

Adverse Effects of Anti-Tuberculosis Drugs in Patients with Pulmonary Tuberculosis Carrying Different Haptoglobin Phenotypes

Tashpulatova Fatima Kudratovna

Doctor of Medical Sciences, Associate Professor of the Department of Infectious Diseases, Pediatric Infectious Diseases, Phthisiology and Pulmonology, Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan

Abstract 226 patients with pulmonary tuberculosis were examined, of whom 144 (64.1%) experienced adverse events (AE) from anti-tuberculosis drugs during treatment. All patients were tested for haptoglobin (Hp) phenotype carriers. Analysis of the obtained data showed that AEs occurred predominantly in patients carrying homozygous variants of haptoglobin Hp1-1 and Hp2-2. It is recommended to determine the haptoglobin phenotype to predict the risk of AE development from anti-tuberculosis drugs.

Keywords Tuberculosis, Haptoglobin, Adverse events, Anti-tuberculosis drugs

1. Relevance

The current epidemiological situation regarding tuberculosis is characterized by changes in its pathomorphism - the emergence and increase in the number of severe, progressive forms of the disease, an increase in the frequency of polyresistant forms of MBT, and drug-induced complications from chemotherapy [9].

Undoubtedly, social and economic shocks, environmental and radiation factors in the regions, the increase in HIV infection, drug addiction, irrational chemotherapy, high frequency of concomitant diseases such as viral hepatitis, CNSLE, diabetes mellitus, and gastrointestinal tract diseases played a major role in this.

While acknowledging the social and hygienic aspects of tuberculosis, one should not forget about its biological characteristics, which may be the most important and at the same time insufficiently studied, which affect the body's reactivity [1]. Biological factors undoubtedly play a crucial role in the development of both the human disease itself and the course of the tuberculosis process and the effectiveness of the treatment being administered. Reflecting the characteristics of the body's response to external influences, reactivity allows for "passing the bridge" between biological and socio-hygienic factors in the development of tuberculosis [1].

Important importance is given to assessing the individual reactivity of the organism from a genetic perspective [3,5]. It has been established that many normal and pathological

reactions of the body are determined by genetic background, which determines the variation of physiological reactions in response to the action of the same factor. Consequently, it can be assumed that the difference in the formation of clinical variants of tuberculosis, the progression of the process, its complications, transition to a chronic form in some and complete recovery in others, along with other factors, is also explained by genetic features [1,8].

The diversity of forms of pulmonary tuberculosis, the chronic nature and phased course of the disease, and the deep impression of the disease on the psychosomatic appearance of the patient indicate a significant influence of reactivity on the course of pulmonary tuberculosis and, at the same time, a change in the body's reactivity under the influence of the disease. All this prompted us to address the problem of reactivity in pulmonary tuberculosis.

One of the genetic markers associated with the occurrence and course of tuberculosis is the haptoglobin (Hp) phenotype, with carriage of homozygous variants, a severe course and low treatment efficacy were noted [6,7,8]. However, we have not encountered any association between the carriage of haptoglobin phenotypes and the development of adverse effects from anti-tuberculosis drugs in the available literature.

Purpose: To study the frequency and nature of adverse effects from anti-tuberculosis drugs in patients with pulmonary tuberculosis carrying different phenotypes of haptoglobin (Hp).

2. Material and Methods

A comprehensive examination of 226 patients with pulmonary tuberculosis aged 17 to 65 who were undergoing

treatment in the therapeutic departments of the Republican Ftiziatrics and Pulmonology Center and the city of Tashkent was conducted. Of the total number of examined, 111 (49.1%) were men and 115 (50.9%) were women.

Among the clinical forms of tuberculosis, infiltrative pulmonary tuberculosis was most common - 134 (59.3%) and fibro-cavernous pulmonary tuberculosis - 30 (13.3%). The first-time identified patients were -85.8%.

In 177 (77.8%) patients, concomitant diseases were identified: COPD - in 31.5%, anemia - in 18%, gastrointestinal tract and liver diseases - in 17%, diabetes mellitus - in 19.3%.

Taking into account the results of the drug resistance test, the examined patients were prescribed, according to WHO standards, first-line anti-tuberculosis drugs - isoniazid, rifampicin, pirazinamide, and etambutol. The patients were hospitalized for 2 to 3 months.

