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PREVALENCE AND SEROLOGICAL ACTIVITY OF HERPESVIRUS INFECTIONS IN PATIENTS WITH RELAPSING–REMITTING MULTIPLE SCLEROSIS

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Abstract.
Background. Persistent herpesvirus infections are increasingly regarded as important environmental factors involved in the pathogenesis of multiple sclerosis. Neurotropic herpesviruses are capable of lifelong latency, periodic reactivation, and modulation of host immune responses, which may contribute to chronic neuroinflammation and demyelination.
Objective. To assess the prevalence and serological characteristics of major herpesvirus infections in patients with relapsing–remitting multiple sclerosis compared with healthy individuals.
Materials and Methods. A total of 120 patients with relapsing–remitting multiple sclerosis (80 women and 40 men, mean age 38 ± 11 years) and 30 age- and sex-matched healthy volunteers were examined. Virus-specific IgM and IgG antibodies to herpes simplex virus types 1 and 2, varicella-zoster virus, Epstein–Barr virus, cytomegalovirus, and human herpesvirus type 6 were determined using enzyme-linked immunosorbent assay. Nonparametric statistical methods were applied.
Results. All patients with multiple sclerosis were seropositive for Epstein–Barr virus, compared with 83% of controls ($p < 0.05$). Elevated IgG titers to Epstein–Barr virus, herpes simplex viruses, and varicella-zoster virus were significantly more pronounced in the multiple sclerosis group. Serological markers of viral reactivation were detected predominantly among patients with multiple sclerosis. In contrast, cytomegalovirus IgG antibodies were more frequently observed in the control group, while human herpesvirus type 6 seropositivity did not differ significantly between groups.
Conclusion. Patients with relapsing–remitting multiple sclerosis demonstrate a higher prevalence and increased serological activity of several herpesvirus infections, even at relatively early stages of the disease. These findings support the role of persistent herpesvirus infections in multiple sclerosis pathogenesis and highlight the importance of comprehensive virological assessment in this patient population.
Key words: multiple sclerosis, herpesviruses, Epstein–Barr virus, seroprevalence, viral persistence, immune dysregulation.

РАСПРОСТРАНЁННОСТЬ И СЕРОЛОГИЧЕСКАЯ АКТИВНОСТЬ ГЕРПЕС-ВИРУСНЫХ ИНФЕКЦИЙ У ПАЦИЕНТОВ С РЕМИТТИРУЮЩИМ РАССЕЯННЫМ СКЛЕРОЗОМ

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Аннотация.

Введение. Персистирующие герпес-вирусные инфекции в последние годы рассматриваются как значимые факторы внешней среды, участвующие в патогенезе рассеянного склероза. Герпес-вирусы обладают выраженной нейротропностью, способностью к пожизненной латенции и реактивации, а также к модуляции иммунного ответа хозяина.
Цель исследования. Изучить распространённость и серологические особенности герпес-вирусных инфекций у больных ремиттирующим рассеянным склерозом в сравнении со здоровыми лицами.
Материалы и методы. Обследованы 120 пациентов с ремиттирующим рассеянным склерозом (80 женщин и 40 мужчин, средний возраст 38 ± 11 лет) и 30 здоровых добровольцев, сопоставимых по полу и возрасту. Методом иммуноферментного анализа определялись вирус-специфические антитела классов IgM и IgG к вирусам простого герпеса 1-го и 2-го типов, вирусу варицелла-зостер, вирусу Эпштейна–Барр, цитомегаловирусу и вирусу герпеса человека 6-го типа. Использовались методы непараметрической статистики.
Результаты. Серопозитивность к вирусу Эпштейна–Барр выявлена у 100% пациентов с рассеянным склерозом и у 83% лиц контрольной группы ($p < 0,05$). У больных рассеянным склерозом отмечались достоверно более высокие титры IgG-антител к вирусу Эпштейна–Барр, вирусам простого герпеса и вирусу варицелла-зостер. Признаки серологической реактивации герпес-вирусов выявлялись преимущественно у пациентов с рассеянным склерозом. Антитела к цитомегаловирусу чаще обнаруживались в контрольной группе, тогда как инфицированность вирусом герпеса человека 6-го типа существенно не различалась.
Заключение. У пациентов с ремиттирующим рассеянным склерозом выявляется более высокая распространённость и серологическая активность герпес-вирусных инфекций, что подтверждает их возможную роль в патогенезе заболевания и обосновывает необходимость дальнейших исследований в данном направлении.
Ключевые слова: рассеянный склероз, герпес-вирусы, вирус Эпштейна–Барр, серопревалентность, персистенция вирусов, иммунная дисрегуляция.

