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"MRI CHARACTERISTICS OF PATIENTS WITH NON-FUNCTIONAL PITUITARY MACROADENOMAS WITH SECONDARY EMPTY SELLA SYNDROME DEPENDING ON THE TREATMENT RECEIVED"

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Abstract
The purpose of the study was to study the MRI characteristics of patients with non-functional pituitary macroadenomas (NFPA) with secondary empty sella syndrome (SEES)_ depending on the treatment received
Material and research methods. A total of 35 patients with macro-NfPA and secondary SEES who applied to the outpatient clinic in 2023 were examined. Of these, 15 (42.9%) were men, 20 (57.1%) were women.
Research methods included: 1) general clinical (study of endocrine, neurological status), 2) instrumental (perimetry for all colors, fundus, visual acuity, ECG, CT/MRI of the sella turcica and adrenal glands, ultrasound of internal and genital organs and etc.), 4) biochemical and hormonal blood tests
Research results. on MRI of the pituitary gland, a double fundus was found in 8 (100%)/13(87%)/10/(83.3%) cases, asymmetry of the sellar fundus was observed in 8 (100%)/10 (66.7 %)/10(83.3%), erosion sellar fundus - in 8 (100%)/8 (53.3%)/9(75%), expansion of the third ventricle - 5 (62.5%)/5 (33.3%)/ 8(66.7%), observations in 1, 2, respectively and 3 groups. Recurrent tumor growth after TAH occurred in 5 patients in group 2 of patients.
Conclusions.1. Among patients with macroNFPA, the most pronounced changes characterizing the development of secondary empty sella syndrome were identified in group 1 – those subject to combined treatment. 2. The most pathognomonic MRI sign in secondary SEES is asymmetry and erosion of the sellar fundus
3. Four months after combined treatment, changes on MRI in group 1 of patients were still most pronounced compared to other groups.
Key words: NFPAs, MRI of the pituitary gland, secondary empty sella syndrome.

Background. Based on an assessment of data from a literature review that showed an overall prevalence of hypopituitarism in SEES of 52%, additional hormonal diagnostic tests are recommended even in asymptomatic patients. Due to paucity of data, it is not possible to make informed recommendations regarding the type and scope of potential hormonal tests. In our expert opinion, for pragmatic reasons, basic diagnostic evaluation should be performed even in asymptomatic patients. This screening should include several measurements: concentrations

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of morning cortisol, free thyroxine (fT4), estradiol in women (who do not have a regular cycle) and testosterone in men, insulin-like growth factor (IFG)-1 and prolactin. This approach is consistent with general recommendations for pituitary testing [1] and appears to offer the best value for money. If abnormalities are detected, additional measurements should be taken: thyrotropin-releasing hormone (TSH) for the thyroid-stimulating axis, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) for the gonadotropic axis. A stimulation test (eg, insulin-induced hypoglycemia test or growth hormone release test [GHRH]-L-arginine) is necessary for a detailed assessment of the somatotropic axis. A corticotropic axis stimulation test, such as an insulin-induced hypoglycemia test or an adrenocorticotropic hormone [ACTH] test, is also recommended, although strictly speaking the latter only tests adrenal function. These recommendations are supported by a recently published review article [2] regarding incidental and symptomatic PES; they have also been confirmed by further review articles [3,4]. Potential factors influencing hormone concentrations should be considered during the basic diagnostic evaluation. For example, the use of oral contraceptives may reduce IGF-1 levels below normal values for gender and age. Regarding the rational weighing of costs and benefits, it should be noted that isolated growth hormone deficiency must be confirmed with at least two stimulation tests before health insurance companies will begin to cover hormone replacement therapy in Germany at the moment.

In asymptomatic patients with an incidental finding of an empty sella turcica, secondary causes should be ruled out first. Based on available data, additional hormonal diagnostic testing is also recommended in asymptomatic patients, based on the cumulative prevalence of hypopituitarism of 52%. Basic diagnostic evaluation includes measurement of morning cortisol concentrations and concentrations of fT4, estradiol or testosterone, IGF-1, and prolactin. If abnormalities or symptoms are detected that, after further examination, may indicate hormonal imbalances, additional hormonal diagnostic tests using stimulation are recommended.

Data on PTSD as an incidental finding are too sparse to allow any evidence-based recommendations to be made regarding the potential indications for hormonal testing or the nature and extent of hormonal testing. The authors recommend baseline neuroendocrinologic testing (fasting cortisol, free thyroxine [fT4], estradiol or testosterone, insulin-like growth factor 1 [IGF-1], and prolactin). There is an unexplained discrepancy between the high prevalence of pituitary insufficiency among individuals with SEES and its low prevalence Vepidemiological studies.

The prevalence of secondary empty sella turcica, i.e., empty sella turcica for no apparent reason, is not precisely known; estimates range from 2% to 20%[5] .

The purpose of the study was to study MRI-characteristics of patients with non-functional pituitary macroadenomas with secondary empty sella syndrome depending on the treatment received

Material and research methods.A total of 35 patients with macroNFPA and secondary SEES were examined,who applied to the outpatient clinic in 2023. Of these, 15 (42.9%) were men, 20 (57.1%) were women, who were constantly monitored over time. Average age: men were 48.12 years, women - 46.15 years. The duration of the disease ranged from 2 months to 5 years. 20 healthy individuals of the corresponding gender and age formed the control group.

A total of 15 TAG (transnasal adenomectomy of the pituitary gland) were performed (candidate of medical sciences Akbutaev A.M.). Repeated operations on the pituitary gland were performed in 5 patients (33.3%) 8 patients received radiation therapy after THA (53.3%) patients.

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Depending on the treatment received, patients were divided into 3 groups: group 1 – patients treated with TAG + Cabergoline + radiation therapy – 8 patients, group 2 – patients treated with TAG + Cabergoline – 15 patients and group 3 – patients treated with Cabergoline – 12 patients.

Research methods included: 1) general clinical (study of endocrine, neurological status), 2) instrumental (perimetry for all colors, fundus, visual acuity, 3) ECG, CT/MRI of the sella turcica and adrenal glands, 4) ultrasound of the internal and genital organs, etc.), 5) hormonal blood tests (GH, IGF-1, LH, FSH, PRL, TSH, ACTH, prolactin, testosterone, estradiol, progesterone, cortisol (ICL method).

The obtained data were processed using Microsoft Excel and STATISTICA_6 computer programs. The arithmetic mean (M) was calculated,standard deviation of the arithmetic mean or error of the meanarithmetic of all n repetitions (m).The reliability of differences in levels between groups was assessed by the confidence interval and Student's test (p). Differences were considered statistically significant at $p<0.05$.

Results research hand their discussion. Table 1 shows the distribution of patients by gender and age (data from a prospective study).

Table 1. Distribution of patients by gender and age (prospective data, n = 151)

Age, years	**Number of men n = 15**	**Number of women n = 20**
30-44	4 (26.7%)	5 (25.0%)
45-59	8 (53.3%)	9 (45.0%)
60-74	3 (20.0%)	6 (30.0%)
75 and older	-	-
Total: n = 35	15 (42.9%)	20(57.1%)

Magnetic resonance imaging (MRI) has become the modality of choice for evaluating the hypothalamic-pituitary axis based on its ability to delineate and distinguish both the pituitary gland, its pathology, and surrounding structures, with great advantage over traditional computed tomography (CT) in patients requiring follow-up without the risk of radiation.

All MRI image slices were reviewed. Cavernous sinus invasion was considered in cases where the tumor volume occupied more than 2/3 of the internal carotid artery [6] or grade 3 and 4 tumors according to Knosp et al. [7] and Edal et al. [8] classifications respectively. Table 2 shows the distribution of patients according to the nature of the formation of the sellar region before treatment.

