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# ОСОБЕННОСТИ ПОСТВИРУСНОГО СИНДРОМА ХРОНИЧЕСКОЙ УСТАЛОСТИ, АССОЦИИРОВАННОГО С МЯГКИМ КОГНИТИВНЫМ СНИЖЕНИЕМ, У ПАЦИЕНТОВ С АТИПИЧНЫМИ ХРОНИЧЕСКИМИ АКТИВНЫМИ ГЕРПЕСВИРУСНЫМИ ИНФЕКЦИЯМИ

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**Резюме.** Согласно современным представлениям, дисфункциональные изменения в работе иммунной системы оказывают влияние на иммунные процессы в ЦНС, способствуя развитию нейроиммуновоспаления, и тем самым опосредованно влияют на скорость прогрессирования нейродегенеративных процессов. Целью нашего исследования явилось изучение распространенности поствирусного синдрома хронической усталости и когнитивных нарушений (aMCI) среди пациентов, страдающих атипичной, хронической активной герпесвирусной инфекцией (АХА-ГВИ).

Под нашим наблюдением находились 126 пациентов обоих полов в возрасте от 18 до 60 лет, страдающих АХА-ГВИ.

Установлено, что моно-ВЭБ инфекцией страдают 27,7%, микст-ВЭБ инфекция наблюдается у 72,3% пациентов. При оценке когнитивного функционирования с использованием шкал CGI, MMSE выявлена частота встречаемости aMCI – 68,3%: при микст-ГВИ она составила – 87,4%, при моно ГВИ – 38,8%. В процессе исследования были выявлены существенные ограничения в применении использованных стандартных шкал в связи с невозможностью проведения комплексной оценки параметров клинического статуса и когнитивных дисфункций, а также корреляции этих параметров и оценки динамики на фоне проводимой иммунотерапии. Для реализации этой цели на дальнейших этапах исследования была использована разработанная нами Шкала оценки критериальных клинических признаков/симптомов пациентов, страдающих АХА-ГВИ с СХУ. Показано, что при микст-ГВИ выраженность симптомов достоверно превышала выраженность симптомов пациентов с моно-ГВИ и составляла 52,7 (43,1-62,2) и 38,0 (31,9-42,8) баллов соответственно ($p \geq 0,05$). Таким образом было

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установлено, что пациенты, страдающие микст-ГВИ, имеют более выраженные, тяжелые проявления СХУ и aMCI, которые в 1,5 раза превышают аналогичные проявления у пациентов с моно-ГВИ, снижая качество жизни этих пациентов, ухудшая их социальную адаптацию, создавая риск развития психогенной депрессии.

Длительная персистенция герпес-вирусов в организме иммуннокомпрометированных людей создает условия для постоянной антигенной стимуляции и иммунного дисбаланс с дебютом вторичного иммунодефицита или клинической манифестацией имеющихся первичных нарушений в иммунной системе, что создает предпосылки для развития нейроиммувопоспалительных изменений в ЦНС и ПНС с последующим формированием клинических проявлений миелоэнцефалита и синдрома хронической усталости с различными когнитивными нарушениями, которые могут быть классифицированы как мягкое когнитивное снижение.

*Ключевые слова: герпесвирусные инфекции, иммунная дисфункция, синдром хронической усталости, когнитивные расстройства, интерферонопатии, иммунотерапия*

# PECULIARITIES OF POST-VIRAL CHRONIC FATIGUE SYNDROME ASSOCIATED WITH MILD COGNITIVE DECLINE IN PATIENTS WITH ATYPICAL CHRONIC ACTIVE HERPESVIRUS INFECTIONS

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**Abstract.** According to modern ideas, changes in the functioning of the immune system affect the immune processes in the nervous system, contributing to the development of neuro-immuno-inflammation and thereby indirectly affect the rate of progression of neurodegenerative processes. The aim of our study was to investigate the prevalence of post-viral chronic fatigue syndrome and cognitive impairment (aMCI) among patients with atypical, chronic active herpesvirus infections (ACA-HVI).

