# THE "ADITTIVE" OR "INTERFERENCE" EFFECT OF THE VHC WITH THE HSV TYPE I, II IN PATIENTS WITH CHRONIC HEPATITIS C?

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***Rezumat***

***Efectul aditiv sau de interferenţă dintre VHC şi HSV I, II la pacienţii cu hepatită cronică virală C, asociată cu infecţia herpetică***

*Cercetările recente sugerează că infecţia herpetică, dezvoltând o stare de imunodeficit, influenţează evoluţia hepatitei cronice virale C. Totodată, hepatita cronică C, influenţând bilanţul Th1/Th2, poate favoriza reactivarea infecţiei herpetice latente. În sudiu au fost înrolaţi 144 bolnavi cu hepatită cronică virală C: 103 – HVC fără HSV I, II şi 41 HVC cu HSV I, II. La pacienţii cu dublă infecţie s-au depistat corelaţii între nivelul anticorpilor anti-HSV I, II şi activitatea AST şi ALT, dintre anti-HSV I, II Ig M şi VHC (NS5). Au fost depistate corelaţii directe între ALT şi IgG; AST şi IgG; IgM şi corelaţii indirecte între ALT şi $CD4^{+;}$ $CD3^{+}$; AST şi $CD4^{+}$. Pentru toţi pacienţii, HCV/HSV I, II + VHC a fost depistat în reactivare, ceea ce ne sugerează ideea că HSV I, II ar fi un factor de risc pentru progresia hepatitei cronice. Rezultatele studiului nostru denotă corelaţii vizibile biochimico-imunologice la pacienţii cu dublă infecţie, explicându-se posibil prin acţiune de interstimulare (efect aditiv) între VHC şi HSV I, II.*

***Cuvinte-cheie**: efect aditiv, hepatita C*

***Резюме***

***Взаимодействие ВГС и герпесной инфекции у больных с хроническим гепатитом С***

*Изучение механизма взаимодействия между различными системами при таких широко распространенных сочетанных патологиях, как гепатит С и HSV-инфекция является актуальной проблемой, решение которой позволит вскрыть патогенетические особенности процесса. Сегодня не вызывает сомнения, что клинические варианты, тяжесть заболевания и прогноз во многом зависят от иммунного ответа на внедрившийся вирус. Цель работы – в сравнительном аспекте установить характер совместного течения хронического гепатита С и HSV I, II их клинико-имунологическую симптоматику. Результаты: У больных HCV/HSV I, II имеет место дисфункция иммунной системы, проявляющаяся дефицитом клеточного (снижение абсолютного содержания в крови CD3- CD4-, CD8-, CD 16-клеток) и активацией гуморального звеньев иммунитета, угнетением функциональной активности лейкоцитов. что свидетельствуют о потенцирующем взаимовлиянии этих двух нозологических форм.*

***Ключевые слова**: герпесная инфекция, гепатит С*

## Introduction

The association between liver diseases and other infectious diseases represents one of the most actual research topics. Analyzing the information contained in specialized publications regarding viral associations, it has been proven that these associations determine a pathology with a more severe evolution, for a longer period of time and on which background, usually, other complications may occur [2, 3,4]. The interaction between two viruses in the organism may develop as either an inter stimulation action

(*additive effect*) or removal of one virus by the other one (*interference effect*) [9].

It has been proven that that the seropositive individuals for HSV I, II and those with genital ulcerative diseases present a higher risk in getting the infection with VHC [5, 6, 7]. The recent researches suggest that the herpetic infection, by creating a specific state of immunodeficiency, may hasten the evolution of the viral chronic hepatitis C [3, 9]. In turn, the viral chronic viral hepatitis C, as alternates the balance Th1/Th2, would create favorable circumstances for the reactivation of the latent herpetic infection. Most previous studies have focused on alternative hypothesis, which is whether herpes virus infections promote HCV replications and thereby results in accelerated progression of liver disease due to HCV (especially on HCV positive liver transplant recipients) [9].

**Objectives**

- To assess the biochemical- immunological particularities of patients with chronic hepatitis C associated with HSV type I and II compared with patients with chronic hepatitis C with HSV – negative.
- To evaluate the correlations between biochemical parameters and humoral and cellular immunological indicators of patients with chronic hepatitis C HSV I, II positive compared with patients with chronic hepatitis C HSV I, II negative.

