GENETIC DIAGNOSTIC METHODS OF PROLIFERATIVE FORMS OF BENIGN BREAST DYSPLASIA

Ivan Lukavenko
Candidate of Medical Science
Assistance Department of Surgery, Traumatology, Orthopedics and Phthisiology
Sumy State University, Ukraine

Diagnosis of proliferative forms of benign breast dysplasia (BBD) is a very important problem. The relationship between the proliferation indicators of breast elements and the level of expression of steroid hormone receptors in particular estrogen in precancerous pathology has been insufficiently studied.

Diagnostic studies of the breast today are focused on the detection of focal neoplasms. The frequency of errors in cytological diagnosis in patients with benign breast tumors reaches 7-20%. Therefore, the diagnosis of precancerous changes in the breast in a significant percentage of cases is impossible.

Recently has been done to study the influence of genetic factors, namely simple single nucleotide polymorphisms, on the human phenotype. There is information about the influence of single polymorphisms of the estrogen alpha gene [1].

Due to the growing incidence of proliferative forms of mastopathy in recent decades and the young age of people suffering from these processes, it remains important to find mechanisms for early diagnosis and the latest criteria for assessing precancerous diseases. However, currently adopted methods for assessing clinical and instrumental indicators and morphological changes are not informative enough. Because they are mostly invasive, this limits their use in general, especially during pregnancy and lactation. In this regard, the search for molecular genetic predictors of precancerous diseases is becoming increasingly important, which determines the relevance of this problem. It can be concluded that the tasks of diagnosing BBD, which are high risk factors for cancer, remain relevant and require further scientific research.

The role of mutations in the BRCA1 and BRCA2 genes in the development of breast cancer has been proven. In the case of the BRCA1 mutation, it is estimated as an 80% probability of developing breast cancer when reaching the age of 70 years. However, mutations in the BRCA1 gene are relatively uncommon in sporadic forms of breast cancer. To date, more than 80 risk factors for breast cancer (BC) have been identified, which can be divided into five classes.

1. Sexual, age, constitutional: female, age over 60 years, tall.
2. Genetic: blood relatives who had breast cancer; family breast cancer; carriers of mutant genes BRCA1 and BRCA2; mutations of other genes - p53, ATM, NBS1, LKB1, ER; genetic syndromes; primary-multiple tumors.

3. Reproductive: early menarche (up to 12 years), late menopause (after 54 years), no pregnancies, late first pregnancy (after 30 years), no lactation, abortion.

4. Hormonal and metabolic disorders: hyperestrogenism, hypothyroidism, pituitary hormone metabolism disorders, menstrual disorders, infertility, gynecological diseases, obesity, diabetes, liver disease, hormone replacement therapy, use of combined oral contraceptives for more than 10 years.

5. Environmental factors: living in economically developed countries, high socio-economic status, exposure to ionizing radiation and chemical carcinogens, abuse of alcohol, fats, etc.

The development of methods for the BBD diagnosis should primarily take into account not only the morphological features of the tissue, but also the presence of estrogen receptors. Modern tactics of treatment of patients with dyshormonal hyperplasia should primarily take into account not only the histological BBD features, but also to analyze the stages of proliferation and the prospects of malignancy, taking into account the EsRα expression.

Databases of patients and morphological drugs were formed according to the following scheme: passport part (surname, sample number, age, sex, nationality, education, place of residence); complaints (pain, tightness, secretions, mastodynia, duration of the disease); genotype by Pvull polymorphism of EsRα gene (C/C, C/T, T/T); anthropometric indicators (weight, height, eye color, foot size); anamnestic data (burdened family history of breast disease, breast injury, previous surgery, hormone intake, abortion, menstrual duration, childbirth and lactation, age and onset of menarche); stressors and bad habits; laboratory indicators; comorbidities; characteristics of neoplasms.

The peculiarities of the anamnesis, stages of diagnosis, clinical picture of proliferative breast dysplasia, consequences of surgical treatment, morphogenesis of neoplasms and genetic features of patients are thoroughly studied. In accordance with the goals and objectives of the first stage, the analysis of somatic and reproductive health of women who participated in the study, carefully studied the family history of diseases of the reproductive system and breast in particular.

All patients were treated surgically. The criteria for selecting patients for the study were traits that are considered an indication for genetic testing for breast cancer.

Using statistical analysis, we studied the relationship of features clinical course of BBD with the main risk factors for the disease. In parallel, the effect of the level of EsRα expression in breast tissue and the allelic distribution of the Pvull polymorphism of the EsRα gene was studied. Given that anthropometric indicators are largely correlated with the development of various pathological conditions, in our study we studied their impact on BBD.

We showed that body weight in patients with BBD proliferative forms is significantly different (F = 8.050; P = 0.001), which depends on the genotype of the Pvull polymorphism of the EsRα gene. Thus, in women with genotype T/T body weight was equal to (66.40 ± 2.97) kg, with genotype T/C - (55.94 ± 1.06) kg, with genotype C/C - (58.89 ± 2.42) kg.
According to Duncan's criterion, it was also proved that in patients homozygous for the main allele (T/T) body weight is significantly higher than in heterozygous carriers with T/C genotypes and in patients with a minor allele (C/C).

It was found that in patients with proliferative forms of BBD with different genotype by PvuII-polymorphism BMI and foot size revealed a significant difference (F = 5,020; P = 0.009 and F = 4,756; P = 0.011, respectively). Using Duncan's criterion, we investigated that the main allele (T/T) homozygotes had significantly higher BMI and foot size than the minor allele (C/C) and heterozygous carriers with T/C genotypes.

In addition to mass-growth parameters, the connections between the genetic distribution of the PvuII polymorphism of the EsRα gene with the color of the iris and nicotine dependence were analyzed. Differences in the values of certain indicators and their dependence on variants of genetic polymorphism were not found ($\chi^2 = 2.235; P = 0.693$ and $\chi^2 = 0.365; P = 0.833$, respectively).

As follows it was found that among the specific symptoms associated with the pathological allele PvuII of the EsRα gene- the duration of mensis and mastodynia. This may be due to progestogen deficiency and estradiol receptor sensitivity. The results of calculations show that BBD begin to form on the background of the preserved menstrual cycle and reproductive function. The crucial role in the development of proliferative foci in BBD is played not by the level of hormones in plasma, but by the state of local estradiol receptors in breast tissue. Probably, it is the activity of the receptor that determines the development of the pathological process.

It is shown that hormone imbalance promotes morphofunctional adjustment. In some women, this process does not go beyond the physiological norm, in others - in conditions of activation of the receptor apparatus of the breast, pathological conditions are formed. Determining the specifics of the histological structure of the tissue, the features of the receptor apparatus of the cell and genetic predictors can be of primary importance in understanding the causes and mechanisms of proliferation in BBD.

References: