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FEATURES OF BIOCHEMICAL INDICES AND CONTENT OF ENZYMES IN THE SERUM OF SYPHILIS PATIENTS WITH VIRAL HEPATITES B AND C IN THE COURSE OF TREATMENT

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Ключевые слова: *вирусный гепатит В, вирусный гепатит С, результаты лечения, сифилис, функциональное состояние печени*

Abstract. *Features of biochemical indices and content of enzymes in the serum of syphilis patients with viral hepatitis B and C in the course of treatment. Zakharov S.V., Zakharov V.K., Gorbuntsov V.V. Objective – before and after the treatment to determine the functional state of the liver, serum levels of enzymes and biochemical indices in syphilis patients with viral hepatitis B and C. The results of the study are based on the data from a comprehensive examination of 35 patients with syphilis alone and 127 patients with syphilis co-infected with viral hepatitis B and C before and after treatment. Test methods: hepatology, rheohepatoigraphy, enzyme content and biochemical parameters determined in the serum. According to the results of radionuclide hepatology it has been established that disorders of the functional capacity of the liver already occur in the early stages of the disease. The most significant disorders have been in the patients with the prescription of infection for more than 12 months and in the patients co-infected with viral hepatitis B and C. A disorder of pigment metabolism and increased activity of transaminases have been revealed in early latent syphilis. In co-infection with viral hepatitis B and C an increase in total bilirubin, Lactate dehydrogenase, Alanine transaminase, Aspartate aminotransferase and albumin has been revealed. Dysproteinemia has been revealed in patients with early latent syphilis co-infected with hepatitis C. Patients with early latent syphilis treated with immunomodulators tend to normalize these indices. In patients with syphilis a disorder of the functional state of the liver have been revealed already at an early stage of the disease. The most pronounced disorder of biochemical parameters and activity of liver enzymes are observed in syphilis patients with viral hepatitis B and C, as well as in patients with early latent syphilis only with the prescription of the infection for more than 12 months; in such a case it is advisable to use drugs affecting the immune system.*

Реферат. *Особенности биохимических показателей и вмісту ферментів у сироватці крові хворих на сифіліс, ко-інфікованих вірусними гепатитами В і С у процесі лікування. Захаров С.В., Захаров В.К., Горбунцов В.В.*

Мета роботи – до та після лікування визначити функціональний стан печінки та вміст у сироватці крові ферментів і біохімічних показників у хворих на сифіліс, ко-інфікованих вірусними гепатитами В і С. Результати дослідження засновані на даних комплексного обстеження до і після лікування 35 хворих тільки на сифіліс і 127 хворих на сифіліс, ко-інфікованих вірусними гепатитами В і С. Методи обстеження: гепатографія, реогепатографія, вміст ферментів і біохімічні показники, які визначалися в сироватці крові. За результатами радіонуклідної гепатографії встановлено, що порушення функціональної здатності печінки виникають уже на ранніх етапах хвороби. Найбільш суттєві порушення були у хворих з давністю інфекції більше 12 місяців і в пацієнтів, ко-інфікованих вірусними гепатитами В і С. Виявлено порушення пігментного обміну, підвищення активності трансаміназ при ранньому прихованому сифілісі. При ко-інфекції вірусними гепатитами В і С спостерігається підвищення загального білірубину, лактатдегідрогенази, аланінамінотрансферази, аспартамінотрансферази й альбуміну. Диспротеїнемія спостерігається у хворих на ранній прихований сифіліс, ко-інфікованих гепатитом С. У хворих на ранній прихований сифіліс, під час лікування яких застосовували імуномодулятори, відзначається тенденція до нормалізації цих показників. У хворих на сифіліс уже на ранніх стадіях захворювання спостерігається порушення функціонального стану печінки. Найбільш виражені порушення

біохімічних показників та активності ферментів печінки спостерігаються у хворих на сифіліс, ко-інфікованих вірусними гепатитами В і С, а також у хворих тільки на ранній прихований сифіліс з давністю зараження більше 12 місяців; у такому випадку доцільно використовувати препарати, що впливають на імунну систему.

In recent years viral hepatitis has become one of the global problems of modern medicine; thus every year about 1.5 million people die of viral hepatitis in the world, and a significant number of the patients become disabled.

Syphilis and parenteral viral hepatitis *B* and *C* have not only identical transmission paths, but the risk groups too, which makes the problem of clinical and epidemiological features of syphilis together with co-infection with viral hepatitis *B* and *C* urgent enough [2, 12].

