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Genetic and Clinic-Pathogenetic Peculiarities of Prediction of Development and the Effects of Obesity at Young Persons.

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ABSTRACT

The article presents the results of a study of taste sensitivity to phenylthiourea in patients with overweight and obesity. The association of the status of taste sensitivity to FTC with features of the clinical course of the disease and the degree of obesity is established. The analysis of the study of anthropometric indices in the study groups is given. The features of the change in the main parameters of the lipid spectrum are shown depending on the change in the sensitivity status to the FTC. The analysis of the parameters of carbohydrate metabolism and indices of the activity of the cytolytic syndrome as a function of sensitivity to FTC was carried out.

Keywords: obesity, overweight, phenylthiocarbamide, arterial hypertension, hyperlipidemia.

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RELEVANCE

Obesity is a common multifactorial disease. According to WHO, there are more than 1.9 billion people in the world who are overweight. Of this number, more than 600 million people are obese. In most developed countries in Europe, between 15 and 25% of the adult population is obese. In recent years, the world has seen an increase in the frequency of obesity in young people, children and adolescents: 25% of adolescents in the world are overweight, and 15% are obese. Russia is in third place in the world in terms of prevalence of obesity and excess body weight: more than 30% of the working-age population suffers from excessive body weight and fat.

The social importance of the problem of obesity is determined by the threat of disability of young patients and a decrease in overall life expectancy due to the frequent development of severe co-morbidities. These include: type 2 diabetes, arterial hypertension, dyslipidemia, atherosclerosis and related diseases, reproductive dysfunction.

It has been established that body weight and propensity to obesity are caused not only by environmental influence (level of physical activity, eating habits, etc.), but also by genetic factors that influence the variation of BMI in the range of 65-80%. To date, more than 600 genes, markers and chromosome regions have been identified that are relevant to the development of obesity. There are mutations of some genes, which cause an increase in BMI and the development of severe forms of monogenic obesity. Dozens of polymorphisms (variable regions) of genes associated with predisposition to obesity are known.

Studies among relatives and twins showed that genetic factors cause the development of obesity in 40-70% of cases. Low birth weight predetermines the development of obesity in the older age group. Inadequate intrauterine development, which may be the result of either a maternal nutrition disorder or placental pathology, presumably programs "economical phenotype" ("economical epigenotype") in order to maximize the offspring's adaptation to survival in conditions of a shortage of energy supply. These processes contribute to the development of obesity and metabolic syndrome with normal and, especially, excessive postnatal nutrition.

With the understanding that obesity is accompanied by a significant number of various complications, there is an increasing interest in the causes of obesity. In this connection, active search for biologically active substances (most often hormones) and genes coding at different stages of their synthesis is conducted. However, it is not possible to find any one substance or gene that would determine the development of obesity. Therefore, at the present time it is necessary to search for markers of genetic predisposition to factors that determine the development of obesity and its complications, primarily cardiovascular. In this case, the method of screening a population to identify people at high risk should be simple and low-cost. The study of the status of taste sensitivity to phenylthiourea (FTC) does not require large material costs, is very fast in execution, and, importantly, at the outpatient stage, non-invasive.

The inherited ability of people to feel or not feel the bitterness of phenylthiocarbamide, first attracted attention more than half a century ago, but it is the subject of numerous population genetic studies conducted today.

It has been established that the ability to taste the taste of this compound is inherited as an autosomal dominant trait. At the end of the 20th century, genes encoding the bitter taste receptors in humans were discovered, they were designated as T2R or Tas2R [E. Adler, 2000]. The gene of taste sensitivity to FTC is located on the 7 chromosome - 7q34. Alleles of the T2R gene encode, in most populations, two varieties of G-protein, which forms taste sensitivity to PTC. These two proteins differ among themselves by amino acids in three positions of the protein chain. Protein testers have proline, alanine and valine in positions 49, 262 and 269, respectively, so this protein is designated as PAV. The non-testosterone protein has other amino acids (alanine, valine, isoleucine, respectively) in these positions and is referred to as AVI. The alleles encoding these proteins are called PAV and AVI [D. Drayna, 2003]. They determine the bimodal distribution of sensitivity thresholds to the FTC and the classical model of recessive inheritance.

The population of people with the ability to sense bitter taste can be divided into 3 categories: "insensitive" having in the genotype two recessive alleles, with an average taste level of bitterness, represented by a heterozygous condition and "hypersensitive" individuals with a set of two dominant alleles.

