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

Dnipro State Medical University
V. Vernadsky str., 9, Dnipro, 49044, Ukraine

Abstract. 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. Zakharov S.V., Zakharov V.K., Gorbuntsov V.V. The 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 hepatites 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 hepatites B and C before and after treatment. Test methods: hepatology, rheogepathography, 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 hepatites 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 hepatites 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 hepatites 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.

Key words: functional state of the liver, results of treatment, syphilis, viral hepatitis B, viral hepatitis C

Цитування
Cited: Medicni perspektivi. 2021;26(3):107-113
https://doi.org/10.26641/2307-0404.2021.3.241971

REFERENCES

M.M. Zaitseva, T.I. Ruzhnyva, V.S. Balanaky, V.B. Voronov, V.V. Gorbuntsov
Dnipro State Medical University
V. Vernadsky str., 9, Dnipro, 49044, Ukraine

e-mail: dsma@dsma.dp.ua

UDC 616.972+616.36-002:616.98:578[0074.616.15]
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 hepatites 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 hepatites B and C urgent enough [2, 12].

Nowadays, since the mid-1990s, the number of cases of viral hepatites 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 monoinfection: quite often in patients with syphilis other sexual transmitted infections (STIs) (clamidiosis, HIV, viral hepatites 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 hepatites 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 hepatites 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 hepatites 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 hepatites, 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 hepaties 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 hepatites 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).
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 %
- $T_{35}$ 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 ($T_{\text{max}}$):
- $T_{35}$ 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 hepatites $B$ 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 hepatites $B$ 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 hepatites $B$ 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 hepatites, 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 hepatites 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 \((6.5\pm0.1)\) while the norm was \(3.5\pm0.1, \(p<0.01\)\);
- in syphilis patients with viral hepatites B and C \((8.7\pm0.2)\) vs. \(6.5\pm0.1\) in patients with syphilis only, \(p<0.05\).

The sublimte 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 hepatites B and C \((80.5\pm1.0\) and \(73.2\pm2.1\)\) to \(6\pm2\) – 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±2.0;
- \(K_2\) – 75.5±2.5.

The albumin concentration was significantly lowered both:
- in patients with syphilis only \((p<0.01)\):
  1) \(K_1\) – 60.0±2.4;
  2) \(K_2\) – 53.2±1.1;
- and in patients co-infected with viral hepatites \((p < 0.05)\):
  1) \(K_1\) – 53.2±1.1;
  2) \(K_2\) – 47.0±1.0.

On the part of the globulin fraction, the most significant changes were revealed in the \(\alpha_2\) and \(\beta\) fractions, both:
- in the K-2 group \((p<0.01)\):
  1) fraction \(\alpha_2\): \(K_1\) – 7.0±0.3; \(K_2\) – 10.7±0.2;
  2) fraction \(\beta\): \(K_1\) – 9.1±0.2; \(K_2\) – 12.4±0.3;
- and in the group of patients co-infected with viral hepatites B and C \((p<0.01)\):
  1) fraction \(\alpha_2\): \(K_1\) – 10.7±0.2; \(K_2\) – 14.3±0.2;
  2) fraction \(\beta\): \(K_1\) – 12.4±0.3; \(K_2\) – 16.1±0.3.

The concentration of \(\gamma\)-globulin was the highest one:
- in patients with a history of infection exceeding 1 year – up to \((24.2\pm1.8)\%\);
- in patients co-infected with viral hepatites B and C – up to \((30.3\pm2.1)\%\);
- in patients of the group \(K_1\) – up to \((17.9\pm1.5)\%\).

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 \(\gamma\)-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:
  1) 20.1±2.1 – in the control group of healthy persons \((p<0.05)\);
  2) 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 hepatites \(B\) and \(C\) we observed an increase in:
- total bilirubin;
- activity of LDH, ALT, AST;
- albumin content.

Disproteoinemia 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:
- Benzathine benzylpenicillin;
- Penicillin G sodium;
- Penicillin G sodium and immunomodulators.

Lasting medications (benzatin benzylphenicillin) 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 negativing CSR. Terms of CSR negativing 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;

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

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 hepatites 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.

Terms of CSR negativing were on average:
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 hepatites B and C; the seroresistance was observed in 16% patients;
3) 12.9 months – for patients with syphilis only; the seroresistance was observed in 9.3% patients;
4) 16.3 months – for patients with early latent syphilis co-infected with viral hepatites B and C, treated with penicillin only; the seroresistance was observed in 17.3% patients;
5) 13.7 months – for patients with early latent syphilis co-infected with viral hepatites B and C, treated with immunomodulatory drugs; the seroresistance was observed in 14.9% patients.

