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Modern Ideas about the Cause and Development of Tuberculosis

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Annatation: Modern science views tuberculosis as a multifactorial disease in which environmental factors closely interact with the human genome and the pathogen Drug-resistant tuberculosis complicates the treatment of patients with resistant strains of tuberculosis and threatens the global process to achieve the goals set by WHO in the Strategy to End Tuberculosis in the World.

Keywords: Mycobacterium tuberculosis, drug resistance, genetic mutations, treatment efficacy.

Modern science views tuberculosis as a multifactorial disease in which environmental factors closely interact with the human genome and the pathogen Drug-resistant tuberculosis complicates the treatment of patients with resistant strains of tuberculosis and threatens the global process to achieve the goals set by WHO in the Strategy to End Tuberculosis in the WorldEffective TB control is particularly difficult in patients with MDR TB, which is characterized by resistance to isoniazid and rifampicin, the two most powerful anti-TB drugs used in standard first-line treatment. World Health Organization experts report that by the end of 2014, 153 countries reported circulating drug-resistant TB strains in the region, 80 of which have continuous surveillance systems in place.

It has been shown that resistance factors that significantly aggravate the transmission of tuberculosis resistant to first-line and second-line drugs and show the importance of conducting broader genetic and molecular studies in this area [22].

Determination of genetic polymorphism of monoresistant mycobacterium tuberculosis to isoniazid and epidemiological assessment of drug-resistant forms of tuberculosis, development of a management strategy aimed at reducing MDR-TB type of tuberculosis in Uzbekistan.[16]

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However, the growing resistance to drugs remains a problem, the following main groups of causes of the growth of drug-resistant tuberculosis are distinguished: bacteriological, pharmacological, clinical and socio-administrative. [2, 16, 24,]

Studies have established that resistance to various anti-tuberculosis drugs (ATPs) has arisen due to inappropriate use, incorrect prescription, poor quality of drugs, and non-compliance with treatment regimens by patients [2].

In modern phthisiology, non-compliance with the necessary requirements in medical practice is an important reason for insufficiently effective therapy along with natural resistance. An important problem is the acquired resistance of Mycobacterium tuberculosis to antibiotics. Resistance to one of

the drugs turns into resistance to several at the same time, and the emergence in medical practice of completely drug-resistant forms of pathogens can make this pathology incurable.

To date, globally there has been an increase in cases of drug resistance (DR) of the causative agent of tuberculosis, in particular, multidrug resistance (MDR) and extensive drug resistance (XDR) of the causative agent of tuberculosis. It has been found that DR negatively affects the results of treatment and increases the economic costs of TB treatment, especially when there is resistance to isoniazid and rifampicin.

WHO distinguishes the following types of drugs: [2016]

- Primary drug resistance is a DR in a patient with tuberculosis who has not previously received anti-TB drugs or was treated with them for no more than 1 month. The study of primary DR using genetic methods makes it possible to predict the epidemiological situation in the region, as it reflects the degree of infection spread among the population;
- Acquired (secondary) drug resistance is a DR formed during the treatment of anti-TB drugs or detected in repeated cases of tuberculosis and confirmed by genotyping.

Recurrent cases, including recurrences of tuberculosis, may also be the result of re-infection [2].

There are the following types of MDR Mycobacterium tuberculosis monoresistance - DR Mycobacterium tuberculosis only to one first-line anti-TB drug; polyresistance - DR to two or more anti-TB drugs, excluding resistance to both isoniazid and rifampicin;

MDR is a special category among multidrug-resistant strains, where there is resistance to both isoniazid and rifampicin, regardless of resistance to other drugs;

XDR is a form of MDR with resistance to at least rifampicin and isoniazid, as well as any of the fluoroquinolones and one of the second-line injectables kanamycin, amikacin, capreomycin. [3]

Such strains can be resistant to 9 drugs. The emergence of variants resistant to antibacterial drugs is a natural phenomenon, an expression of the adaptation of species to the environment [21].

The development of LU in mycobacteria is regarded as a manifestation of one of the forms of bacterial cell variability under the influence of chemotherapy drugs. Rifampicin resistance identified by phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. The situation is complicated by an increase in the number of Mycobacterium tuberculosis MDR strains, as well as species with an increased ability to transmissibility, such as strains of the Beijing Mycobacterium tuberculosis family [18].

While multidrug-resistant strains and MDR can be treated with second-line antibiotics, XDR, which is resistant to second-line antibiotics, leaves no treatment options for the clinician. The effectiveness of the treatment of patients with MDR/XDR Mycobacterium tuberculosis is only 54% MDR and 28% with high DR, with a positive therapeutic outcome compared to drug-sensitive 83% of cases [18].

