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ETIOLOGIC FACTOR IN THE DEVELOPMENT OF MYOCARDITIS IN THE KHARKIV REGION

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According to the research conducted in the last decade, there has been growth in the non-coronary disease infarction among all cardiovascular diseases, and their share among the causes of temporary or persistent disability, invalidism and deaths are steadily increasing.

The prominent place among all non-coronary heart diseases is taken by myocarditis, which predominantly affects young people of working age (30-40 years old). According to the bibliography, the prevalence of myocarditis is 20% of the non-coronary heart lesions and by different authors 5 - 11% of the total amount of diseases of the cardiovascular system. To date, there are no clear criteria of infectious myocarditis, which is associated not only with numerous etiological factors and the diversity of clinical implications of the disease. It is widely accepted that myocarditis is natural complication of infectious diseases in which any infectious agent may be the etiological factor [1, 2, 3]. However, at the present stage bacterial pathogens are inferior to viral [4]. The etiologic factor in the development of myocarditis can be any infectious agent, but viruses are considered the most common cause of myocarditis.

In recent years, particular attention has been given to clarify the exact etiology of myocarditis because further patient monitoring and treatment success depends largely on it [5, 6].

Until recently, Cocksackie virus of group A, B was considered the most cardiotropic [7, 8]. However, the role of enteroviruses has been recently reviewed in favor of persisting viruses and especially family Herpesviridae [9, 10]

The nature of viruses that can cause damage to the myocardium is varied. According to the result of endomyocardial biopsy, frequency of virus detection in myocardium, by to different authors, ranges from 3 to 60% [11].

Optimization of myocarditis diagnosis using noninvasive tests will not only reveal the true extent of the disease but may also enable to examine viral myocarditis as a much more common pathology than it seems at present and will increase understanding of the significance of this pathology in the cardiovascular continuum.

The aim of the paper is to establish the presence of cardiotropic viruses (HSV1,2, VZV, EBV, CMV, HHV6, HEV A, HEV B, ECHO, HAdV) in biological

fluids of patients with subacute (2 to 6 months) and chronic (more than 6 months) forms of infectious myocarditis as the main factor of chronic myocarditis development; set viral nature of chronic and subacute myocarditis based on the results of endomyocardial biopsy (EMB).

Material & methods. 87 people diagnosed with infectious myocarditis (IM), who were receiving outpatient and / or inpatient treatment in hospitals of Kharkiv were examined. The average age of the main group was (27 ± 7,4) years old. The main group of subjects was divided into two subgroups. The first subgroup comprised 44 patients in subacute myocarditis (SM) (disease duration from 2 to 6 months), the second - 43 patients with chronic myocarditis (CM) (over 6 months), including chronically recurrent or primary chronic myocarditis. The diagnosis was established according to the recommendations of the Association of Cardiologists of Ukraine and experts of the European Society of Cardiology, in accordance with the definitions of disease formation in the International Classification of Diseases (ICD-10) in the tenth revision. The control group involved 40 healthy people of the same age of patients surveyed major groups.

Blood and other biological fluids were subject to examination. Patients of the main group have also had their biopsy material, obtained as a result of endomyocardial biopsy, and pericardial fluid, derived as a result of diagnostic and therapeutic puncture under hydro pericarditis, examined. EMB was obtained for analysis in polymerase chain reaction (PCR) from 17 patients (median left ventricular ejection fraction - 35.0%, range - from 9% to 59 %) (ML «Synevo»). PCR was performed to determine the genomic sequence of enterovirus (HEV), adenovirus (HAdV), human cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), human herpes virus 6 (HHV6) and influenza A viruses and B, Varicella-Zoster virus (VZV), enteric cytopathogenic human orphan virus (ECHO).

The results are statistically processed on the computer with standard software Excel and Statistica 6.

Results. According to epidemiological data, etiology of viral myocarditis has changed much within the last 70 years: the proportion of enterovirus myocarditis is steadily decreasing and the so-called non-enterovirus diseases: adenoviruses, hepatitis C and herpesvirus are increasing. Our research confirms the global trend of reducing the role of enteroviruses in infectious myocarditis (Fig. 1).

In the course of this investigation, herpesvirus markers in biological material from patients in the form of mono-infection or mixed infections were found in 67 patients with myocarditis, which amounted to 87%. While in the control group, similar markers have been found only in 9 patients or in 22.5% of cases. Herpesvirus detection rate is almost 7 times the allocation of other viruses in the IM.