Thus, the ability to sense the taste of FTC in individual divorces is of great clinical interest. One of the effective approaches for revealing the hereditary nature of multifactorial diseases is the determination of associations of these types of pathology with genetic markers. Accumulation of these markers for a particular disease with a greater frequency than in the general population may indicate the importance of genetic mechanisms in the genesis of the disease and help in their prediction and prevention.

Establishment of the relationship of the status of taste sensitivity to FTC with a hereditary predisposition to the development of obesity and the peculiarities of its clinical picture may allow organizing in the primary health care unit screening activities and determine the contingent for primary and secondary prevention programs for the development of obesity and diseases associated with it and, therefore, Clinical course and the possibility of developing serious complications.

MATERIALS AND METHODS.

The material for the study was the results of a survey of 320 patients aged 19 to 59 years who had a body mass index (BMI) of more than 25 kg / m2, received for examination and treatment in the Higher Voluntary Hospital № 4. This study is a retrospective, case-control study in which the degree of taste sensitivity to phenylthiocarbamide was determined in patients with overweight and obesity in 2 groups, taking into account individual taste sensitivity and the presence of concomitant diseases.

A set of clinical, biochemical and instrumental methods of investigation was used to solve the tasks set in the work. All subjects underwent anthropometry (measurements of height and weight and calculated BMI = weight (kg) / height (m2), RT, OT / OB, the percentage of adipose tissue was determined from bioimpedance measurements). In each group, the prevalence of this or that cardiovascular risk factor was calculated in absolute and in percentages. Risk factors such as sex and age, abdominal fat deposition, hypercholesterolemia, atherosclerosis of various vascular pools, nephropathy, and diabetes mellitus were studied. All patients under study had different degrees of increase in blood pressure, which was necessarily taken into account in both groups. In all patients, the level of triglycerides, total cholesterol, was evaluated and, as necessary, its fractions (high and low density lipoproteins) were evaluated. In the same way, all patients had an analysis of the incidence of concomitant symptoms (dyspnea, edema, palpitation). The analysis of asymptomatic lesion of target organs (ankle-brachial index (LAD), pulse wave velocity (PRV), left ventricular myocardial mass index (LVMI) was also analyzed in detail. A separate analysis of anthropometric parameters (BMI, waist circumference (OT), hip circumference (OB), and ratio of these indicators OT / OB) in the groups "non-testers" and "testers".

The single nucleotide polymorphism rs9939609 of the FTO gene was performed by real-time polymerase chain reaction (PCR) using allele-specific primers (Applied Biosystems) using an Applied Biosystems 7500 Real Time PCR System.

Data received in the work was processed using the software package Statistica. Data are presented as "mean ± standard deviation". To assess differences in quantitative characteristics between groups (with their distribution close to normal), one-way ANOVA variance analysis was used. Differences were assessed as significant at $p < 0.05$. In cases of a large number of independent parallel comparisons (multiple comparisons), the threshold was reduced to 0.005.

METHODS OF CLINICAL RESEARCH

As a basis for determining the sensitivity to phenylthiourea (FTC), a method was used to determine the sensitivity to phenylthiourea, developed in 1949 by H. Harris and H. Kalmus. In 100 ml of distilled water, a 260 mg FTC sample was dissolved. The initial solution (dilution 0) is obtained, each subsequent dilution was reduced by half. Thus, a series of 14 dilutions of PTC in a progression of 2.6 g per 1 liter of distilled water was used, with the presentation of the test subject in order from the lowest value (0.08 mg / l) until a clear sense of bitterness. The subject was asked to place a strip of filter paper on the root of the tongue, previously

moistened in a solution of PTC of known concentration. Thus, the individual ability or inability to sense the bitter taste of phenylthiourea for each patient was determined.

Each trial began with the use of a solution with the lowest concentration of the preparation (dilution 14) of phenylthiourea. In the case when the examinees confirmed the sensation of bitter taste, they were asked to make one more test (to increase their concentration) to test their sensations. When confirming the positive result of sensitivity, the previous dilution number was recorded. According to the results of the study, all subjects were divided into 2 groups: "testers", i.e. sensing the bitter taste of FTC in the dilutions from 5 to 14 and "non-testers" - absolutely not sensing the taste of FTC or sensing it in the dilutions from 0 to 4.

RESULTS AND THEIR DISCUSSION

The results of a survey of 120 patients with a body mass index of more than 25 kg / m2 showed that among the examined patients "non-testers" were 73 people (60.8%), including 48 men (62.3% of all men surveyed) and 25 women (58.1% of all women surveyed). "Testers", i.e. 47 persons (39.2%) were found to be persons who felt the taste of the FTC in the dilutions from 5 to 14, among them 18 men (37.7%) and 29 women (41.9%). Thus, gender differences in the study groups were found ($\chi 2$ (1) = 0.307, p = 0.580).The analysis of the average threshold values of sensitivity to FTC with regard to gender is presented in table. 1.

Table 1: Average thresholds of sensitivity to the FTC depending on gender

Gender	Mean sensitivity to PTC	p *
Men (n = 177)	3.80 ± 0.44	0.760
Women (n = 143)	4.17 ± 0.39	
Total sample (n = 320)	3.99 ± 0.42	

* - according to Mann-Whitney U-criterion

From the data of table 1 it can be seen that with an average sensitivity level in the sample corresponding to the threshold value of "non-testers", there are reliable gender differences. When analyzing the ratio of "testers" and "non-testers" in groups of patients, depending on the degree of hypertension, it was found that in the group of patients with AH of 1-2 degrees of "non-testers" was 2 times more than "testers". And in the group of patients with AH of 3 degree the number of "testers" and "non-testers" was approximately the same.

In the study of the hereditary history 51 cases (69.9% of the total number of patients in the group) were identified for the presence of cardiovascular diseases in the immediate family in the group of patients with non-testers. In the group of patients with AH "testers", 28 patients (59.6% of the total number of patients in the group) with a hereditary anamnesis were identified.

The study of concomitant clinical symptoms showed that dyspnea was detected in 38 (31.7%) of the patients examined. The incidence of this symptom was higher in the group of non-testers: the proportion of such patients in the group was 31.5% (23 patients) versus 21.3% (10 patients) in the group of patients with AH testers ($\chi 2$ (1) = 4.988, p = 0.026, ϕ = 0.177, p = 0.002). Edema was observed in one third of the examined (41 people). In the group of non-testers, the proportion of patients with edema was 41.1% (30 people), and in the AH group, "testers" - 23.4% (11 people) ($\chi 2$ (1) = 9.162, p = 0.002; Φ = 0.239, p = 0.002). Complaints against heart palpitations were presented at the time of the study by 43.3% of patients (52 patients). In the first group, the incidence rate of this symptom is 50.7% (37 people), and in the second group - 27.7% (13 patients) ($\chi 2$ (1) = 5.524, p = 0.019, ϕ = 0.186, p = 0.019).

The mean value of the LIP was 0.868 ± 0.020 in the group of patients with non-testers, and in the second group of testers, the average LPI was 0.831 ± 0.041. LPI less than 0.9 was detected in 36 patients (30%), of which 28 patients (77.8%) were included in the non-test group. The average value of the SWR in the sample was 10.24 ± 0.2 m / s. In the group of patients with non-testers, this indicator was 11.09 ± 0.12 m / s, and in the AG testers group - 9.38 ± 0.28 m / s. More than 10 m / s were detected in 102 patients (85%), of whom 66 (64.7%) were non-testers. The mean LVMI was found to be 109.44 ± 1.23 g / m2. In the group of patients with non-testers, this indicator was equal to 110.74 ± 1.21 g / m2, and in the AG test group, 108.13 ± 1.24 g / m^2.

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Among the parameters of lipid metabolism in the patients examined, OXC, LDL, HDL, TG were determined and the coefficient of atherogenicity was calculated. The most atherogenic lipid profile is observed in the group of absolute non-testers, somewhat less in the group of insensitive and hypersensitive, and the lowest in patients with moderate sensitivity to FTC. When comparing the average values of lipid metabolism in groups of "non-testers" and "testers", a significantly higher level of OXC, LDL, and TG was found in the group of "non-testers".

Further, a detailed analysis of taste sensitivity to the FTC was carried out, taking into account the anthropometric parameters of the subjects. For this purpose, we estimated the body mass index, waist circumference, hip circumference and the ratio of these indices.In table. 2 presents the results of the analysis of anthropometric indicators in the study groups.