**Material and methods**

The clinical material has been selected based on the Clinic Republican Hospital during 2002–2005. There were 144 patients enrolled in the research, having chronic hepatitis of C viral etiology, from different regions of the country, who were divided in two groups (depending on the presence or absence of the herpetic infection, type I, II): 103 patients with viral chronic hepatitis C, without the herpetic infection; 41 patients with viral chronic hepatitis C, in association with the herpetic infection type I, II. At the same time, in this research have been included: 20 more patients with the herpetic infection type I, II and 20 people served as healthy group.

Before giving the hepatitis diagnosis, a complex of laboratory: biochemical parameters, serological markers (antibodies anti VHC Ig G, anti VHC Ig M, ARN VHC quantitative; and anti HSV I+II Ig G and Ig M), parameters for humoral and cellular immunological status and instrumental researches were performed. The value of the indices' immune parameters was used to determine the degree and the type of immune disorders using the absolute value T lymphocytes - CD3, CD 4, CD8 (Zemskii A.) [1, 8]: (***the indicator value of a patient/the indicator value of a healthy person) – 1 x 100.*** If the obtained value is negative, marked with a "-", then the patient has immune insufficiency. If the patient's result is marked with "+", it stands for the hyper function of the immune system.

± 1-33% – immune disorders, 1st degree; 34-66% – immune disorders, 2nd degree; 66% or more – immune disorders, 3rd degree.

**Results**

To the patients with chronic hepatitis C in association with the HSV I, II were identified of biochemical changes which are being noticed by the increased activity of the AST and Rittis index at 1/2 of the patients. There have been recorded differences of ALT and AST values, depending on the phase of the herpetic infection, so in the active phase of the herpetic infection (n=33) there have been obtained higher levels of ALT ($p<0.05$), AST ($p<0.05$), versus the patients with the herpetic infection in the inactive phase.

The evaluation of the parameters that illustrate the activity of the humoral immunity in the group of patients with chronic hepatitis C in association with the HSV type I and II, highlighted the following ideas:

- From the concentration of different groups of immunoglobulin, it's distinguished a more specific variation for the groups Ig A and Ig G; the concentration of IgA was high at the patients with mixed infections, overcoming 1.2 of the analogic parameter at the patients with VHC (mono infection), $p<0.05$ and 1.5 of those patients from the healthy group, $p<0.01$.
- The variations of the serum level of Ig G were obvious, this way an increased value of this factor was recorded at the patients with mixed infections, versus those with mono infection, $p<0.05$ and from the healthy group, $p<0.05$.
- The absolute value of $CD20^+$ lymphocytes at the patients with VHC+HSV I, II has the tendency to grow, being considered as high for more than half of the patients.
- The leukocyte /B lymphocyte ratio at the patients with associated infections, constituted -16.9 ± 2.07, having differences statistically veracious with a homonymous factor from the healthy group people - 29.1 ± 0.25, $p<0.001$.
- The immunoreglator index (CD3/CD4) at the patients with chronic hepatitis C and HSV I, II constituted 1.6 ± 0.14 compared with the same index in patients with chronic hepatitis C without HSV I, II – 4.08 ± 0.23.

According to our date, we suggest using the leukocytes/B-lymphocytes ratio and immunoreglator index are a simple indicators of immunoseverity

in patients with chronic hepatitis C associated with HSV I, II.

The patients with viral chronic hepatitis C in association with the HSV I, II developed a deficiency of T lymphocytes, not only taking them from the T-helpers (CD4) but also T-suppressors (CD8).

- Between the characteristic parameters of the patients with VHC with HSV I, II and those with VHC, have been proven statistical differences regarding the absolute number of T $CD3^+$. T $CD3^+$ was 1.7 times lower at the patients with VHC + HSV I+II than at the patients with mono infection.
- T $CD4^+$ at the patients with VHC + HSV I, II recorded lower values than at the patients with HCVC, $p<0.01$ as well as versus the healthy group, $p<0.05$.

In the chronic viral C hepatitis associated with the HSV I, II, a 2nd degree immune disorder is determined, associated with immunodeficiency, manifested by the deficiency of T total lymphocytes and the subpopulations T $CD4^+$, T $CD8^+$, and the immunoreglator factor. In the VHC mono infection was found a 2nd degree immune disorder type immune stimulation, manifested by the increased of T total lymphocytes, the T $CD4^+$and B- lymphocytes and immunoreglator index.

