or hypopituitarism, and microadenomas - tumors up to 10 mm are rarely identified due to minor symptoms of the disease. Due to the minor clinical symptoms of the disease, endocrinological manifestations may not cause concern in patients with IPA, especially in the early stages of the disease. Violations of sexual functions by gynecologists and sexologists are regarded as cases of fertility, which in women is associated with menstrual irregularities (secondary amenorrhea, oligomenorrhea), in men with decreased libido or impotence and are less likely to seek medical help in the early stages of the disease. In connection with the growth of the tumor process, as often noted in patients with IPA with a tumor size of up to 20 mm and giant, signs of secondary hypothyroidism are detected, including symptoms such as apathy, hypothermia, dry skin, thirst, bradycardia, hypotension, etc. or secondary adrenal insufficiency - weakness, fatigue, hypotension.

Important hypothalamic manifestations that can occur in patients with IPA in combination with secondary hypothyroidism are weight gain and/or weight loss, drowsiness, autonomic crises, dizziness, lack of smell, memory loss, and apathy.

In general, the analysis of the survey showed that patients with IPA have a whole range of disorders that should direct the endocrinologist to conduct special brain examinations using X-ray, CT and MRI studies.

**Conclusions.** The clinical picture of IPA at the time of diagnosis consists mainly of neuro-ophthalmic, hypopituitary, neurological and psychopathological symptoms, which requires knowledge of the characteristics of this disease by doctors of various specialties (ophthalmologists, gynecologists, urologists, sexologists, neuropathologists, therapists, neurosurgeons and, of course, endocrinologists) for earlier (at the stage of the absence of severe complications) diagnosis.

Thus, the conducted clinical studies have shown that in patients with IPA with a tumor size of more than 10 mm and with a giant size, the disease is associated with more pronounced clinical manifestations, an aggressive course, a large number of clinical symptoms, early development of refractoriness to therapy, and an unfavorable prognosis of the disease. These patients are characterized by frequent manifestation of symptoms, such as decreased vision, diplopia, lacrimation, oligomenorrhea, galactorrhea, headaches, memory loss, vegetative vascular disorders. This is of great importance in the early diagnosis and identification of the risk of developing this disease. Based on the foregoing, it can be noted with confidence that the totality of the detection of signs can be the object of differentiated diagnostic screening and monitoring in patients with IPA.

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