GENE POLYMORPHISM OF GLUTATIONETRANSFERAZ SYSTEM AND EXPRESSIVENESS INTOXICATION SYNDROME IN PATIENTS WITH PULMONARY TUBERCULOSIS

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ABSTRACT — The problem of tuberculosis spread is still topical throughout the world. There is no control epidemiological situation, so it is explained a number of problems, including forming serious adverse effects with long-term treatment with anti-TB medicines, the reduction of compliance and, as a consequence, refusal to the treatment with frequent formation of pharmacoresistant forms of tuberculosis. It is very important to improve efficiency and safety of a particular treatment in this situation. One of the tools of personality medicine is a pharmacogenetic study of the biotransformation is involved in the metabolism of anti-TB medicines. From these opinion, the definition of polymorphic gene genotypes of glutathione, can solve the problem of the formation of undesirable side effects and develop algo-rhythms are effective and safe treatment.

KEYWORDS — tuberculosis, unwanted side effects, pharmacogenetics, gene polymorphism of glutathione, personalized medicine.

INTRODUCTION

According to WHO, 9.4 million people in the world fall ill with TB and 1.3 million died each year [7, 11]. In 2014, TB killed more than 1.5 million people. In 2015, the world was found 9.6 million new TB cases, which exceeds the long-exponent of the previous year (http://www.postsovet.ru/blog/asia/622025.html). One of the strategically important issues related to the treatment of tuberculosis patients, is pro-continue to increase in the prevalence of medicine-resistant strains mikobakteries tuberculosis, reaching in Russia 30% of patients with newly diagnosed pulmonary tuberculosis and 60% in patients with relapses [5, 7, 8, 10, 12]. Formation of the resistance of the strains require the Office to strengthen modes of treatment for TB, which inevitably increases the number of unwanted side reactions anti-TB medicines [12, 13, 14]. The degree of clinical severity of the unwanted side reactions often requires discontinuation that contributes to the spread of disease, to attract additional economic cost and causes health medical and social and economic losses [4, 6, 9, 11, 13]. The most common adverse reactions of anti-TB medicines are hepatotoxic, the frequency of reaches 47% [11, 13].

In assessing the role of trigger factors in the emergence of the unwanted side reactions the value given to the study of metabolism of medicine [1, 2, 3, 4, 8, 14].

The enzymes of glutathione-S-transferase (GST), performing antioxidant and detoxifying role, provide cell resistance to lipid peroxidation, reactive metabolites of medicine involved in the formation of resistance to le medicament and preventing damage DNA [7, 13]. Multiplicity phi physiologically different system functions GST interindividual variability due to the presence of mutant alleles, reduce or block the expression of genes in many studies also associated with increased risk of disease [3, 7, 14].

In the liver of expressed isoenzymes GST potentially important are the GSTM1 and GSTT1, which describes a "null polymorphism" show full of-presence of proteins [2, 7], which is directly correlated with the severity of intoxication-foot syndrome and the incidence of the unwanted side reactions in the appointment anti-TB medicines. In this connection, it is relevant, of the present study and its practical feasibility of doubts does not cause-evaporated.

THE PURPOSE OF STUDY

to study gene polymorphism of glutathione in correlation with the severity of intoxication syndrome in patients with pulmonary tuberculosis of Astrakhan region (AR).

MATERIALS AND METHODS

The study involved 76 patients suffering from pulmonary tuberculosis treated in stationary-in GBUZ AO "Regional Clinical TB Dispensary" in Astrakhan in 2014. At the age of 18 to 65 years. Men — 56 (73.7%), women — 20 (26.3%). Patients unemployed working age were 54 (71.05%). City residents —

44.7%, rural — 55.3%. Contact with patients with tuberculosis was established in 20 (26.3%) patients. It is revealed by uptake of patients — 49 (64.47%), fluorography during medical examinations — 27 (35.53%). Annual fluorography were 10 (13.16%), were not surveyed for 2–3 years, a greater number of patients 38 (50%) and 28 (36.84%) — were not surveyed Fluorographic more than 3 years. In our study, newly diagnosed patients was — 56 (31.8%) and 20 (26.32%) were observed with a relapse of a specific process in the lungs. Distribution of patients according to clinical forms of tuberculosis were as follows: disseminated — tuberculosis, 27 (35.5%), infiltrative — 32 (42.1%), cavernous — 2 (2.6%), fibrocavernous — 15 (19.8%). Most common clinical forms were determined, with the collapse of lung tissue (r = 0,6). Determination of polymorphisms of genes GSTM1, GSTT1 was performed by polymerase chain reaction, pre-isolate DNA from the blood samples in the laboratory of D.O. Ott Research Institute of Obstetrics and Gynecology, Northwest Branch of RAMN, St. Petersburg.

All patients were divided into 5 groups: 1 — patients who develop enzyme GSTM1 performed (n = 27), 2 — patients with "zero" genotype, production of enzymes GSTM1 not performed (n = 49), 3 — patients who have expressed the GSTT1 enzyme-processing is performed (n = 63), 4 — patients with "zero" genotype, GSTT1 enzyme production is not carried out (n = 13) and 5 — patients with "zero" genotype on the development of both enzymes (n = 6). Intensity of intoxication syndrome was assessed using a scale proposed by Kibrik B.S., Tchelnokova O.G. [5]. The results were processed using a statistical software package for Windows 7. The level of reliability of statistical hypothesis was 0.05 ($p < 0.05$) by Student's test.

THE RESULTS OF THE STUDY

At admission to the hospital the symptoms of intoxication in different clinical forms of the five groups of patients had varying degrees of severity and duration (Table. 1).