Nowadays, since the mid-1990s, the number of cases of viral hepatitis *B* and *C* associated with the injection drug addiction and sexually transmitted diseases has increased significantly [15].

Most often and prior to other organs the liver of a person with syphilis is being damaged [12]. The liver is too sensitive to the syphilitic infection, so the disorder of its biochemical parameters occurs in early stages of the infection and is characterized by disorders of conjugation processes and increase in the urea and creatinine concentration in serum. The syphilitic infection can cause the cytolytic syndrome in the liver that leads to an increase in the serum content of [2]:

- bilirubin and γ -globulins;
- uric acid;
- triglycerides;
- cholesterol;
- β -lipoproteins.

There is no doubt that the intercurrent diseases such as hepatitis, HIV, tuberculosis and others affect the immune system; and immunodeficiency develops, this may result in [2, 7, 10, 11, 13, 14, 16]:

- serous resistance;
- clinical and serological recurrences;
- specific affection of nervous and cardiovascular systems;
- congenital syphilis.

As for now, syphilis is not always mono-infection: quite often in patients with syphilis other sexual transmitted infections (STIs) (chlamydiosis, HIV, viral hepatitis *B* and *C* and others) are revealed; nevertheless the features of the clinical course, serological reactions, liver function and immune system disorders are almost have not been studied.

Unfortunately, such an important problem is not reflected in the protocols (guidelines) for the treatment of patients with syphilis co-infected with viral hepatitis *B* and *C*.

The objective – to determine the functional state of the liver, serum levels of enzymes and biochemical indices of syphilis patients with viral hepatitis *B* and *C* before and after the treatment.

MATERIALS AND METHODS OF RESEARCH

A comprehensive study of the liver functional state in 127 patients with early forms of syphilis (primary, secondary and early latent one) co-infected with viral hepatitis *B* and *C* has been carried out. The group of comparison (control) consists of 30 practically healthy persons and 35 patients with infectious forms of syphilis only.

The research was conducted in accordance with the principles of bioethics set out in the WMA Declaration of Helsinki – “Ethical principles for medical research involving human subjects” and “Universal Declaration on Bioethics and Human Rights” (UNESCO).

We have examined:

- 30 healthy persons (the control group K-1);
- 35 patients with the infectious forms of syphilis only (the control group K-2);
- 127 patients with contagious forms of syphilis co-infected with viral hepatitis, divided into three groups:
 - 1) group 1 – patients with syphilis co-infected with viral hepatitis *B* (59 persons);
 - 2) group 2 – patients with syphilis co-infected with viral hepatitis *C* (25 persons);
 - 3) group 3 – patients with syphilis co-infected with viral hepatitis *B* and *C* (43 persons).

Among the patients with syphilis:

- women made up 62%;
- men – 38%.

Patients of the control group K-2 (persons with syphilis only) were distributed in the following way:

- primary syphilis – 10 persons;
- secondary syphilis – 10 persons;
- latent early syphilis – 15 persons.

Among 127 syphilis patients with viral hepatitis there was such a distribution:

- primary syphilis – 30 persons;
- secondary syphilis – 33 persons;
- latent early syphilis – 64 persons.

For diagnosis of syphilis, serological methods have been used:

- the classical complex of serological reactions (CSR);
- Enzyme-linked immunosorbent assay (ELISA) for IgM and IgG;
- the reaction of passive hemagglutination (RPGA);

- immunofluorescence reaction with absorption (RIF-abs) and RIF-200, – and also Hbs Ag and HCV Ag have been examined in patients [9].

We have determined:

- total and direct bilirubin – by Jendrassik–Grof method;

- urea – by the enzymatic method;

- uric acid – using sodium permanganate;

- Lactate dehydrogenase (LDH) – by Sewell–Tovarek method;

- Gamma-glutamyl transferase (GGT) – by the enzymatic colorimetric method;

- total serum proteins – by the biuretic method;

- protein fractions – by electrophoresis on paper;

- thymol turbidity test – by McLagan method;

- sublimate test – by Grinstedt method;

- the activity of Alanine transaminase (ALT) and Aspartate aminotransferase (AST) – by Reitman and Frankel method;

- hepatography – by T. P. Syvichenko method;

- rheogepathography – by G. P. Matveykov method [3, 4].

As a material for research, the venous blood of patients with syphilis and viral hepatitis *B* and *C*, of practically healthy people and patients with syphilis only has been used.