Under our supervision were 126 patients of both sexes aged 18 to 60 years with ACA-HVI.

It was established that mono-EBV infection affects 27.7%; mixed EBV infection is observed in 72.3% of patients. When assessing cognitive functioning using CGI, MMSE scales, the incidence of aMCI was found to be 68.3%: with mixed HVI – 87.4%, with mono HVI – 38.8%. During the study, significant limitations were identified in the use of standard scales due to the impossibility of conducting a comprehensive assessment of clinical status parameters and cognitive dysfunctions, as well as correlation of these parameters and assessment of dynamics of the immunocorrection. To achieve this goal the Scale of assessment of the criterion clinical symptoms of patients with ACA-HVI with CFS was used. It was shown that in mixed-HVI, the severity of symptoms exceeded the severity of symptoms of patients with mono-HVI and was 52.7 (43.1-62.2) and 38.0 (31.9-42.8) points, respectively ($p \geq 0.05$). Thus, it was found that patients suffering from mixed HVI have more pronounced, severe manifestations of CFS and aMCI, which are 1.5 times higher than similar manifestations in patients with mono-HVI, significantly reducing the quality of life of these patients, worsening their social adaptation.

Prolonged persistence of herpes viruses in immune-compromised people creates conditions for constant antigenic stimulation and immune imbalance with the onset of secondary immunodeficiency or clinical manifestation of existing primary disorders in the immune system, which creates the prerequisites for the development of neuro-immuno-inflammatory changes in nervous system, followed by the formation of clinical manifestations of ME/CFS with different cognitive impairments that may be classified as aMCI.

*Keywords: herpesvirus infections, immune dysfunction, chronic fatigue syndrome, cognitive disorders, interferonopathies, immunotherapy*

## Introduction

In recent years, the prevalence of viruses belonging to the Herpesviridae family has become pandemic [1, 3]. In this regard, the Herpesviridae family study is of great interest in the etio-and immunopathogenesis of some infectious and non-infectious diseases, tending to a chronic progressive course and characterized by torpidity to ongoing standard therapy, the clinical picture of which is often atypical, polysymptomatic and polysyndromic. Possessing pronounced neuro- and immunotropism, herpes family viruses are able to persist for a long time in neuroglial cells, neurons, cells of the immune system, causing the development of chronic systemic and neuroimmune inflammation, clinically accompanied by the meningoencephalitis (ME) symptoms, post-viral chronic fatigue syndrome and immune dysfunction, including signs of amnestic mild cognitive impairment (aMCI) [2, 7, 11, 12, 14, 15]. It is known that one of the aMCI causes is neuroinflammation induced by a viral process of a predominantly integrative type [5, 6, 8, 10]. The leading clinical manifestations of aMCI are: progressive memory impairment, visual-spatial functions, fatigue, rapid exhaustion with little physical and mental stress, emotional lability, and personality changes in general [8].

According to modern concepts, dysfunctional changes in the immune system affect the immune processes in the CNS, contributing to the development of neuro-immuno-inflammation and thus indirectly affect the rate of neurodegenerative progression. Along with this, the results of studies evaluating various parameters of the cellular and humoral parts of the immune system, cytokine profile, interferon system in aMCI are few and often contradictory.

**The aim of our study** was to study the prevalence of aMCI among patients suffering from atypical, active chronic mono and mixed herpesvirus infections (ACA-HVI), as well as to clarify immuno-pathogenetically significant disorders in the mechanisms of immune antiviral defense and the interferon system dysfunction.

## Materials and methods

Study group (SG) included 126 patients of both sexes aged 18 to 60 years, suffering from atypical ACA-HVI. The comparison group (CG) consisted of 30 apparently healthy individuals matched by sex and age with GI patients. The study was approved by the Ethics Commission, and informed consent was obtained from all patients to participate in the study and to process personal data in accordance with the World Medical Association's Declaration of Helsinki (WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, 2013).