REMISSIYALANUVCHI TARQOQ SKLEROZLI BEMORLARDA GERPESVIRUS INFEKSIYALARINING TARQALISHI VA SEROLOGIK FAOLLIGI

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Annotatsiya.
Kirish. So‘nggi yillarda doimiy (persistiruvchi) gerpesvirus infeksiyalari tarqoq skleroz patogenezida muhim tashqi omil sifatida ko‘rilmoqda. Gerpesviruslar umrbod latent holatda saqlanishi, davriy reaktivatsiyalanishi va immun tizimni modulyatsiya qilish qobiliyatiga ega bo‘lib, surunkali neyroinflamatsiya va demiyelinizatsiya jarayonlariga hissa qo‘shishi mumkin.
Tadqiqot maqsadi. Remissiyalanuvchi tarqoq sklerozli bemorlarda asosiy gerpesvirus infeksiyalarining tarqalishi va serologik xususiyatlarini sog‘lom shaxslar bilan solishtirib baholash.
Materiallar va usullar. Tadqiqotga remissiyalanuvchi tarqoq skleroz bilan og‘rigan 120 nafar bemor (80 ayol va 40 erkak, o‘rtacha yosh 38 ± 11 yil) hamda yoshi va jinsi bo‘yicha mos 30 nafar sog‘lom ko‘ngilli jalb etildi. Qonda oddiy gerpes virusi 1- va 2-tiplari, variatsella-zoster virusi, Epshteyn–Barr virusi, sitomegalovirus va inson gerpes virusi 6-turiga qarshi IgM va IgG antitanachalar immunoferment tahlil yordamida aniqlandi. Statistik tahlilda noparametrik usullar qo‘llanildi.
Natijalar. Tarqoq sklerozli bemorlarning barchasida Epshteyn–Barr virusiga nisbatan seropozitivlik aniqlandi, nazorat guruhida esa bu ko‘rsatkich 83% ni tashkil etdi ($p < 0,05$). Tarqoq sklerozli bemorlarda Epshteyn–Barr virusi, oddiy gerpes viruslari va variatsella-zoster virusiga qarshi IgG titrlari sezilarli darajada yuqori bo‘ldi. Viruslarning serologik reaktivatsiya belgilari

asosan tarqoq sklerozli bemorlarda kuzatildi. Sitomegalovirusga qarshi antitanachalar esa ko‘proq nazorat guruhida aniqlangan.
Xulosa. Remissiyalanuvchi tarqoq sklerozli bemorlarda gerpesvirus infeksiyalarining yuqori tarqalganligi va serologik faolligi aniqlanib, bu holat ushbu viruslarning kasallik patogenezidagi ehtimoliy rolini tasdiqlaydi va chuqurroq tadqiqotlar o‘tkazish zarurligini ko‘rsatadi.
Kalit so’zlar: tarqoq skleroz, gerpesviruslar, Epshteyn–Barr virusi, seroprevalentlik, virus persistensiyasi, immun disbalans.

Introduction. Multiple sclerosis is a chronic immune-mediated demyelinating disease of the central nervous system characterized by inflammation, neurodegeneration, and progressive disability. Despite decades of research, the exact etiology of multiple sclerosis remains incompletely understood. Current pathogenetic concepts emphasize a complex interaction between genetic susceptibility, immune dysregulation, and environmental triggers. Among environmental factors, viral infections-particularly persistent neurotropic viruses-have attracted sustained scientific interest. Herpesviruses, due to their lifelong latency, neurotropism, and capacity for immune modulation, are considered especially relevant in this context.

Members of the Herpesviridae family, including herpes simplex virus types 1 and 2, varicella-zoster virus, Epstein–Barr virus, cytomegalovirus, and human herpesvirus type 6, establish lifelong persistence after primary infection. These viruses can reactivate periodically, often subclinically, and interact with both innate and adaptive immune responses. In recent years, Epstein–Barr virus has emerged as a leading candidate environmental factor in multiple sclerosis pathogenesis. Large epidemiological and immunological studies have demonstrated an almost universal seropositivity for Epstein–Barr virus among patients with multiple sclerosis, significantly exceeding that observed in healthy populations [1]. Elevated titers of antibodies against Epstein–Barr virus nuclear antigens and viral capsid antigens have been associated with an increased risk of disease development and higher disease activity [2].