After analyzing the given data, at the patients with HCVC associated with HSV I, II was established a correlations between level anti HSV I, II Ig M with activity of AST ($r=0.65$, $p<0.001$) and ALT ($r=0.86$, $P<0.01$). It's notable the interrelation between the anti HSV I, II Ig M with the non-structured part of the virus C (NS5) ($r=0.44$ $p<0.01$).

The character of the immunologic and biochemical parameters' interrelation in the viral C hepatitis associated with the herpetic infection type I and II, caught our eye. This way, there have been found direct correlations between ALT and AST with humoral immunologic parameters, as ALT and Ig G ($r=0.62$, $p<0.01$) and AST with Ig G ($r=0.59$ $P<0, 01$) and with Ig M ($r=0.51$, $p<0.01$). There have been found indirect correlations between the levels of biochemical markers and the absolute value of the immune competent cells: ALT with $CD4^+$ ($r=-0.36$ $p<0.05$), $CD3^+$ ($r=-0.49$, $p<0.01$), AST with $CD4^+$ ($r=-0.48$ $p<0.05$), $CD3^+$ ($r=-0.42$, $p<0.01$). Our research highlights that for all the patients with HCV C +HSV I, II VHC is in a reactivation phase, which makes us concern that the herpetic infection might hurry the evolution of the chronic C hepatitis.

**Discussions**

Our study is the first research effectuated in the Republic of Moldova regarding the interaction between VHC and HSV I.II, evaluated from the expressivity of liver biochemical syndromes, by evaluating the complete immunogram. Our research highlights that for all the patients with chronic hepatitis C associated with HSV I and II, the virus C is in a reactivation phase, which suggest that the herpetic infection does appear to promote VHC reactivation. This phenomenon has been called "*cofactor type interrelation*". The analysis of laboratory data highlights some of the particularities that differentiates chronic hepatitis C (mono infection) from the chronic hepatitis C associated with HSV I, II. This way, the parameters of the cytolysis are more pronounced at the patients with associated infections than those with mono infection.

Our study demonstrates that latent HSV type I, II infection is correlated with necroinflamatory activity (ALT, AST) among HCV-infected patients. This suggests that a masked HSV type I, II infection may interfere with the clinical outcome of chronic hepatitis C and favor or accelerate the evolution to progression liver disease. Suggestively, our observations showed that latent HSV type I, II infection has some influence on the immunological status of chronic HCV infection and in the promotion of HCV replication. The mechanism behind these interactions are unclear. Viral reactivation may merely be a marker of a more profound immunosuppressed state promoting both HCV and herpes virus reactivation. It is common knowledge that HSV particles may persist for decades after self-limited acute infection and clinical recovery [7, 8, 9]. In addition, infections by HSV are ranging from an asymptomatic subclinical infection in healthy individuals, and to disseminated disease in immunocompromised patients [2, 3, 4].

Our study showed that in patients with chronic hepatitis C associated with HSV I, II developed the immunodeficiency compared with patients without HSV I, II who developed immune disorder type immune stimulation. Alternatively, more specific interactions may exist. The researchers demonstrate that the primary infection by hepatomimetic viruses (HSV, CMV, EBV) is often associated with a vigorous T lymphocyte response [4, 5, 8]. HSV reactivation develop frequently when T lymphocyte-mediated immunity is compromised or HSV may contribute to further T lymphocyte hyporesponsiveness [2, 6, 7].

We suggest that the latent infections by HSV type I, II may play a significant role in the progression of liver disease in HCV-infected patients and may deteriorate the prognosis of those patients in relation with the response to antiviral therapy. Repeated measurements of HSV type I, II infection markers in combination with periodic health examinations of study subjects may provide useful information on

their clinical outcome and identify development and progression of liver diseases in HCV infected patients.

**Conclusions**

In the chronic viral C hepatitis associated with the HSV type I and II, a 2nd degree immune disorder is determined, associated with immunodeficiency, manifested by the deficiency of T total lymphocytes CD3 and the subpopulations T $CD4^+$, T $CD8^+$, and the immune regulator factor; leukocyte/ B- lymphocyte factor. It is visible the presence of a correlation between immunological response and biochemical processes that take place in the liver at the HCVC+HSV I, II patients, possibly as a result of the inter stimulation (additive) effect between VHC with HSV.

The research of herpes virus infection type I, II in chronic hepatitis C patients is important because of at least 2 reasons: the diagnosis and the precocious treatment of this disease, which would prevent any other complications to the patients with VHC; and the patients with the infectious pathology detected may serve as target for the screening of chronic viral C hepatitis patients.

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