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Clinical, Neuroimaging and Histological Characteristics of Non-functioning Pituitary Adenoma in Patients with Growth Hormone Deficiency

Mukhlisa Yu. Shakirova[1]; Yulduz M. Urmanova, PhD, ScD[1,2*]

[1]*Tashkent Medical Pediatric Institute*
[2]*Republican Specialized Scientific-Practical Medical Center of Endocrinology named after Academician Ya. Kh. Turakulov*
Tashkent, Uzbekistan

Abstract

The aim of this study was to determine the clinical and diagnostic markers of tumor aggressiveness that are predictive of tumor recurrence in patients with non-functioning pituitary adenoma (NFPA) and growth hormone deficiency.

A total of 87 patients with NFPA and growth hormone deficiency were enrolled in the study, including 31 patients after transsphenoidal hypophysectomy (postoperative follow-up from 1 to 3 years). The mean age of patients was 32.2±2.5 years. The search for clinical and diagnostic markers of NFPA aggressiveness that are predictive of tumor recurrence after transsphenoidal hypophysectomy revealed a direct correlation with such risk factors as the young age of the patient, large tumor size, asymmetry and deformation of the pituitary gland, signs of tumor invasion into surrounding tissues, arteries, and cavernous sinus, panhypopituitarism, and the small-cell and/or dark-cell chromophobic adenomas. Preliminary data, as well as a number of studies, confirm that predictors of pituitary tumor recurrence and markers of persistent disease activity still have to be identified in order to improve the long-term management of NFPA.**(International Journal of Biomedicine. 2018;8(3):197-200.)**

Key Words: non-functioning pituitary adenoma • transsphenoidal hypophysectomy • pituitary gland • growth hormone deficiency

Abbreviations

BMI, body mass index; **ESS,** empty sella syndrome; **GHD**, Growth hormone deficiency; **IGF-1**, insulin-like growth factor 1; **NFPA**, non-functioning pituitary adenoma; **PG**, the pituitary gland; **QL**, the quality of life; **TC**, thigh circumference; **TSHE**, transsphenoidal hypophysectomy; **WC**, waist circumference.

Introduction

Non-functioning pituitary adenomas (NFPAs) account for 14%–54% of pituitary adenomas and have a prevalence of 7–41.3/100,000 population.[1,2] Benign in origin and not provoking a hormonal hypersecretory syndrome, NFPAs are clinically challenging because they present at a late stage with local mass effects or hypopituitarism with GHD and disorders in sexual and reproductive functions. At the time of initial diagnosis, visual field defects are detected in 60%–80% of NFPA patients.[3,4]

Recurrence is one of the most troublesome clinical outcomes of NFPA. A previous meta-analysis[5] found that NFPA recurs most often between one and five years after surgery, and that the rate of recurrence decreases after 10 years. Unfortunately, until recently there has been no consensus

[*]***Corresponding author**: Yulduz M. Urmanova, PhD, ScD. Republican Specialized Scientific-Practical Medical Center of Endocrinology; Tashkent, Uzbekistan. E-mail: yulduz.urmanova@mail.ru*

on the prognostic predictors of NFPA recurrence. No single convincing prognostic factor for recurrence was identified in a meta-analysis study on NFPA.[5] In most studies, clinical factors of age, gender, tumor size and tumor invasion have had no predictive value for recurrence. Recently, many other factors have been introduced that influence the proliferation of pituitary adenomas, such as angiogenesis, apoptosis, Ki-67, growth factors, oncogenes, tumor suppressor genes and hormone receptors.[6-9]

The search for diagnostically significant markers of aggressiveness of NFPA in predicting the post-operation period (tumor recurrence, the need for re-operation or radiotherapy) remains an urgent problem.

The aim of this study was to determine the clinical and diagnostic markers of tumor aggressiveness that are predictive of tumor recurrence in patients with NFPA and GHD.

Materials and Methods

We analyzed the data of 87 NFPA patients (44 women and 43 men) with GHD, including 31 patients after TSHE (postoperative follow-up from 1 to 3 years). The mean age of patients was 32.2±2.5 years.

Methods of investigation included: 1) general clinical examination, assessment of neurological status, anthropometry (height, weight, TC, WT, BMI); 2) instrumental methods of examination (visual field perimetry, colour vision, fundus oculi, visual acuity, ECG, CT/MRI of sella turcica and adrenal glands, ultrasound of reproductive organs); 3) determination of blood hormones (GH, IGF-1, LH, FSH, PRL, TTG, ACTH, testosterone, estradiol, progesterone, cortisol) in RIA using "Gamma-12" and "Strantg 300," and 4) histological examination of postoperative specimens; 5) assessment of QL by QoLAGHD questionnaire (Quality of Life Adults with growth Hormone deficiency, KIMS Study Questionnaire).

Statistical analysis was performed using statistical software package SPSS version 20.0 (SPSS Inc, Chicago, IL).

The study was approved by the Republican Specialized Scientific-Practical Medical Center of Endocrinology Ethics Committee. Written informed consent was obtained from each patient.

Results

The age-gender distribution of NFPA patients is presented in Table 1. Thirty-one NFPA patients after TSHE were divided into 3 groups depending on the histological characteristics (Table 2).

Table 1.

The age-gender distribution of NFPA patients

Age, years	Number of men	Number of women
18 – 29	10	12
30-44	12	9
45-59	13	16
60-74	7	3
≥75	2	3

Table 2.