The main results of the treatment

The main value (months) seroresistance (%)

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 hepatites 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 benzathinebenzylpencillin. 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 hepatites, 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.

REFERENCES

1. Antomonov MYu. [Mathematical processing and analysis of biomedical data]. 2nd ed. Kyiv; 2017. p. 578. Russian.
2. Zakharov SV, Zakharov VK. [Syphilis and the liver]. Dermatovenerologiya. Kosmetologiya. Seksopatologiya. 2015;1-2:81-85. Ukrainian.
3. Kamysnikov VS. [Clinical laboratory diagnostics (methods and interpretation of laboratory studies)]. Moskva: MEKolinform; 2015. p. 720. Russian.
4. Polukhina EV, Glazun LO. [Rheographic methods for studying the vascular system]. Tutorial. Khabarovsk: Institute for Advanced Training of Health Professionals; 2006. p. 98. Russian.
5. [On the approval of clinical protocols of granting medicare to the patients with the dermatological diseases. Order of the Ministry of Health of Ukraine dated 08.05.2009 No. 312]. Ukrainian. Available from: https://zakon.rada.gov.ua/rada/show/v0312282-09#Text
6. [On improvement of dermatological help to the population of Ukraine]. Order of the Ministry of Health of Ukraine dated 07.06.2004 No. 286]. Ukrainian. Available from: https://zakon.rada.gov.ua/rada/show/v0286282-04#Text
7. Radionov DV. [Seroresistance after treatment of syphilis and some reasons for its oc-currence]. Ukrainskyi zhurnal dermatolohii, venerolohii, kosmetolohii. 2014;1(52):7-13. Russian.
8. Rebrova OYu. [Statistical analysis of medical data. Application of Statistica applications]. Moskva: Mediasferа; 2018. p. 312. Russian.
9. [Modern approaches to laboratory diagnosis of syphilis. Guidelines. Order of the Ministry of Health of Ukraine dated 22.11.2013 No. 997]. Ukrainian. Available from: https://zakon.rada.gov.ua/rada/show/v0997282-13#n11
10. Seha AC, Zhang X-H, Li T, Zheng H-P, Yang B, Yang L-G, Salazar JC, Cohen MS, Moody MA, Radolf JD, Tucker JD. A systematic review of syphilis serological treatment outcomes in HIV-infected and HIV-uninfected persons: rethink-ing the significance of serological non-responsiveness and the serofast state after therapy. BMC Infect Dis. 2015;15:479. doi: https://doi.org/10.1186/s12879-015-1209-0
11. Russell NK, Nazar K, Pino S del, Gonzalez MA, Bermúdez XPD, Ravasi G. HIV, syphilis, and viral hepatitis among Latin American indigenous peoples and Afro-descendants: a systematic review. Rev Panam Salud Publica. 2019;43:e17. doi: https://doi.org/10.26633/RPSP.2019.17
12. Pizzarossa AC, Rebella M. Hepatitis in patients with syphilis: an overlooked asso-ciation. BMJ Case Rep. 2019;12(1):bcr-2018-226918. doi: https://doi.org/10.1136/bcr-2018-226918
13. Mutagoma M, Nyirazimyaye L, Sebuhoro D, Riedel DJ, Ntaganira J. Syphilis and HIV prevalence and associated factors to their co-infection, hepatitis B and hepatitis C viruses prevalence among female sex workers in Rwanda. BMC Infect Dis. 2017;17:525. doi: https://doi.org/10.1186/s12879-017-2625-0
14. Zakharov SV, Zakharov VK, Gorbunsov VV. The content of cytokines in the blood serum of patients with early latent syphilis in process of treatment. Medicni perspektivi. 2019;24(3):96-101. doi: https://doi.org/10.26641/2307-0404.2019.3.181889
15. Zhang C, Ren Q, Chang W. Epidemiological Features and Risk Factors for Acquiring Hepatitis B, Hepatitis C and Syphilis in HIV-Infected Patients in Shaanxi Province, Northwest China. Int J Environ Res Public Health. 2020 Mar;17(6):1990. doi: https://doi.org/10.3390/ijerph17061990
16. Angeleri P, Levite V, Vidiella G, Solari J, Corona E, Adaszko D, Adaszko A, Moyano C, Bouchet D, Cuello H, Molfese V, Skarzaukas R, Vila M, Falistocco C, Pando MA. Viral hepatitis and Treponema pallidum prevalence in persons who underwent premarital blood tests in Argentina. Sci Rep. 2019;9:9611. doi: https://doi.org/10.1038/s41598-019-45891-9