**Anamnesis and physical examination**

All Herpes virus (HI) patients were surveyed using questionnaires specially developed by us in order to identify the features of the epidemiological and infectious anamnesis, and identify the main clinical/criteria signs and symptoms of ACA-HVI [4].

Cognitive functioning was assessed by the CGI (Clinical Global Impression) and MMSE (Mini-Mental State Examination) scales [13].

**Laboratory diagnostics**

The study included complex analysis consisting of the traditional methods (history taking, physical examination methods, CBC, etc.), serodiagnostic methods (IgM VCA EBV, IgG VCA EBV, IgM CMV, IgG CMV IgM HSV1 / 2, IgG HSV1 / 2) using ELISA test systems, NPO Diagnostic Systems (Russia), and the PCR method of the AmpliSense test system (Russia) to detect the virus genome in biomaterials (blood, saliva, urine, scrapings from the tonsils and posterior pharyngeal wall). To assess the functioning of antiviral immunity (immunogram, INF-status, etc.) features, flow cytometry and ELISA methods were used. Statistical analysis was performed using the Microsoft Excel 2019, Statistica 2.0 software package.

## Results and discussion

When analyzing the etiological structure of morbidity in the observed groups, we established the frequency of occurrence of mono- and mixed-HVI. It is noteworthy that the Epstein-Barr virus (EBV) was the dominant virus in both groups of patients. According to the data obtained, 27.7% of patients suffered from mono-EBV infection, and 72.3% – from mixed-EBV infection (Figure 1).

In the structure of these infections, combinations of EBV + CMV + HHV type 6 are in the lead (14.7%); EBV+CMV+HSV type 1 (12.4%); EBV + CMV + HSV type 1 + HHV 6 type (12.4%), as well as EBV + HHV 6 type and EBV + HSV type 1 – 8.8% each. Further, the distribution of mixed infections according to the occurrence of combinations is as follows: EBV+CMV (8.8%); EBV+CMV+HSV2, EBV+CMV+ HHV type 6 (14.7%) and rarer combinations (less than 27.3%) (Figure 2).

In the patients suffering from mono- ACA-HVI clinical picture, the leading clinical manifestations of HSV1/HSV2 were vesicular rashes on the skin and mucous membranes of various prevalence and localization. Among the predominant symptoms, subfebrile condition, regional lymphadenopathy, the appearance of chills, headache, hyper- and paresthesias in certain dermatomes, prodromes preceding and accompanying HVI recurrence, as well as the presence of cognitive impairment, sleep disorders, insomnia, and a pronounced decrease in working capacity were identified.

