MOLECULAR GENETIC BASIS OF FAMILY PITUITARY ADENOMA

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INTRODUCTION

Motivation and goals Most works on the analysis of molecular genetic defects in pituitary adenomas (PA) are devoted to the study of 1-2 candidate genes. In this regard, it is promising to introduce high-throughput parallel sequencing technologies, which can simplify the diagnosis of monogenic diseases associated with several candidate genes.

Relevance.

The first morphological description of the structure of the pituitary gland, which was made by P. I. Peremezhko, dates back to 1867. He showed that the pituitary gland has a cortical layer (anterior lobe), a cavity of the medullary appendage and a white medullary layer (posterior lobe). In subsequent years, the function regulating the activity of peripheral endocrine glands, melanostimulating hormone, lipotropin, vasopressin, and oxytocin was studied [1]. The functions of the pituitary gland were studied by P. Marie; in 1886, he published his observations of patients with acromegaly and a review of five previous publications. Three years later, V. Horsley performed the first transcranial operation on the pituitary gland, but described it only in 1906, since the successful operation was overshadowed by its late complications. The first transsphenoidal approach was used in 1907 by H. Schloffer, guided in topical diagnosis by a lateral radiograph of the skull base. Unfortunately, he was not able to assess the size of the tumor, and the operated patient died 2 months later from acute intracranial hypertension. Despite this sad event, transsphenoidal pituitary surgery developed, and significant contributions to its development were made by O. Chiari., AB Kanavel, AE Halstead, H. Cushing, N. Dott. Since 1919, pneumoencephalography began to be used to more clearly visualize pituitary adenomas. In the 1950s Interest in transsphenoidal surgery has increased. With the advent of cortisone and antibiotics, mortality and long-

term survival rates have improved. Intraoperative imaging in the form of real-time fluoroscopy has been revolutionary for pituitary surgery. Lumbar puncture air or contrast solution was injected directly into the pituitary gland to monitor tumor removal. Surgical treatment of pituitary adenomas developed in various directions, and in 1965 J. Hardy first used a microscope to perform a total adenomectomy of the pituitary gland. G. Guiot in 1963 used endoscopy to optimize control over the progress of the operation during sublabial transsphenoidal surgery. HB Griffith and R. Veerapen in 1987 used the endonasal transsphenoidal approach and thereby determined the further development of endoscopic pituitary surgery. Fluoroscopy and radiography were the main methods of imaging pituitary adenomas until the 1970s, when computed tomography (CT) and magnetic resonance imaging (MRI) became available, allowing visualization of the pituitary gland and more precise surgical planning. Subsequently, methods of intraoperative studies CT, MRI and ultrasonography appeared. After gliomas and meningiomas, pituitary adenomas occupy the third place in incidence among all intracranial tumors [16]. Hormonally active pituitary adenomas are detected in 20 cases per 1 million population, and inactive ones - in 70–90 cases per 1 million population. According to Belarusian authors, as a result of analysis of biopsy material, the mass fraction of pituitary adenomas among all intracranial tumors in 1991–1995. was 6%, and in 2003–2005. decreased to 4.37%. At the same time, pituitary adenoma was more common in women 20–30 and 50–60 years old [15].

MATERIALS AND METHODS

26 families were examined: 58 patients, of whom 36 (62.1%) were men and 22 (37.9%) women with family hypertension of various types of secretion; there were 17 families with a homogeneous type (with somatotropinomas 13, prolactinomas 2, corticotropinomas 1, inactive hypertension 1), with a heterogeneous type - 9, of which 7 families with somatotropinomas/inactive hypertension, 2 families with prolactinomas/inactive hypertension. The number of family members with hypertension ranged from 2 to 7. Representatives of families from the group of isolated hypertension, to exclude MEN syndromes, underwent laboratory and instrumental examinations: determination of PTH, ultrasound of the thyroid and parathyroid glands, MSCT/MRI of the abdominal cavity and retroperitoneal space. Using the MagNA Pure LC DNA Isolation Kit I, leukocyte DNA was isolated for these patients, and a gene panel was created using the Ion AmpliSeqTM Designer program (MEN1, CDKN1B, PRKAR1A, GNAS, AIP, SDHA, SDHB, SDHC, SDHD, PRKCA, CDKN2C, CDKN2A, POU1F1, PTTG2), high-throughput parallel sequencing was carried out on an Ion TorrentTM PGMTM sequencer (Thermo Fisher Scientific - Life Technologies, USA).

RESULTS

somatotropinomas (n=39) became the predominant type of AG secretion, followed by inactive pituitary adenomas (n=11), prolactinomas (n=6), and corticotropinomas (n=2) were rare. Somatotropinomas were more often detected in men than in women (27M:12F), as were inactive hypertension (7M:4F). The median age of patients was 43.4 years [19-81]. The average height for men is 186 cm, for women – 170 cm. The maximum level of growth hormone at the onset of the disease was 513 ng/ml, and IGF-1 was 1517 ng/ml. MRI of the brain more often visualized pituitary macroadenomas; tumor sizes ranged from 3 to 32 mm. In most patients, adenomas extended in more than two directions. Neoplasms with suprasellar growth and limitation of visual fields or other direction of extrasellar growth were identified in a larger number of patients. Achievement of the target level of GH (<2.5 ng/ml) and normal level of IGF-1 during therapy was detected only in 13 patients (33.3%). Of the 58 patients, 20 family representatives underwent genetic research using the above gene panel. According to the results of a study in 2 families, in 4 patients with somatotropinomas, AIP p.R271W and p.A411GfsX47 mutations were identified, in 1 patient polymorphisms with unproven pathological significance were identified in the SDHA gene p.V589V, also in 1 patient with the McCune-Albright syndrome phenotype A heterozygous substitution p.S163P was identified in the SDHB gene.

CONCLUSIONS

male predominance was revealed among patients with familial pituitary adenomas, which is the opposite of the situation in sporadic forms of the disease. Genetic changes were identified in 20% of the families examined.

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