The mathematical processing of the digital material has been carried out using a software package for processing and analysis of statistical information with the use of methods of biometric analysis implemented in packages of licensed software EXCEL 2003[®] and STATISTIKA 6.1 (Stat Soft Inc., S/N HGAR 909 E-415882 FA) [8].

The difference in indices with $p < 0.05$ was considered as probable one.

To identify the relationships between the indices, Friedman's nonparametric variance analysis with the definition of χ^2 was used. Significance of indices was considered significant if χ^2 value exceeded the critical one ($\chi^2 = 3.84$) [1].

RESULTS AND DISCUSSION

The examined patients with syphilis, without hepatitis *B* and *C* (control group K-2 – 35 patients), did not reveal the statistically significant disorders of rheogram characteristics. Only the patients with syphilis co-infected with viral hepatitis *B* tended to decrease in the amplitude β ; those patients revealed a statistically significant decrease of mean values of T_β and elevated Q . The degree of disorders was the most significant in 95 % of patients with secondary and 65 % ones with tertiary latent syphilis:

- index β – (9.1 ± 0.4) mm ($p < 0.05$);

- T_β – from 0.14 to 16 s;

- Q_y – up to 0.60 – 67 s.

Substantial changes in individual rheogram parameters were observed in syphilis patients with viral hepatitis *C* and especially in patients with secondary and early latent syphilis which were characterized by:

- a decrease in the duration of the rheograms recovery;

- prolonged time after systolic wave elevation – which all can be interpreted as the indicators of inflammatory changes and circulatory disorders in the liver.

According to the results of studying hepatography in the group K-2 (patients with syphilis only), statistically significant decrease in the index of secretion and excretion (C total) was revealed. According to the analysis of hepatograms in syphilis patients with viral hepatitis *B*, it was found that:

- C total reached 65 %;

- $T_{1/2}$ increased on average up to (6.0 ± 0.2) min. ($p < 0.05$).

Syphilis patients with viral hepatitis *C* revealed the reliable increase of the average time (T) in the isotope maximal accumulation (T_{max}):

- $T_{1/2}$ increased up to 6.5 min.;

- T of excretion – up to 30 min.;

- C total – up to 70%.

In the group of syphilis patients with viral hepatitis *B* and *C* it was determined that:

- K_2 was reduced to 5%;

- K_3 was reduced to 25%;

- G increased up to 14.1 ± 15.3 ;

- T of excretion increased up to 45 min.

Studying the radionuclide hepatography allowed to ascertain disorder of liver function already in the early stages of infection in the group of patients with syphilis only. Significant disorders were observed in syphilis patients with viral hepatitis *B* and *C* due to the development of inflammatory process in the liver – in the form of hepatocyte disturbances and liver clearance. The most significant disorders of the liver function were noted in patients with secondary and early latent syphilis, with an infection period of more than 1 year, co-infected with viral hepatitis *B* and *C*.

The study of the bilirubin exchange in the group K-2 (patients with syphilis only) showed a moderate increase in the total bilirubin concentration in the blood by 1.5 times (8.2 ± 0.1 vs. 4.9 ± 0.1 , $p < 0.05$). In the group of syphilis patients with viral hepatitis, the increase of the general bilirubin level was more significant (by 1.9 times). In both groups of patients being under study such increase was caused by the **direct bilirubin** concentrations.

The study of the liver cell enzymes activity indicated an increased penetration of hepatocytes involved in the synthesis of enzymes which are part

in the metabolism of those cells. We established a significant ($p < 0.05$) increase in the activity of transaminases, namely ALT:

- in the group K-2 – by 1.6 times compared with the group K-1;

- in the group of syphilis patients with viral hepatitis B and C:

1) by 3.2 times compared with the K-1 group;

2) by 2.5 times compared with the K-2 group.

The most significant shift towards the increase in the **thymol turbidity test** was:

- in patients with syphilis only having the history of infection over 1 year (6.5 ± 0.1 while the norm was 3.5 ± 0.1 , $p < 0.01$);

- in syphilis patients with viral hepatitis B and C (8.7 ± 0.2 vs. 6.5 ± 0.1 in patients with syphilis only, $p < 0.05$).

The **sublimite test** in patients with syphilis was reduced and also depended on the time of infection; the most significant changes towards the decrease of this sample were established under co-infection with viral hepatitis B and C (80.5 ± 1.0 and 73.2 ± 2.1) to 6 ± 2 – the index in the group K-1, $p < 0.05$. Such violations revealed by this index testify to disorder of the synthesis of proteins in the liver.