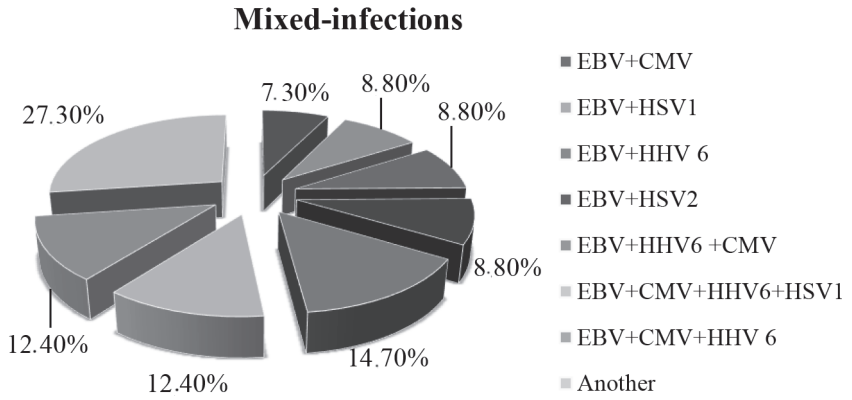


**Figure 1. Etiological structure of mixed EBV infections**

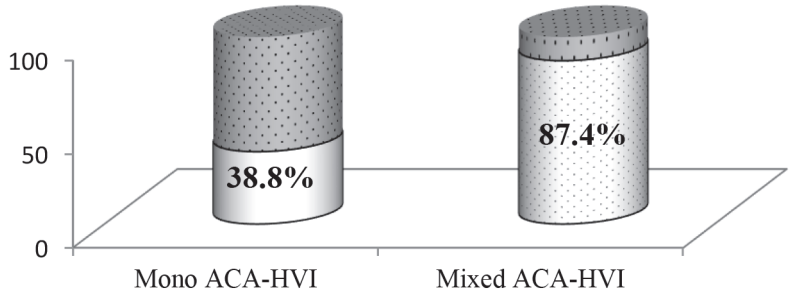


**Figure 2. Frequency of aMCI occurrence in patient groups with mono- and mixed herpesvirus infections (%)**

In patients suffering from mixed ACA-HVI there were more pronounced complaints and clinical manifestations of dysfunction in the CNS, ANS and PNS, that included a prolonged feeling of severe weakness, chronic fatigue, and poor tolerance to adequate physical activity. In addition, patients were worried about excessive sweating, intermittent pain in the throat, in muscles and joints, headaches, subfebrile temperature, lymphadenopathy, sleep disturbance, decreased memory, attention, intelligence (cognitive dysfunction), less often – psychogenic depression.

When assessing cognitive functioning using the CGI (Clinical Global Impression) scale and the Mini-Mental State Examination (MMSE), it was found that in patients with ACA-HVI, the incidence of aMCI was 68.3%. At the same time, in patients with mixed HVI, the incidence of aMCI was higher (87.4%), than in patients with mono HVI (38.8%) (Figure 2).

The SG (patients diagnosed with aMCI) included patients with ACA-HVI who had an MMSE score of ≥ 27 and met the diagnostic criteria for aMCI syndrome at the stage of mild cognitive decline.

It is known that MCI can be an initial stage of many neurodegenerative diseases, established on the results of neuropsychological testing, complaints of cognitive impairment by the patient or his relatives, the absence of significant disturbances in the patient's daily activities, and the exclusion of other causes of cognitive decline. Indicators of neuropsychological scales for aMCI are intermediate between the corresponding age norm and dementia values characteristic.

In our study, the use of these scales was of great diagnostic value in the period of screening assessing amnestic and cognitive impairment in order to identify cognitive dysfunctions that meet the aMCI criteria in CFS. However, these scales had some limitations as they did not allow to assess comprehensive parameters of the clinical status and cognitive dysfunctions, as well as the dynamics and correlation of these parameters against the background of the ongoing integration program for correcting the immune system of immunocompromised patients suffering from ACA-HVI. To achieve this goal, at further stages of the study, we developed the Scale for assessing the criterial clinical signs/symptoms of patients suffering from ACA-HVI with CFS [4].

A comparative assessment of the criterial CFS signs/symptoms severity in patients suffering from

**TABLE 1. COMPARATIVE ASSESSMENT OF THE CRITERIAL CFS SIGNS/SYMPTOMS SEVERITY IN MONO AND MIXED HVI, Me ($Q_{0.25}$-$Q_{0.75}$)**