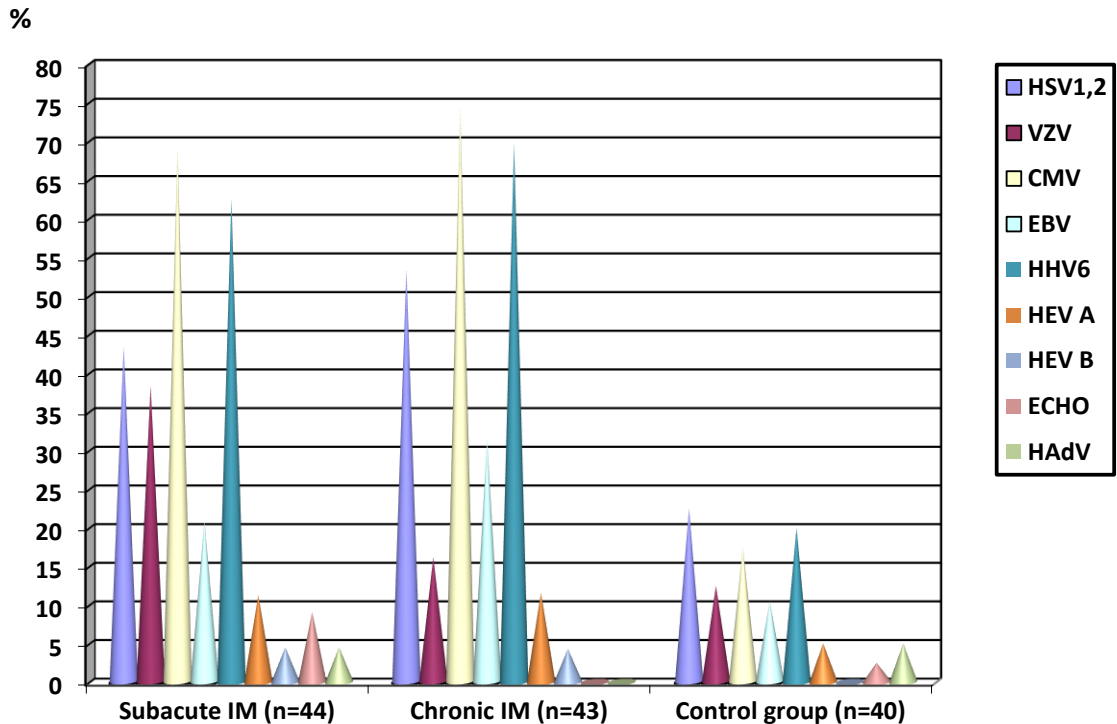


Figure 1 – Identifying markers of cardiotropic virus in patients with infectious myocarditis

Different types of herpesvirus with varying frequency were found in the main (SM and CM) and control groups. According to our data, antigens of CMV, HHV6 were found in 60-70% of patients suffering from subacute myocarditis, and almost 40% of patients in this group had markers HSV1,2 and VZV. In patients with chronic myocarditis the percentage of CMV and HHV6 markers identification reached 70-75%, HSV1,2 -

exceeded 50%, EBV - 31,4%. While VZV markers did not much exceed the performance of the control group (16.2% and 12.5% respectively). Determining markers of enteroviruses in the study groups and the control group were not significantly different.

In most cases, the infection by two or more viruses is marked. As shown in Figure 2, in patients with myocarditis combination of AG of different types of herpesvirus prevails.

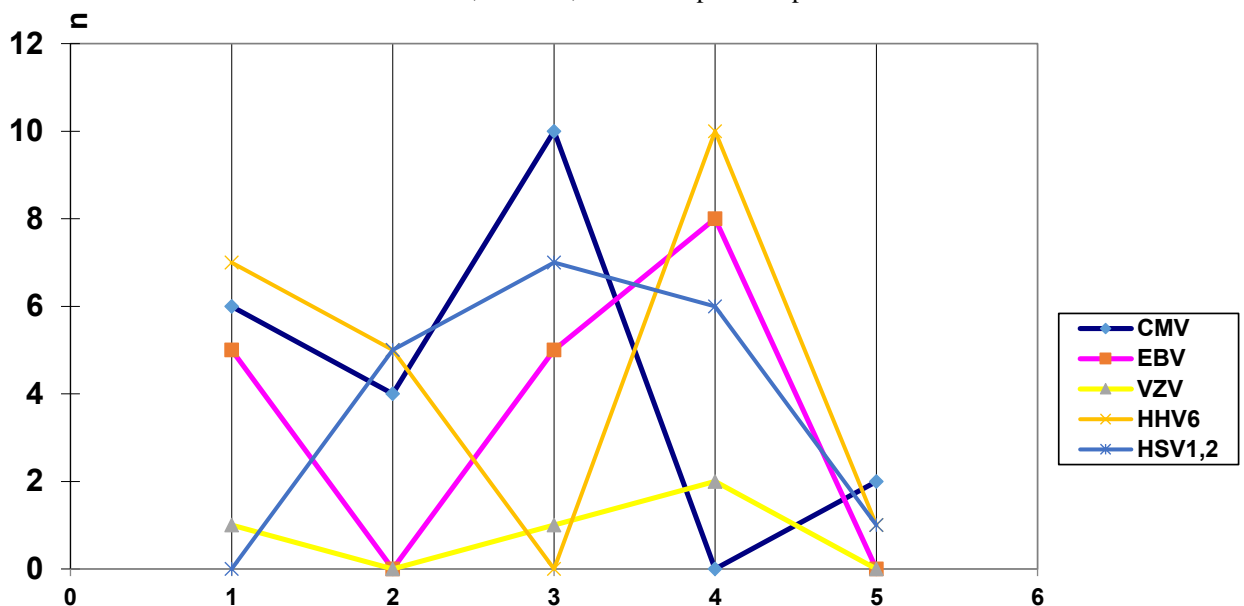


Figure 2 – Combination of antigens of different types of herpesvirus infection in patients with myocarditis

Our data detection of mixed infections indicates a very significant (75%) share of the combination of five different herpesvirus in patients with myocarditis. It is

predominantly a combination of HHV6 with CMV, HSV1,2, EBV and VZV. 63% of cases of herpesvirus antigens detection is presented by a combination of three (30%), four (31%) and five (2%) viruses in the vast

majority in patients with chronic myocarditis. The data can be used not only to choose the etiotropic treatment of myocarditis, but also as a diagnostic criteria when combined with a history of clinical indicators.

In comparison of herpesvirus DNA detection in patients with SM in blood and biopsies (Fig. 3), it was revealed that markers of CMV and HHV6 were almost equally met both in blood and in heart biopsies. Viruses

HSV1,2 and VZV were more often detected in the blood than in the EMBS (3 and 1.5 times respectively). This gives reason to believe that the identification of herpesvirus markers in the blood of patients with SM can be used for non-invasive etiological diagnosis of subacute viral myocarditis.

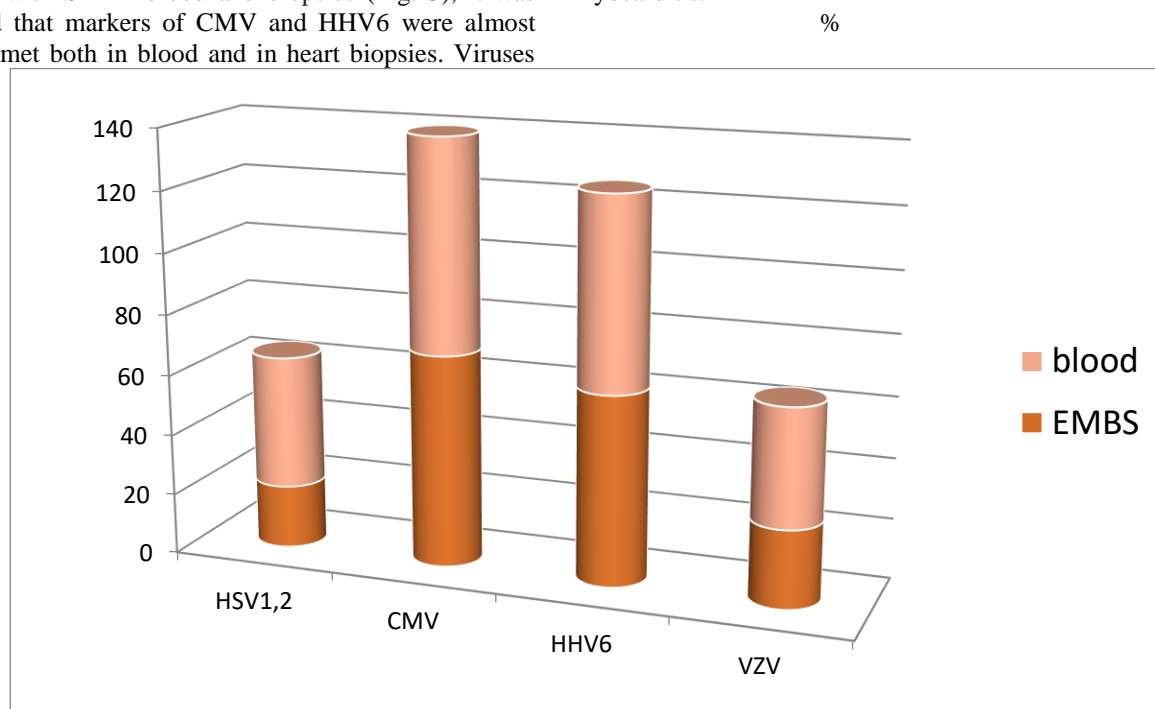


Figure 3 – Comparison of herpesvirus DNA detection in patients with SM in blood and EMBS

Viral genomes are often found in biopsies of patients with infectious myocarditis. The data show that the persistence of different viruses may play a role in the pathogenesis of subacute viral myocarditis much more frequently than it was thought until now. Development and introduction into medical practice of new non-invasive methods of myocarditis diagnosis and their etiology specification will enable to examine viral myocarditis as a much more common pathology than it would seem.

Conclusion. To conclude, the investigation has shown that:

1) during virological examination of biological material of myocarditis patients, a high proportion (87%) of antigens of Herpesviridae viruses were revealed;

2) in patients with myocarditis, association of herpesvirus antigens of various types (in 75% of detection) dominate, while in healthy people of the control group - mono infection can be detected more often;

3) chronic myocarditis patients in 61% of cases are detected with three or four antigens of viruses of the family Herpesviridae, basically HHV6 with CMV, HSV1,2, EBV; with subacute myocarditis – HHV6 with CMV, HSV1,2 and VZV;

4) the findings point to the need for mandatory examination for Herpesviridae virus of patients diagnosed with myocarditis.

References:

1. Maze, S. S. Myocarditis: unresolved issues in diagnosis and treatment [Text] / S. S. Maze, R. J. Adolph // Clin. Cardiol. – 1990. – V. 13 (2). – P. 69 – 79.
2. Lamparter, S. Acute parvovirus B19 infection associated with myocarditis in an immunocompetent adult [Text] / S. Lamparter // Hum. Pathol. – 2003. – V. 34, № 7. – P. 725 – 728.
3. Gaaloul, I. Sudden unexpected death related to enterovirus myocarditis: histopathology, immunogistochemistry and molecular pathology diagnosis at post-mortem [Text] / I. Gaaloul // BMC Infect. Dis. – 2012. – V. 12. – P. 212.
4. Dennert, R. Acute viral myocarditis [Text] / R. Dennert, H. L. Crijns, S. Heymans // Eur. Heart J. – 2008. – № 29. – P. 2073 – 2082.
5. Rose, N. R. Viral damage or «molecular mimicry» – placing the blame in myocarditis [Text] / N. R. Rose // Nat. Med. – 2000. – V. 6. – P. 631 – 632.
6. Aoyama, N. National survey of fulminant myocarditis in Japan: therapeutic guidelines and long-term prognosis of using percutaneous cardiopulmonary support for fulminant myocarditis (special report from a scientific committee) [Text] / N. Aoyama, T. Izumi, K. Hiramori // Circ J. – 2002. – V. 66. – P. 133 – 144.
7. Orinlus, E. The late cardiac prognosis after Coxsackie-B infection [Text] / E. Orinlus // Acta Med. Scand. – 1968. – V. 183. – P. 235 – 237.
8. Rong, Q. Infection of hepatitis B virus in extrahepatic endothelial tissues mediated by endothelial progenitor cells [Text] / Q. Rong // Virol. J. – 2007. – № 4. – P. 36.

9. Takano, H. Active myocarditis in a patient with chronic active Epstein-Barr virus infection [Text] / H. Takano // *Int. J. Cardiol.* – 2008. – V. 130. – P. 1874 – 1754.
10. Levegue, N. A fatal case of Human Herpes virus 6 chronic myocarditis in an immunocompetent adult [Text] / N. Levegue, C. Boulagnon, C. Brasglet // *Journal of Clinical Virology.* – 2011. – Vol. 52. – P. 142 – 145.
11. Yilmaz, A. Comparative evaluation of left and right ventricular endomyocardial biopsy: differences in complication rate and diagnostic performance. [Text] / A. Yilmaz, I. Kindermann, M. Kindermann // *Circulation.* – 2010. – Vol. 122. – P. 900 – 909.

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Introduction. According to the research conducted in the last decade, there has been growth in the non-coronary disease infarction among all cardiovascular diseases. The prominent place among all non-coronary heart diseases is taken by myocarditis, which predominantly affects young people of working age (30-40 years old). According to the bibliography, the prevalence of myocarditis is 20% of the non-coronary heart lesions and by different authors 5 - 11% of the total amount of diseases of the cardiovascular system. To date, there are no clear criteria of infectious myocarditis. It is widely accepted that myocarditis is natural complication of infectious diseases in which any infectious agent may be the etiological factor. Until recently, Coxsackie virus of group A, B was considered the most cardiotropic. However, the role of enteroviruses has been recently reviewed in favor of persisting viruses and especially family Herpesviridae. Optimization of myocarditis diagnosis using noninvasive tests, will not only reveal the true extent of the disease but may also enable to examine viral myocarditis as a much more common pathology than it seems at present and will increase understanding of the significance of this pathology in the cardiovascular continuum. **Material & methods.** 87 people diagnosed with infectious myocarditis were examined. Blood and other biological fluids were subject to examination. Patients of the main group have also had their biopsy material, obtained in a result of endomyocardial biopsy, and pericardial fluid, derived as a result of diagnostic and therapeutic puncture under hydro pericarditis, examined. PCR was performed to determine the genomic sequence of enterovirus (HEV), adenovirus (HAdV), human cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), human herpes virus 6 (HHV6) and influenza A viruses and B. **Results & discussion.** Our research confirms the global trend of reducing the role of enteroviruses in infectious myocarditis. In the course of this investigation, herpesvirus markers in biological material from patients in the form of monoinfection or mixed infections were found in 67 patients with myocarditis, which amounted to 87%. While in the control group, similar markers have been found only in 9 patients or in 22.5% of cases. Herpesvirus detection rate is almost 7 times the allocation of other viruses in infectious myocarditis. Different types of herpesvirus with varying frequency were found in the

main (SM and CM) and control groups. According to our data antigens of CMV, HHV6 were found in 60-70% of patients suffering from subacute myocarditis, and almost 40% of patients in this group had markers HSV1,2 and VZV. In patients with chronic myocarditis the percentage of CMV and HHV 6 markers identification reached 70-75%, HSV1,2 - exceeded 50%, EBV - 31,4%. While VZV markers did not much exceed the performance of the control group (16.2% and 12.5% respectively). Determining markers of enteroviruses in the study groups and the control group were not significantly different. Our data detection of mixed infections indicates a very significant (75%) share of the combination of five different herpesvirus in patients with myocarditis. It is predominantly a combination of HHV6 with CMV, HSV1,2, EBV and VZV. The data can be used not only to choose the etiotropic treatment of myocarditis, but also as a diagnostic criteria when combined with a history of clinical indicators. In comparison of herpesvirus DNA detection in patients with SM in blood and EMBS, it was revealed that markers of CMV and HHV6 were almost equally met both in blood and in heart biopsies. Viruses HSV1,2 and VZV were more often detected in the blood than in the EMBS (3 and 1.5 times respectively). This gives reason to believe that the identification of herpesvirus markers in the blood of patients with AM can be used for non-invasive etiological diagnosis of subacute viral myocarditis. Development and introduction into medical practice of new non-invasive methods of myocarditis diagnosis and their etiology specification will enable to examine viral myocarditis as a much more common pathology than it would seem. **Conclusion.** During virological examination of biological material of myocarditis patients, a high proportion (87%) of antigens of Herpesviridae viruses were revealed. In patients with myocarditis, association of herpesvirus antigens of various types (in 75% of detection) dominate, while in healthy people of the control group - mono infection can be detected more often. Chronic myocarditis patients in 61% of cases are detected with three or four antigens of viruses of the family Herpesviridae, basically HHV6 with CMV, HSV1,2, EBV; with subacute myocarditis – HHV6 with CMV, HSV1,2 and VZV. The findings point to the need for mandatory examination for Herpesviridae virus of patients diagnosed with myocarditis. **Key words:** myocarditis, Herpesviridae virus, endomyocardial biopsy.