Table 2: Comparative analysis of anthropometric parameters in patients with AH depending on the status of sensitivity to FTC

The indicator	"Non-testers" (n = 173)	"Testers" (n = 147)	p *
BMI, kg / m2	32.1 ± 0.37	29.18 ± 0.40	0.006
RT, cm	96.21 ± 1.39	87.81 ± 1.23	0.004
OB, cm	89.64 ± 1.12	84.75 ± 0.82	0.005
OT/OB	1,073 ± 1,241	1,036 ± 1,005	0.007

* - the significance level of p is determined by the Mann-Whitney U criterion for the RT / OB index; Student's t-test for BMI, OT, OB

Prisravneniisrednikhznacheniyantropometricheskikhparametrov v gruppakh «non-testerov» i «testerov» bylovyyavleno, v gruppe «non-testery» posravneniyu s gruppoy «testery» dostovernoboleyevysokoyesredneyeznacheniye IMT, OT, OB i OT/OB.Gruppa «non-testery» vklyuchala 42% (31 chelovek) bol'nykh s izbytochnoymassoytelapri IMT=25,1-29,9 kg/m2; 27% issleduyemykh (20 chelovek) imeli 1 stepen' ozhireniya (IMT=30,1-34,9 kg/m2); 2 stepen' ozhireniya (IMT=35,1-39,9 kg/m2) imeli 20% patsiyentov (14 chelovek); 11% issleduyemykh (8 chelovek) v dannoygruppeimelimorbidnoyeozhireniye (IMT >40 kg/m2). Absolyutnoyebol'shinstvopatsiyentovsostavlyalimuzhchiny (65,8%).

Gruppa «testery» vklyuchala 22% (10 chelovek) bol'nykh s izbytochnoymassoytelapri IMT=25,1-29,9 kg/m2; 34% issleduyemykh (16 chelovek) imeli 1 stepen' ozhireniya (IMT=30,1-34,9 kg/m2); 2 stepen' ozhireniya (IMT=35,1-39,9 kg/m2) imeli 25% patsiyentov (11 chelovek); 22% issleduyemykh (10 chelovek) v dannoygruppeimeliozhireniye 3 stepeni (IMT >40 kg/m2). V etoygruppebol'shinstvopatsiyentovtakzhesostavlyalimuzhchiny (61,7%). V gruppe «testery» primernoodinakovoyekolichestvolitsvstrechalos' sredipatsiyentov s izbytochnoymassoytela, ozhireniyem 2 i 3 stepeni i nemnogobol'shesredilits i 1 stepen'yuozhireniya.

When comparing the average values of anthropometric parameters in the groups of "non-testers" and "testers", a significantly higher average value of BMI, OT, OB, and OT / OB was found in the group of "non-testers" compared to the "testers" group.The group "non-testers" included 42% (31 people) of patients with excessive body weight with a BMI = 25.1-29.9 kg / m2; 27% of the studied (20 people) had 1 degreeObesity (BMI = 30.1-34.9 kg / m2); 2 degree of obesity (BMI = 35.1-39.9 kg / m2) had 20% of patients (14 people); 11% of the studied (8 people) in this group had morbid obesity (BMI> 40 kg / m2). The absolute majority of patients were men (65.8%).

The "testers" group included 22% (10 people) of patients with excess body weight with a BMI = 25.1-29.9 kg / m2; 34% of the subjects (16 people) had 1 degree of obesity (BMI = 30.1-34.9 kg / m2); 2 degrees of obesity (BMI = 35.1-39.9 kg / m2) had 25% of patients (11 people); 22% of the studied (10 people) in this group had obesity of grade 3 (BMI> 40 kg / m2). In this group, the majority of patients were also men (61.7%). In the "testers" group, approximately the same number of individuals were found among patients with overweight, obesity 2 and 3 degrees, and slightly more among individuals and 1 degree of obesity.

Thus, in the "non-testers" group, significant gender differences were found, since men were almost 2 times more likely than in the "testers" group, while the average level of sensitivity to FTC in the first group was significantly lower. Most often among "non-testers" there were people with 1 and 2 degrees of arterial hypertension, which can allow the earliest diagnosis of hypertension taking into account the definition of taste

sensitivity to FTC. An aggravated history of cardiovascular diseases, as well as such accompanying symptoms as dyspnea, edema and heart palpitations in the group "non-testers" met on average 15% more often than in the group "testers". Asymptomatic lesion of target organs was most often detected in the group "non-testers". The proportion of patients from this group was more than 70% with a decrease in LIP, more than 60% in patients with an increase in PAD and LVMI. In the study of lipid metabolism (OX, LDL, HDL, TG) and anthropometric parameters (RT, OB, OT / OB), the increases in baseline values in both groups were revealed, but they were maximal in the group insensitive to FTC. The greatest number of "non-testers" was seen among persons with overweight, almost half as many among individuals and 1 and 2 as obesity, and the lowest among those with morbid obesity.