Table 2.
Distribution of patients according to the nature of growth of the formation of the sellar region before treatment into groups

Diagnosis of the disease	**1 group – TAG + Cabergoline + radiation therapy (n=8)**	**Group 2 – TAG+ Cabergoline (n=15)**	**Group 3 – Cabergoline (n=12)**

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hemorrhage into the stroma	5(62.5%)	-	-
parasellar invasion	4 (50%)	7 (46.7%)	2 (16.7%)
suprasellar growth	8 (100%)	6 (40%)	3 (25.0%)
infrasellar extension	4 (50%)	3 (20%)	-
expansion of the third ventricle	8 (100%)	5 (33.3%)	-

Note: NFPA – non-functional pituitary adenoma

The maximum mean tumor diameter determined at diagnosis was 34.7 ± 7.6 mm.As can be seen from Table 2, hemorrhage into the pituitary stroma occurred in 5 (62.5%) cases in group 1 of patients, parasellar invasion – in 4 (50%)/7 (46.7%)/3(16.7%) suprasellar growth – in 8(100%)/6 (40%)/3 (25%), infrasellar expansion -4 (50%)/3 (20%)/0, expansion of the third ventricle - 8(100%)/5 (33.3%)/0 observations in groups 1, 2 and 3, respectively.
Total4 (50%)/7 (46.7%)/3(16.7%)All tumors had signs of parasellar invasion (22% unilateral invasion, 62% bilateral invasion). Infrasellar invasion has been observed in4 (50%)/3 (20%)/0 observations.Suprasellar spread of any degree was observed with a frequency8(100%)/6 (40%)/3 (25%),cohorts. Of these, the third ventricle and/or brain parenchyma tissue (grade 4, according to Edal et al. [13]) were present in8(100%)/5 (33.3%)/0all cases (Table 2).

Table 3 givescharacteristics of MRI results of the sellar region after treatment after 4 months

Table 3.
Characteristics of MRI results of the sellar region after treatment after 4 months

Characteristics on MRI	**1 group – TAG + Cabergoline + radiation therapy (n=8)**	**Group 2 – TAG+ Cabergoline (n=15)**	**Group 3 – Cabergoline (n=12)**
double bottom	8(100.9%)	13 (86.6%)	10 (83.3%)
average level of pituitary gland volume	0.21±0.03 cm 3	0.33±0.09 cm 3	0.38±0.06 cm 3
sellar floor asymmetry	8(100.9%)	10 (66.7%)	10 (83.3%)
sellar floor erosion	8(100.9%)	8 (53.3%)	9 (75.0%)
expansion of the third ventricle	5 (62.5%)	5 (33.3%)	8 (66.7%)
regrowth of residual tumor tissue after surgery	-	5 (33.3%)	-

Note: NFPA – non-functional pituitary adenoma

As can be seen from Table 2, on MRI of the pituitary gland, a double bottom was found in 8 (100%)/13(87%)/10/(83.3%) observations, sellar floor asymmetry– y8 (100%)/10 (66.7%)/10(83.3%),sellar floor erosion– 8 (100%)/8 (53.3%)/9(75%),expansion of the third ventricle - 5 (62.5%)/5 (33.3%)/8(66.7%), observations in groups 1, 2 and 3, respectively. Recurrent tumor growth after TAH occurred in 5 patients in group 2 of patients.

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It should be noted that according to the authors, transsphenoidal resection of a pituitary adenoma decreased pituitary hormone levels immediately after surgery, returning to preoperative levels 4 months after surgery. Similar time trends were found in all patients with NFPA tumors. Similarly, "total hormone levels" decreased on the first postoperative day and then increased during the 4-month follow-up period. In patients with pituitary adenomas, PRL levels >200 ng/ml were positively correlated with the extent of pituitary adenoma resection [9]. However, in the case of the development of secondary SPTS, most often such recovery is not observed.

Both Hardy and Knosp described qualitative methods for assessing adenomas, but these methods have different clinical implications in assessing the extent of cavernous sinus invasion, suprasellar extension, and chiasmal compression. In addition, these methods are not sufficient to assess the extent of disease and volume response to various therapies [10]. The spread of pituitary adenomas and the response to downsizing treatment are unpredictable, the authors noted.

Thus, according to MRI data of the pituitary gland of the examined 3 groups of patients with NAH and secondary SEES, the most pronounced disorders were identified in 1 group of patients. 4 months after combined treatment, changes in this group of patients were still most pronounced.

Conclusions.1. Among patients with macroNFPA, the most pronounced changes characterizing the development of secondary empty sella syndrome were identified in group 1 – those subjected to combined treatment. 2. The most pathognomonic MRI sign in secondary SEES is asymmetry and erosion of the sellar floor

3. 4 months after combined treatment, changes on MRI in group 1 of patients were still most pronounced compared to other groups.

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