| Symptom | Mixed HVI | Mono HVI |
|---|---|---|
| **Severe fatigue** | 5.0 (5.0-5.0) | 5.0 (5.0-5.0) |
| **Poor tolerance to adequate exercise** | 5.0 (5.0-5.0) | 5.0 (5.0-5.0) |
| **Prolonged subfebrile condition** | 4.0 (3.5-4.5) | 2.5 (2.0-3.0)* |
| **Pain and discomfort in the throat** | 4.0 (3.5-4.5) | 3.0 (2.5-3.5)* |
| **Excessive sweating, chilliness, sensitivity to cold** | 3.5 (2.5-4.5) | 2.5 (2.0-3.0) |
| **Headache, migraine** | 4.0 (3.5-4.5) | 2.5 (2.0-3.0)* |
| **Regional lymphadenopathy** | 4.5 (4.0-5.0) | 3.5 (3.0-4.0)* |
| **Increased fatigue, decreased productivity** | 5.0 (4.5-5.0) | 3.5 (3.0-4.0)* |
| **Neurological disorders (paresthesia, synesthesia, sensory disorders, low muscle tone, etc.)** | 3.5 (2.5-4.0) | 2.0 (1.4-2.5) |
| **Decreased memory, concentration** | 2.4 (1.5-4.0) | 2.0 (1.0-2.3) |
| **Cephalgia, arthralgia, myalgia** | 3.3 (2.1-4.2) | 2.0 (1.5-2.5) |
| **Sleep disorders (insomnia or increased sleepiness)** | 4.0 (2.5-5.0) | 2.5 (2.0-2.7) |
| **Panic attacks, mood disorders, emotional lability, psychogenic depression, etc.** | 4.5 (3.0-5.0) | 2.0 (1.5-2.3)* |
| **Sum of points** | 52.7 (43.1-62.2) | 38.0 (31.9-42.8)* |

Note. *, significant differences between the parameters of the mono-HVI and mixed-HVI , $p < 0.05$.

mono and mixed herpes virus infections was made (Table 1).

It was shown that in patients suffering from mixed HVI, the severity of symptoms significantly exceeded the severity of symptoms in patients with mono-HVI: 52.7 (43.1-62.2) and 38.0 (31.9-42.8) points, respectively ($p \geq 0.05$). Thus, it was found that patients suffering from mixed HVI have more pronounced, severe manifestations of CFS and aMCI, that were 1.5 times higher than similar manifestations in patients with mono- HVI, significantly reducing patient quality of life, worsening their social adaptation, placing them at risk for the psychogenic depression development.

It is obvious that the presence of an adequate, simple and convenient tool for identifying and assessing the criterial signs/symptoms of CFS helping the doctor assess the existing disorders of the clinical and cognitive status, determine their severity, will allow timely diagnosis of existing disorders, and dynamic assessment of the therapy effectiveness, as well as in a timely manner to include the patient in the increased risk of developing severe cognitive impairment and psychogenic disorders.

According to modern concepts, the progression of neurodegeneration in aMCI is facilitated by a long-term latent activation of the innate immune response mechanisms in the central nervous system (neuroinflammation), one of the causes of which may be the atypical active chronic course of herpes virus infections, mostly with neutrotropism. In the brain with aMCI, pathological activation of microglial cells is noted, their secretion of excessive levels of pro-inflammatory cytokines, free radicals, and the neurotransmitter glutamate, increasing neuronal damage. The relationship between markers of systemic inflammation, individual indicators of immunity and neuroinflammation in aMCI is being studied. It has been shown that the presence of chronic systemic inflammation increases the risk of developing aMCI by 1.5-1.8 times.

## Conclusion

Long-term persistence of viral and bacterial agents in the body of immunocompromised people creates conditions for constant antigenic stimulation. As a result, there is a breakdown of adaptation mechanisms with depletion of immune homeostasis reserves and immune imbalance with the onset of secondary immunodeficiency or clinical manifestation of existing primary disorders in the immune system (congenital immunity errors). All together, it leads to the chronic pathology, allergization of the body, changes in the autoimmune profile of patients, and creates the prerequisites for the neuro-immuno-inflammatory changes in the CNS and PNS, followed by the clinical manifestations of encephalomyelitis and chronic fatigue syndrome (ME/CFS), and various cognitive impairments that can be classified as mild cognitive impairment (aMCI).

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