Patients in group I on admission observed following symptoms: weight loss — 1 (3.7%); fever — 18 (66.7%); asthenia, marked weakness — 4 (14.8%); increased sweating — 3 (11.1%); hypotension — 0; signs lymphostasis as pastosity and swelling of the lower extremities — 0; changes in general blood test (ESR acceleration, leukocytosis shift formula to the left) — 12 (44.4%). The duration of symptoms of intoxication before admission amounted la 33 ± 6 days, amid ongoing detoxification therapy was 7 ± 3.

Group II on admission observed: weight loss — 38 (77.6%); fever — 44 (89.8%); asthenia, expressed ALS-Bost — 41 (83.7%); increased sweating — 36 (73.5%); hypotension — 21 (42.9%); DIGITS lymphostasis with a pastosion and edema of lower extremities — 24 (49%); changes in general blood test (ESR acceleration, leukocytosis shift formula to the left) — 46 (93.9%). The duration of symptoms of intoxication symptoms to admission was 39 ± 7 days, amid ongoing detoxification therapy was 18 ± 5.

Group III patients on admission to hospital noted: weight loss — 4 (6.3%); fever — 26 (41.3%); asthenia, marked weakness — 13 (20.6%); increased sweating — 2 (3.2%); hypotension — 1 (1.6%); signs lymphostasis as pastosity and swelling of the lower extremities — 0; changes in general blood test (ESR acceleration, leukocytosis shift formula to the left) — 8 (12.7%). The duration of symptoms of intoxication before admission was 18 ± 2 days, amid ongoing detoxification therapy was 7 ± 3.

Table. 1. *The duration of the clinical manifestations of the symptoms of intoxication in patients with TB patients, carriers of different alleles of polymorphic GSTM1 and GSTT1*

Monitoring Groups	Polymorphic genotypes	Number(n)	Duration / night (before admission and during therapy)	Significant differences
№ 1	polymorphic genotype GSTM1 (+/+; +/0)	n = 27	33 ± 6; 7 ± 3;	P1=0,001
№ 2	polymorphic genotype GSTM1 (0/0)	n = 49	39 ± 7; 18 ± 5;	P2=0,001
№ 3	polymorphic genotype GSTT1 (+/+; +/0)	n = 63	18 ± 2; 7 ± 3;	P3=0,001
№ 4	polymorphic genotype GSTT1 (0/0)	n = 13	45 ± 5; 24 ± 4;	P4=0,001
№ 5	polymorphic genotypes GSTM1 (0/0) + GSTT1 (0/0)	n = 6	65 ± 5; 29 ± 7.	P5=0,001

Note: *P1 — significant differences between the duration of intoxication syndrome on therapy in patients with genotype GSTM1 (+/+; +/0) VScGSTM1 (0/0); P2 — significant differences between the duration of intoxication syndrome on therapy in patients with genotype GSTT1 (+/+ +/0) VScGSTT1 (0/0); P3 — significant differences between the duration of intoxication syndrome on therapy in patients with genotype GSTM1 (+/+; +/0) VSGSTM1 (0/0) + GSTT1 (0/0); P4 — significant differences between the duration of intoxication syndrome on therapy in patients with genotype GSTT1 (+/+ +/0) VSGSTM1 (0/0) + GSTT1 (0/0) and P5 — significant differences between the duration of in-syndrome to toxic therapy in patients with genotype GSTM1 (+/+; +/0) VSGSTM1 (0/0) + GSTT1 (0/0).*

Patients of group IV at admission noted: weight loss — 5 (38.5%); fever — 13 (100%); asthenia, marked weakness — 10 (76.9%); increased sweating — 8 (61.5%); hypotension — 8 (61.5%); lymphostasis signs of pastiness and edema of the lower extremities — 6 (46.2%); changes in general blood test (ESR acceleration, leukocytosis shift formula to the left) — 12 (92.3%). The duration of symptoms of intoxication before admission was 45 ± 5 days, amid ongoing detoxification therapy was 24 ± 4.

Patients Group V on admission was observed in the following symptoms: weight loss — 6 (100%); fever — 6 (100%); Al-shadowing, marked weakness — 6 (100%); increased sweating — 5 (83.3%); hypotension — 5 (83.3%); lymphostasis signs of pastiness and edema of the lower extremities — 4 (66.7%); changes in general blood test (ESR acceleration, leukocytosis shift formula to the left) - 6 (100%). The duration of symptoms of intoxication before admission was 65 ± 5 days, amid ongoing detoxification therapy was 29 ± 7.

In this regard, we consider promising further research intended inductors and / or donatorovglutationa TB patients, to increase detoxification and antioxidant function of glutathione.

CONCLUSIONS

1. Analysis of the clinical manifestations of intoxication syndrome in patients with pulmonary tuberculosis showed that in patients with "zero" genotype to develop enzymes GSTM1, GSTT1 (II, IV, V group) intoxication symptoms significantly (r = 0,8 p = 0,001) are more pronounced and durable, even against the detoxification therapy, which will require the combined purpose of TB medicines, thus contributing to increased risk of PND.

2. detoxification therapy, the appointment of inductors and donators of glutathione in patients with tuberculosis "zero" genotypes GSTM1, GSTT1, should personalized implemented throughout the specific chemotherapy because accumulating xenobiotics and endogenous metabolites of TAP will contribute to the lengthening of the period of intoxication, formation of the NDP, reduction of compliance, the possibility of refusing specific chemotherapy and as a consequence, an increase in the prevalence of tuberculosis infection.

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