СПИСОК ЛІТЕРАТУРИ

1. Антомонов М. Ю. Математическая обработка и анализ медико-биологических данных. 2-е изд. Киев, 2017. 578 с.
2. Захаров С. В., Захаров В. К. Сифиліс і печеніка. Дерматовенерологія. Косметологія. Сексопатологія. 2015. Т. 1-2. С. 81-85.
3. Камышников В. С. Клиническая лабораторная диагностика (методы и трактовка лабораторных исследований). Москва: МЕД-пресс-информ. 2015. С. 720.

4. Полухина Е. В., Глауз Л. О. Реографические методы исследования сосудистой системы, учеб. пос. Хабаровск: Институт повышения квалификации специалистов здравоохранения, 2006. 98 с.

5. Про затвердження клінічних протоколів надання медичної допомоги хворим на дерматологічні захворювання: наказ МОЗ України від 08.05.2009 р. № 312. URL: https://zakon.rada.gov.ua/rada/show/v0312282-09#Text

6. Про удосконалення дерматологічної допомоги населенню України: наказ МОЗ України від 07.06.2004 р. № 286. URL: https://zakon.rada.gov.ua/rada/show/v0286282-04#Text.

7. Радионов Д. В. Серорезистентность после лечения сифилиса и некоторые причины ее возникновения. Укр. журнал дерматол. венерол. Косметол. 2014. Т. 52, № 1. С. 7-13.

8. Реброва О. Ю. Статистический анализ медицинских данных. Применение прикладных программ. Statistica. Москва: МедиаСфера. 2018. 312 с.

9. Сучасні підходи до лабораторної діагностики сифілісу: метод. рек.: наказ Міністерства охорони здоров’я України від 22.11.2013 р. № 997. URL: https://zakon.rada.gov.ua/rada/show/v0997282-13#n11

10. A systematic review of syphilis serological treatment outcomes in HIV-infected and HIV-uninfected persons: rethinking the significance of serological non-responsiveness and the serofast state after therapy / A. C. Seña et al. BMC Infect Dis. 2015. Vol. 15. P. 479. DOI: https://doi.org/10.1186/s12879-015-1209-0

11. HIV, syphilis, and viral hepatitis among Latin American indigenous peoples and Afro-descendants: a systematic review / N. K. Russell et al. Rev Panam Salud Publica. 2019. Vol. 43. P. e17. DOI: https://doi.org/10.26633/RPSP.2019.17

12. Pizzarossa A. C., Rebella M. Hepatitis in patients with syphilis: an overlooked asso-ciation. BMJ Case Rep. 2019. Vol. 12, No. 1. P. bcr-2018-226918. DOI: https://doi.org/10.1136/bcr-2018-226918

13. Syphilis and HIV prevalence and associated factors to their co-infection, hepatitis B and hepatitis C viruses prevalence among female sex workers in Rwanda / M. Mutagoma et al. BMC Infect Dis. 2017. Vol. 17. P. 525. DOI: https://doi.org/10.1186/s12879-017-2625-0

14. Zakharov S. V., Zakharov V. K., Gorbuntsov V. V. The content of cytokines in the blood serum of patients with early latent syphilis in process of treatment. Медичні перспективи. 2019. Т. 24, № 3. С. 96-101. DOI: https://doi.org/10.3390/ijerph17061990

15. Zhang C., Ren Q., Chang W. Epidemiological Features and Risk Factors for Acquiring Hepatitis B, Hepatitis C and Syphilis in HIV-Infected Patients in Shaanxi Province, Northwest China. Int J Environ Res Public Health. 2020. Mar. (Vol. 17, No. 6). P. 1990. DOI: https://doi.org/10.3390/ijerph17061990

16. Viral hepatitis and Treponema pallidum prevalence in persons who underwent premarital blood tests in Argentina / P. Angeleri et al. Sci Rep. 2019. Vol. 9. P. 9611. DOI: https://doi.org/10.1038/s41598-019-45891-9

Стаття надійшла до редакції 21.04.2021