To identify the association between the frequency, nature, and characteristics of NA manifestation and the carriage

of genetic markers, the haptoglobin (Hr) phenotype was determined by electrophoresis of the blood serum disc in a polyacrylamide gel according to the Davis method, modified by N.A. Osina (1982).

3. Results and Discussion

During treatment, 144 (64.1%) patients developed TN due to anti-tuberculosis drugs (Table 1). In our work, we used the syndromic classification of adverse effects from anti-tuberculosis drugs.

Skin allergic reactions were noted in 29.6%, liver damage syndrome in 22.8%, gastrointestinal tract damage in 13.1%, and nervous system damage in 14.5% of patients. Combined syndrome (combination of several adverse phenomena) was detected in 15% of patients. Only 4% of patients had cardiovascular system damage.

Table 1. Frequency and nature of TN from anti-tuberculosis drugs in the examined patients, %

Group of patients	Frequency HY	Dermal allergic syndrome	Damage syndrome				Combined syndromes
			Liver	Ventricle Intestinal tract	Nerve system	Cardiovascular system	
226	<u>145</u> 64,1±4,5	<u>43</u> 29,6±3,7	<u>33</u> 22,8±3,4	<u>19</u> 13,1±2,8	<u>21</u> 14,5±2,0	<u>6</u> 4,01±1,7	<u>23</u> 15,9±3,0

Note - % was calculated relative to the number of patients with NY.

It was established that isoniazid (46.7%) and rifampicin (33.3%) were the drugs most frequently causing NA from anti-tuberculosis drugs.

It was established that in homozygous variants of Hp (1-1 and 2-2) in patients with tuberculosis, NA occurred in 78.3±6.7 and 81.2±3.6% of patients. A different picture was observed in the heterozygous variant of the Hp 2-1 phenotype: out of 77 patients, NA occurred in only 25 (32.4±5.3%). Consequently, individuals with homozygous variants of the Hp (1-1 and 2-2) phenotype have a predisposition to the development of NA from chemopreparations.

Dalle, we were interested in the nature of NA from anti-tuberculosis drugs in patients with different phenotypes of haptoglobin.

Table 2. Frequency of adverse reactions to anti-tuberculosis drugs in patients with different haptoglobin phenotypes

	Total number of patients	Patients without NA	Patients with NIAs
Hp1-1	37 (16,4±6,0)	8(21,7±6,7)	29(78,3±6,7) P ₁ ≤0,001
Hp2-2	112 (49,6±4,7)	21(18,8±3,6)	91(81,2±3,6) P ₂ ≤0,001
Hp2-1	77 (34,0±6,0)	52(67,6±5,3)	25(32,4±5,3) P ₃ ≤0,001

It was noted that in carriers of the homozygous Hp 1-1 phenotype, the frequency of liver damage significantly

increases to 58.6±9.1% (p≤0.001), while skin allergic syndrome, nervous system damage syndrome, and a combination of several syndromes occurred equally often (10.4% each).

In carriers of another homozygous phenotype, Hp 2-2, a relatively high frequency of skin allergic syndrome (38.4%) and combined syndromes (16.5%) is observed, while gastrointestinal tract (15.4%), liver, and nervous system (12.1%) damage syndromes occur almost equally frequently.

A somewhat different pattern is observed in carriers of the heterozygous Hp 2-1 phenotype, where nervous system damage syndrome is common (28%), followed by skin-allergic syndrome (20%), and liver and gastrointestinal tract damage in 16% of patients.

Table 3. Degree of severity of adverse effects from anti-tuberculosis drugs in patients carrying different phenotypes of haptoglobin

Patients with phenotypes	Degree of gravity		
	lungs	Moderate severity	severe
Hp 1-1 n=29	5(17,2±7,0)	22(75,9±8,0)*	2(6,9±4,0)
Hp 2-2 n=91	16(17,6±4,0)	61(67,0±5,0)*	14(15,4±4,0)
Hp 2-1 n=25	16(64,0±9,0)*	9(36,0±10,0)	-

Note-*. significant difference between the indicators

The analysis of the severity of adverse events in patients carrying different haptoglobin phenotypes is of interest (Table 3).

It was established that in carriers of homozygous haptoglobin phenotypes Hp 1-1 and Hp 2-2, moderate and severe adverse events prevailed, while in the heterozygous variant Hp 2-1, mild adverse events were more common.