Groups of patients depending on the histological characteristics of NFPA

Group 1		Group 2		Group 3	
n	%	n	%	n	%
24	77.5	6	19.3	1	3.2%
Total: 31					

As can be seen from Table 2, the number of patients (Group 1) with large-cell chromophobic adenoma (24/77.5%) were the most prevalent. Small-cell NFPAs were identified in 6(19.3%) patients (Group 2). We observed a giant recurrent malignant dark-cell adenoma with brain metastases in only one case (3.2%) in a teenage girl (Group 3).

Clinical manifestations of NFPA in the form of endocrine and neurologic disorders were detected in 41.5% and 32.8% of patients, respectively. Symptoms of neuro-ophthalmic disorders were detected in 25.7% of patients.

In women, NFPA was accompanied by obesity, primary and secondary hypothyroidism, secondary hypogonadism, the syndrome of persistent galactorrhea/amenorrhea (symptomatic and idiopathic forms), diabetes insipidus, and ESS. In men, NFPA was accompanied by obesity, primary and secondary hypothyroidism, secondary hypogonadism, diabetes insipidus, and gynecomastia.

According to an MRI of the brain and PG, endosellar tumors were detected in 15(48.4%) patients, endo-extrasellar tumors (mainly with suprasellar growth) - in 16(51.6%) patients. In MRI, a soft tissue structure of NFPA was diagnosed in 16(52%) patients and a cystic structure in 11(35.5%) patients. The structure of NFPA was represented by a hemorrhagic component in 4(12.9%) cases, and both cystic and hemorrhagic components were found in 2(6.4%) of them. A pituitary microadenoma (<1cm) was identified in 18(58.1%) patients, a pituitary macroadenoma (>2cm) in 12(38.7%) patients and a giant pituitary adenoma in 1(3.2%) patient.

The next step of our research was to look for the most significant aggressiveness markers that play a predictive role in patients with remission and tumor recurrence after TSHE. Further, we determined the significance of the differences between such parameters as the number of patients during the remission period and the number of relapses after TSHE, with different parameters taken into account. The results of multifactorial analysis showed that there were many such markers (Fig.1).

After analyzing the data on the frequency of remissions and NFPA recurrence, a correlation relationship between different parameters and the frequency of recurrences was selectively studied.

Further, we studied risk factors (markers of NFPA aggressiveness) for the probability of NFPA recurrence in the postoperative period. Table 3 shows the predictive power of aggressiveness markers, depending on various indicators. Thus, the developed scale of aggressiveness markers of NFPA allows identifying factors according to three degrees, in view of which it is possible to plan a set of measures for preventing tumor recurrence.

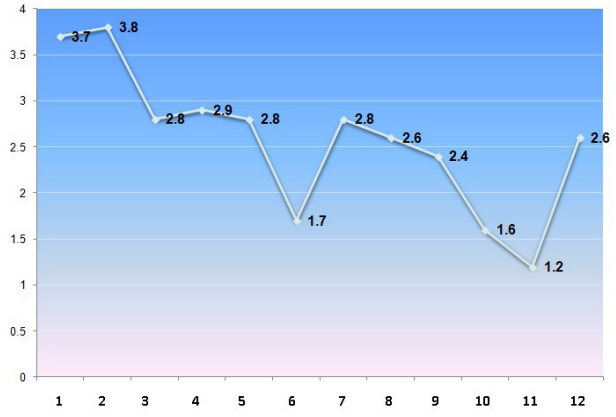

Fig. 1.

1 - small-cell NFPA; 2 - adenoma size; 3 - hypopituitarism; 4 - tumor invasion; 5- tumor hemorrhage; 6 - rapidly progressive disease course; 7 - age; 8 - severity of disease; 9 - disease duration; 10 - asymmetry of PG; 11 - skull trauma; 12 - GHD

Table 3.

Probability of NFPA recurrence in the postoperative period

Predictive power	RR	Rusk factors
Very high	>3.0	Young age of the patient; large tumor size, asymmetry and deformation of PG; signs of tumor invasion into surrounding tissues, arteries, and cavernous sinus; panhypopituitarism; the small-cell and/or dark-cell chromophobic adenomas.
High	2.0-3.0	Disease duration; age; rapidly progressive disease course; high blood cholesterol; MRI tumor hemorrhage.
Moderate	1.5-2.0	Skull trauma; GHD; adenoma size, high IGF-1 levels.

Approximately half of the patients with NFPA have a residual tumor after surgery.[10-14] To date, there is no reliable marker to predict tumor regrowth after surgery. Several large series of studies evaluating postoperative tumor recurrence and regrowth have shown that the presence of residual tumors and/or follow-up duration appear to be the two major determinants of recurrence and regrowth.[13-16] Determining prognostic markers of NFPA aggressiveness has a large clinical value. Comparative analysis of the results obtained revealed a direct correlation with such risk factors as the young age of the patient, large tumor size, asymmetry and deformation of PG, signs of tumor invasion into surrounding tissues, arteries, and cavernous sinus, panhypopituitarism, and the small-cell and/or dark-cell chromophobic adenomas. It should be emphasized that stereotactic tumor biopsy is effective in predicting NFPA recurrence in the postoperative period. Our preliminary data, as well as a number of studies, confirm that predictors of pituitary tumor recurrence and markers of persistent disease activity still have to be identified in order to improve the long-term management of NFPA.

Competing interests

The authors declare that they have no competing interests.

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