There are currently 600,000 TB patients in the world who are shedding Mycobacterium tuberculosis with MDR, while only 125,000 cases have been registered. The low effectiveness of treatment (up to 52%) in these patients is due to the late detection of LU, the late start of the use of rational chemotherapy, which leads to the development of widespread destructive changes in the lungs, prolongation of the cessation of bacterial excretion, and chronicity of the process. [7.8]

Yablonsky P.K. [2016] indicates that a sharp increase in the structure of DR occurs due to the growth of MDR and XDR, which amounted to 81.9% compared to previous years (28.5% in 1984-1988). With extrapulmonary tuberculosis, the growth of DRs of Mycobacterium tuberculosis continued at a faster pace. The author points out that a rapid aggravation of the process was observed due to the increase in MDR/XDR strains - from 10.5% to 69.5%. [21].

The researchers note that in tuberculous spondylitis, the most severe and common form of osteoarticular tuberculosis, out of 78 Mycobacterium tuberculosis isolates with an MDR/XDR resistance profile, 70 (89.7%) belonged to the Beijing genotype. The growth rates of XDR in

pulmonary tuberculosis exceeded those in extrapulmonary tuberculosis - from 26.8% to 39.5%. The authors believe that the situation with DR of Mycobacterium tuberculosis in all localizations of the disease can be characterized as tense with unpredictable consequences [6.7.8]

Currently, true genetic and acquired resistance is distinguished [16]: true genetic resistance, being a species trait of the pathogen, is associated with the absence of a target for the action of an antibiotic or, poor permeability of the cell wall, in some cases manifests itself in the form of efflux. Thus, Mycobacterium tuberculosis has true genetic resistance to many antimicrobial drugs belonging to the families of penicillins, β-lactams, macrolides, carbapenems, cephalosporins, tetracyclines; the acquired resistance of Mycobacterium tuberculosis is formed due to the development of point mutations in chromosomes and the formation of new genes that control the synthesis of new enzyme proteins that destroy specific PTPs.

Acquired LU is divided into primary and secondary. Primary DR is defined in patients who become infected with drug-resistant strains of Mycobacterium tuberculosis, despite the fact that these patients have not previously taken anti-TB drugs. Secondary LU develops during the treatment of a patient with tuberculosis, the development of this phenomenon takes 3-6 months from the start of therapy [11,14,17].

The danger to patients is represented by multidrug-resistant strains simultaneously resistant to isoniazid and rifampicin. Diseases caused by such isolates of Mycobacterium tuberculosis are known to be progressive and difficult to treat. There are results of analysis of MDR clinical isolates of Mycobacterium tuberculosis with multiple gene mutations, some of which relate to isoniazid. This drug has become the most widely used drug in the treatment of tuberculosis caused by drug-susceptible strains of mycobacteria, along with rifampicin and pyrazinamide. In addition, prophylactic isoniazid monotherapy has been used in the treatment of occult tuberculosis [15,18].

It has been established that inhibition of the synthesis of mycolic acids, a component of the cell wall of Mycobacterium tuberculosis, by isoniazid leads to deprivation of acid resistance. The presence of mycolic acids in Mycobacterium tuberculosis makes it resistant to many types of treatment, and their synthesis is absolutely necessary for the survival of this pathogen.

A number of studies have shown that isoniazid works against active mycobacteria in the presence of oxygen. The drug is not active under anaerobic conditions against bacteria that are in a latent state. Along with this, the temperature regime is of no small importance, so at 37 ° C the activity increases and decreases at 4 ° C, which shows the connection of isoniazid with the enzymatic activity in the bacterial cell. Further manifestation of antibacterial activity, which depends on the activation of the catalase-peroxidase enzyme, KatG, inside the bacterial cell [20].

Like other anti-TB drugs, resistance to isoniazid appeared in Mycobacterium tuberculosis soon after its introduction and has reached high levels over the past 20 years. Several intracellular targets of this drug are known - a complex of enzymes involved in the synthesis of mycolic acids. Mutations in the genes encoding these proteins (inhA, acpM, and kasA) can cause resistance to isoniazid.

According to Burmistrova I.A. [2018], resistance to isoniazid with preserved sensitivity to rifampicin occurs in 12.1% of bacterial excretors. Polychemoresistance with fixed resistance to isoniazid significantly complicates the prognosis of the disease. [5,6]

According to a number of authors, resistance to isoniazid not only increases the risk of developing MDR, but is also the most important factor in an unfavorable long-term outcome of treatment [9].