The haptoglobin glycoprotein we studied is produced in the liver and transported to other organs, where it functions as an alternative electron carrier in the respiratory chain and stimulates primary antibody production. The main physiological role of Hp is the formation of a strong complex with hemoglobin (Hb), Hp-Hb, preserving iron in the Hb molecule [11].

With different Hp phenotypes, the property of Hp to form an Hp-Hb complex with Hb changes. The hemoglobin-binding capacity decreases from Hp 2-1 to Hp 2-2 [19]. Consequently, there is a significant difference in the formation of the Hp-Hb complex among different Hp phenotypes. The heterozygous phenotype Hp 2-1 forms a strong, stable Hp-Hb complex. At the same time, individuals with homozygous phenotypes Hp 1-1, especially Hp 2-2, experience a defect in the process of Hp-Hb complex formation, which leads to disruption of normal oxygen transport to tissues, and in turn, to the exacerbation of hypoxia that occurs in tuberculosis, and disturbance of tissue respiration. According to K.S. Kazakov, this is one of the key mechanisms for the development of adverse effects from anti-tuberculosis drugs [6].

In addition, peroxidase activity decreases, and Hb denaturation increases. All this creates a closed vicious cycle that leads to the disruption of electron transfer in the cytochromes of the respiratory chain and, consequently, to the disruption of energy substrate formation [11].

4. Conclusions

Thus, tuberculosis patients carrying homozygous variants of haptoglobin phenotypes Hp 1-1 and Hp 2-2 are predisposed to frequent development of adverse effects from anti-tuberculosis drugs, indicating the necessity of including haptoglobin phenotype determination in the battery of laboratory tests before initiating chemotherapy.

REFERENCES

- [1] Averbakh M.M., Litvinov V.I., Malenko A.F., Mostovoy Yu.M., Moroz A.M., Nikonenko B.V., Pospelov L.E., Khomenko A.G., Chukanova V.P. Problems of Heredity in Lung Diseases /Ed. by A.G. Khomenko.- Moscow: Meditsina, 1990. - 240 p.
- [2] Baisenbayeva R.U. Haptoglobin. - Alma-Ata, 1983. - 126 p.
- [3] Kaminskaya G.O., Firsova V.A., Ovsyankina E.S. Relationship between the course of tuberculosis in adolescents and indicators of acute phase blood proteins and genetic variants of haptoglobin // Probl. Tuberk.- 1997.- No. 6.- P. 36-40.
- [4] Osina N.A. Standardization of blood serum protein electrophoresis results in polyacrylamide gel // Lab. Delo. - 1982. - No. 8. - P. 463-466.
- [5] Pavlova M.V., Skvortsova L.A., Kondakova M.N., Kovaleva R.G. The role of comprehensive genetic prognosis in the treatment and prevention of respiratory tuberculosis in adolescents // Probl. Tuberk. Bolezn. Legk. - 2005. - No. 8. - P. 30-33.
- [6] Kazakov K.S. Immunobiochemical aspects of the pathogenesis of side effects in tuberculosis chemotherapy (clinical and experimental study): Dissertation for Doctor of Medical Sciences. - Tashkent, 1975. - 420 p.
- [7] Parpieva N.N. Characteristics of the course and treatment of pulmonary tuberculosis combined with diabetes mellitus in individuals with different haptoglobin phenotypes: Dissertation for Doctor of Medical Sciences. - Tashkent, 2002.- 270 p.
- [8] Saidova Sh.M. Characteristics of the course and treatment effectiveness of pulmonary tuberculosis in patients with concomitant pathology and different haptoglobin phenotypes: Dissertation for Candidate of Medical Sciences. - Tashkent, 2001. - 145 p.
- [9] Skvortsova L.A., Pavlova M.V., Kandakova M.I. The role of genetic factors in the clinical presentation of respiratory tuberculosis // Proceedings of the 8th Russian Congress of Phthisiologists. - Moscow, 2007. - P.187.
- [10] Global tuberculosis report 2023, World Health Organization 2023, P. 75.
- [11] Keil W., Geserick G., Nocek G. Haptoglobintyp und Isoantikörper: anti- A und anti-B // Folia Haematol. -1982. - Vol. 109, N 2. - P. 324-333.