Definitely, the concentration of total serum protein in patients with syphilis only did not differ significantly ($p > 0.01$):

- $K_1 - 75.5 \pm 2.0$;

- $K_2 - 75.5 \pm 2.5$.

The albumin concentration was significantly lowered both:

- in patients with syphilis only ($p < 0.01$):

1) $K_1 - 60.0 \pm 2.4$;

2) $K_2 - 53.2 \pm 1.1$;

- and in patients co-infected with viral hepatitis ($p < 0.05$):

1) $K_1 - 53.2 \pm 1.1$;

2) $K_2 - 47.0 \pm 1.0$.

On the part of the globulin fraction, the most significant changes were revealed in the α_2 and β fractions, both:

- in the K-2 group ($p < 0.01$):

1) fraction α_2 : $K_1 - 7.0 \pm 0.3$; $K_2 - 10.7 \pm 0.2$;

2) fraction β : $K_1 - 9.1 \pm 0.2$; $K_2 - 12.4 \pm 0.3$;

- and in the group of patients co-infected with viral hepatitis B and C ($p < 0.01$):

1) fraction α_2 : $K_1 - 10.7 \pm 0.2$; $K_2 - 14.3 \pm 0.2$;

2) fraction β : $K_1 - 12.4 \pm 0.3$; $K_2 - 16.1 \pm 0.3$.

The concentration of γ -globulin was the highest one:

- in patients with a history of infection exceeding 1 year – up to (24.2 ± 1.8)%;

- in patients co-infected with viral hepatitis B and C – up to (30.3 ± 2.1)%;

- in patients of the group K_1 – up to (17.9 ± 1.5)%.

The hyperfermentemia was determined according to the results of:

- alkaline phosphatase studies:

1) in syphilis patients with viral hepatitis B – 121.3 ± 3.5 ($p < 0.05$);

2) in syphilis patients with viral hepatitis C – 124.1 ± 4.0 ($p < 0.05$),

while this index was equal to:

1) 0.2 ± 2.0 – in the control group of healthy subjects ($p < 0.05$);

2) 85.4 ± 3.8 – in patients with syphilis only ($p < 0.01$);

- LDH ($p < 0.05$):

1) in syphilis patients with viral hepatitis B – 385.5 ± 4.3 ;

2) in syphilis patients with viral hepatitis C – 389.1 ± 4.0 ,

while this index was equal to:

1) 341.3 ± 2.8 – in the control group of healthy subjects;

2) 357.1 ± 3.1 – in patients with syphilis only.

The increase of γ -glutamyltranspeptidase was the most significant in both groups of patients with syphilis:

- co-infected with viral hepatitis B – 57.1 ± 3.2 ;

- co-infected with viral hepatitis C – 59.3 ± 2.9 ,

while this index was equal to:

- 20.1 ± 2.1 – in the control group of healthy persons ($p < 0.05$);

- 40.1 ± 2.3 – in patients with syphilis only ($p < 0.05$).

Syphilis patients with viral hepatitis C presented the significant disorders in biochemical indices of blood, which in general were similar to those indices in syphilis patients with viral hepatitis B. Unlike the group of patients co-infected with viral hepatitis B, the patients co-infected with viral hepatitis C presented:

- an increase in total bilirubin – by 5.5 times;

- a decrease in uric acid – by 1.5 times.

The comparative analysis of biochemical parameters in the control group (healthy persons) and in patients with syphilis only revealed disorder of pigment metabolism and increase in transaminase activity, being the most significant in patients with early latent syphilis, the infection duration of more than a year.

In syphilis patients with viral hepatitis B and C we observed an increase in:

- total bilirubin;

- activity of LDH, ALT, AST;

- albumin content.

Disproteinemia was established in patients with early latent syphilis co-infected with viral hepatitis C.

Treatment of syphilis patients was conducted in accordance with the acting normative documents of the Ministry of Health of Ukraine [6, 5]. The following drugs were used:

- Benzathienbenzylpenicillin;
- Penicillin G sodium;
- Penicillin G sodium and immunomodulators.

Lasting medications (benzathienbenzylpenicillin) were used in the treatment of patients with primary syphilis and secondary syphilis with a period of infection attaining duration for 6 months. In the duration of infection from 6 months and up to 12 months, Penicillin G sodium was used.