Along with this, the resistance of mycobacteria to isoniazid occurs due to hyperproduction of targets for the action of active forms of the drug. For example, proteins involved in the transport of mycolic acid precursors and its biosynthesis: acylated carrier protein (acpM gene), synthetase (kasA gene) and reductase (inhA gene) of the carrier protein. Most of the mutations are found in the promoter regions of these genes. The degree of resistance associated with overproduction of targets is usually lower than with mutations in the catalase-peroxidase genes. The overall prevalence of isoniazid resistance exceeds 13% [23,24]

The lack of accelerated diagnosis of tuberculosis with resistance to isoniazid with preserved sensitivity to rifampicin may be the reason for the low effectiveness of therapy and lead to amplification of DR, including the formation of MDR.

Detection of LU by cultural methods on dense nutrient media takes at least 10-12 weeks. The currently used molecular genetic methods for the rapid detection of MDR pathogens meet the task, but are not generally available, require special laboratory equipment, additional staff training. The molecular genetic cartridge method allows simultaneous detection of Mycobacterium tuberculosis DNA in diagnostic material and mutations in the rpoB gene associated with the development of DR to rifampicin, often associated with resistance to isoniazid. Studies have shown high sensitivity (96-100%), specificity (100%), biosafety of the method [7.8]

Petrova L.V. [2019] studied the effect of using the molecular genetic method PCR-RT in the algorithm of microbiological diagnostics of 344 patients with MDR tuberculosis on the effectiveness of chemotherapy. It has been shown that the use of RT-PCR to determine mutations in samples of diagnostic material associated with LU to rifampicin, isoniazid and fluoroquinolones, and early prescription of the appropriate chemotherapy regimen based on this study, followed by correction of the treatment regimen based on the results of phenotypic methods of testing LU, allows, on average, to 3.6 to 2.5 months To reduce the time of cessation of bacterial excretion, determined by the method of sowing. [13,16]

The study studied the frequency, spectrum and nature of the primary DR of Mycobacterium tuberculosis isolated from patients with infiltrative pulmonary tuberculosis over a 9-year period. An increase in the frequency of DR of Mycobacterium tuberculosis by 1.4 times was revealed, as well as an increase in resistance to a larger number of anti-TB drugs. A 3-fold increase in the proportion of MDR pathogens was established. [11,12]

The authors studied DR, the spectrum of mutations that cause resistance to rifampicin and isoniazid, viability, cytotoxicity, and performed genotyping of 111 clinical isolates of Mycobacterium tuberculosis. Spoligotyping revealed 28 spoligotypes; the largest number of strains belonged to the Beijing and LAM genetic families. Typing of 59 strains of the SIT1 spoligotype (Beijing) made it possible to differentiate 19 variants of IS6110-RFLP profiles: 13 were individual, 6 were represented by clusters. Clusters A0 and B0 included the largest number of strains of Mycobacterium tuberculosis 21 (35.6%) and 17 (28.8%), respectively.

A comparative evaluation of the effectiveness of tuberculosis chemotherapy in 185 patients with pulmonary tuberculosis, determined using the GeneXpert MTB/RIF cartridge test system and determined by inoculation on liquid media, was carried out. The appointment of chemotherapy based on the results of the GeneXpert MTB/RIF test, followed by correction based on the results of seeding for Bactec MGIT 960, significantly improves treatment outcomes in patients with tuberculosis with MDR pathogen, both in terms of the rate of cessation of bacterial excretion and the rate of closure of destruction, compared with the group, where the correction of treatment was carried out only by the result of inoculation on liquid media.

Regional studies in the Republic of Uzbekistan showed that the prevalence of MDR tuberculosis among newly diagnosed patients was 23%, and among relapses 62%. The results of the DOTS strategy have shown the failure of first-line therapy among some patients. A high level of tuberculosis with MDR was detected in the RRC. 13% of never treated TB patients were infected with MDR strain

According to Sayfutdinov Z.A., in 2010-2021. was conducted sensitivity tests for isoniazid in 10 815 cultures of Mycobacterium tuberculosis, and the results of the study showed that resistance to this drug was 58%. However, studies in some years have shown that this figure was 73% (2011), 61% (2012) and 66% (2016, 2018).

Given the importance of mutations in the InhA gene in the development of MDR TB strains, a broader study of this mutation simultaneously showed that Mycobacterium tuberculosis induces cross-resistance to the drug proteonamide/ethionamide, which is a 2-line anti-TB drug. Although the

mutation in the InhA gene detected by molecular genetic analysis (17%) was lower than resistance to ethionamide/prothionamide detected by phenotypic DST (31%), early diagnosis (within 2-3 days) and timely application of appropriate therapy patients reduces the interval for issuing results to 45 days.

To date, attempts are being made to improve preventive and therapeutic measures for tuberculosis infection. The coincidence of the DR spectrum of MBT cases from contact of children and adults with the source of infection was confirmed [1,2].

Attempts are being made to develop a model of a patient with drug-resistant pulmonary tuberculosis. Further study of drug resistance creates promising opportunities for limiting resistance in TB infection.

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