With regard to the effect on the risk of developing obesity, the most studied is polymorphism rs9939609 T / A of the FTO gene. When analyzing the frequency distribution of genotypes and alleles of a given polymorphism, statistically significant results were revealed in our sample. Thus, the frequency of the allele A in the group of subjects with overweight was statistically significantly higher than among those with normal body weight (50% vs 31.9%, $p < 0.05$). The distribution of genotypes in the group of children with overweight (TT - 25.3%, TA - 49.4%, AA - 25.3%) differs significantly from the distribution in the group with the average PR (TT - 44.7%, TA - 46.8%, AA - 8.5%, $p < 0.05$). Carriers of at least one risk allele (A) have almost 2 times higher chances of developing excess body weight (OR = 1.88, CI = 1.012-3.493), and carriers of the homozygous genotype of risk AA have a 2.3 times higher chance of developing excessive Body weight (OR = 2.27, CI = 1.083-4.768). Thus, we identified the association of the rs9939609A allele of the FTO gene with overweight in the examined group of individuals.

However, despite the lack of statistically significant data in the analysis of the distribution of frequencies of genotypes and alleles for most of the studied genes, in many cases, the hypothesis of a direct connection with the risk allele for obesity body weight was confirmed at the level of the trend (based on a comparison of occurrence frequency of risk alleles between Obesity confirmed at the level of the trend (based on a comparison of occurrence frequency of risk alleles between samples with different performance RF). Using statistical analysis we were able to sformirova s group of genes for polygenic analysis.

It was found that the number of risk alleles rs9939609 A of the FTO gene in the total sample was associated with BMI ($r = 0.2193$, $p < 0.01$, $n = 95$), FTC ($r = 0.2055$, $p < 0.05$, $N = 89$), the level of HDL ($r = -0.3318$, $p < 0.01$, $n = 74$), glucose ($r = 0.1839$, $p < 0.05$, $n = 63$), the coefficient of atherogenicity ($r = 0.3394$, $p < 0.01$, $n = 71$).

In addition, it was shown that the level of HDL is significantly higher in the carriers of the normal homozygous genotype rs9939609 T / T for the FTO gene than in the schoolchildren who have at least one risk allele (2.01 ± 0.57 mmol / l, $n = 27$, And 1.63 ± 0.59 mmol / L, $n = 47$, respectively, $p < 0.01$), and the glucose level is lower (4.6 ± 0.43 mmol / L, $n = 53$, and 4.8 ± 0.5 mmol / l, $n = 110$, $p < 0.01$).

CONCLUSION

Obesity is a multifactorial disease, and in the number of pathogenetic mechanisms of its occurrence and development include not only metabolic status disorders, but also malnutrition, human age, features of its somatic constitution and nervous system, bad habits (especially smoking) , Etc. Many diseases also contribute to the development of this pathological condition (diabetes, hypothyroidism). Within the framework of one work, it is impossible to consider all these factors.

However, consideration of the informativeness of individual risk factors from among those analyzed in different age groups is of considerable interest. The obtained results allowed to determine the quantitative contribution of different indicators to the formation of an integral measure of the risk of obesity. Unfortunately, this value is not stable and changes significantly with age. The role of the body mass index was most significant in the middle age group. The contribution of total cholesterol, insignificant at a young age, becomes extremely high in people older than 25-30 years. And only the definition of taste sensitivity to the FTC remains a fairly strong determinative factor throughout life.

In this study, we also confirmed the relationship between the AA genotype of the FTO gene and the body weight and the level of FTC in the group of patients we surveyed. Most likely, this is due to the fact that

FTO is expressed mainly in the hypothalamus, then the connection with obesity is realized through a change in eating behavior. Meanwhile, the entire set of genes that determine the synthesis of receptors of taste cells in the population are represented by several copies of the same gene (genetic polymorphism). Accordingly, people who inherited different copies of the gene differ in taste sensitivity (phenotypic polymorphism). Thus, the lack of taste sensitivity to FTC is an epigenetically mediated triger of fat accumulation in the body. The observed patterns of multidirectional and not always monotonous changes in individual risk factors for the development of obesity in combination with the FTK index seem to be very useful when considering the complex issues of the pathogenesis of this multifactorial disease.In this regard, it is important to distinguish among patients who are not sensitive to FTC in the group of genetic risk, for which recommendations for weight control will avoid the development of obesity in the future.

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