The effectiveness of treating patients with syphilis was evaluated according to the terms of negating CSR. Terms of CSR negating were on average:

- in patients with primary syphilis treated with prolonged penicillin:

- 1) 5.9 months – for patients with syphilis only;
- 2) 8.8 months – for syphilis patients with viral hepatitis B and C;

Terms of CSR negating were on average:

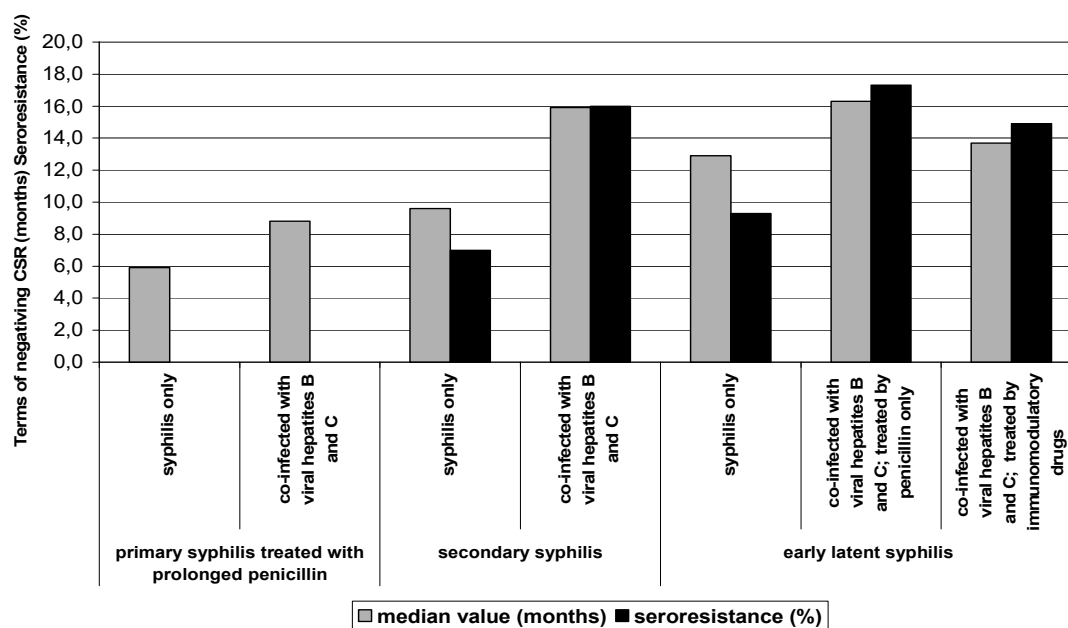
- in patients with secondary syphilis

- 1) 9.6 months – for patients with syphilis only; seroresistance was observed in 7.0% patients;
- 2) 15.9 months – for syphilis patients with viral hepatitis B and C; the seroresistance was observed in 16% patients;

- in patients with early latent syphilis only:

- 1) 12.9 months – for patients with syphilis only; the seroresistance was observed in 9.3% patients;
- 2) 16.3 months – for patients with early latent syphilis co-infected with viral hepatitis B and C, treated with penicillin only; the seroresistance was observed in 17.3% patients;
- 3) 13.7 months – for patients with early latent syphilis co-infected with viral hepatitis B and C, treated with immunomodulatory drugs; the seroresistance was observed in 14.9% patients.

The main results of the treatment are shown on the Figure.



The main results of the treatment

The analysis of studying blood biochemical indices and enzyme activity after the treatment showed pathological changes in liver parenchyma in syphilis patients:

- co-infected with viral hepatitis B and C;
- with an infection period of more than a year.

Patients with early latent syphilis, in the treatment of which immunomodulatory drugs were used, tended to normalize those indices.

CONCLUSIONS

1. Patients with syphilis reveal a disorder of the liver functional capacity already in the early stages of infection.

2. The most significant disorder of the blood biochemical indices and enzyme activity are observed due to the chronic inflammatory process in syphilis patients with viral hepatitis B and C.

3. Based on a long follow-up after the treatment (the results of clinical and serological and biochemical studies) in the treatment of primary syphilis, it is advisable to use benzathine benzylpenicillin. In duration of the infection from 6 to 12 months, the advantage is to prescribe penicillin G, and in duration of the infection for more than 12 months and co-infection with viral hepatitis, it is advisable to prescribe drugs of immuno-regulatory action.

4. Prospects for further research: recent studies have shown that concomitant diseases such as viral hepatitis, chlamydia, genital herpes affect the course of syphilitic infection and can be one of the causes of the seroresistance. Further study of this topical issue of modern syphilology will provide an opportunity to propose more effective treatment methods.

Conflict of interests. The authors declare no conflict of interest.

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