In addition to Epstein–Barr virus, other herpesviruses may contribute to disease mechanisms through molecular mimicry, bystander activation, epitope spreading, and chronic immune stimulation within the central nervous system. Varicella-zoster virus has been implicated in immune-mediated vasculopathies and demyelinating syndromes, while human herpesvirus type 6 has demonstrated the ability to infect oligodendrocytes and astrocytes, potentially interfering with myelin maintenance [3]. Herpes simplex viruses, although classically associated with mucocutaneous and encephalitic manifestations, may also modulate peripheral and central immune responses through repeated reactivation cycles.

Despite growing evidence, data on the comparative prevalence and serological activity of multiple herpesviruses in patients with multiple sclerosis remain heterogeneous and region-dependent. Differences in population genetics, viral epidemiology, diagnostic methods, and clinical characteristics of patient cohorts complicate interpretation. In Central Asia, and particularly in Uzbekistan, systematic data addressing herpesvirus infections in multiple sclerosis are limited. This gap is clinically relevant, as understanding regional patterns of viral exposure and immune response may inform both pathogenetic hypotheses and individualized therapeutic strategies.

The present study was conducted at the Department of Neurology of Samarkand State Medical University and aimed to investigate the prevalence and serological characteristics of major herpesvirus infections in patients with relapsing–remitting multiple sclerosis in comparison with a healthy control group. Special attention was paid to markers of viral reactivation and to quantitative differences in antiviral IgG titers, which may reflect chronic immune stimulation and persistent antigenic load.

Aim of the Study. The aim of this study was to evaluate the prevalence and serological activity of herpesvirus infections, including herpes simplex virus types 1 and 2, varicella-zoster virus, Epstein–Barr virus, cytomegalovirus, and human herpesvirus type 6, in patients with relapsing–remitting multiple sclerosis compared with healthy individuals.

Materials and Methods. A cross-sectional observational study was performed. One hundred and twenty patients with a confirmed diagnosis of relapsing–remitting multiple sclerosis

were examined. Diagnosis was established according to the revised McDonald criteria, taking into account clinical presentation, magnetic resonance imaging findings, and cerebrospinal fluid analysis when available [4]. The patient cohort consisted of 80 women and 40 men aged from 15 to 63 years, with a mean age of 38 ± 11 years. Disease duration at the time of examination ranged from 1 to 22 years and averaged 8.52 ± 0.79 years. All patients were in a clinically stable phase without signs of acute relapse at the time of blood sampling.

The control group included 30 apparently healthy volunteers matched for age and sex, with no history of demyelinating, autoimmune, or chronic infectious diseases. None of the control participants were receiving immunomodulatory or immunosuppressive therapy.

Venous blood samples were collected from all participants under standardized conditions. Serum was separated and stored according to manufacturer recommendations until analysis. Serological testing was performed using enzyme-linked immunosorbent assay kits to detect virus-specific IgM and IgG antibodies to herpes simplex virus types 1 and 2, varicella-zoster virus, Epstein–Barr virus, cytomegalovirus, and human herpesvirus type 6. All assays were performed using commercially available kits produced by Vector-Best (Novosibirsk, Russian Federation) in accordance with the manufacturer's protocols. Optical density was measured using a calibrated microplate reader, and antibody titers were calculated based on standard curves provided with each kit.

The presence of IgG antibodies was interpreted as evidence of previous infection and viral persistence, while detection of IgM antibodies was considered indicative of recent infection or viral reactivation. For Epstein–Barr virus, antibodies against Epstein–Barr nuclear antigen were specifically analyzed, as they reflect long-term immune memory and cumulative antigenic exposure.

Statistical analysis was carried out using nonparametric methods due to non-normal distribution of most variables. Quantitative data are presented as mean values with standard deviations. Group comparisons were performed using the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Differences were considered statistically significant at $p < 0.05$.

To enhance transparency and originality, summarized comparative data are presented in tabular form, reflecting both prevalence and relative antibody titers.

Results. Serological analysis demonstrated a high overall prevalence of herpesvirus infections in both patients with multiple sclerosis and healthy controls; however, significant quantitative and qualitative differences were observed between the groups.

IgG antibodies to herpes simplex virus types 1 and 2 were detected in 94% of patients with multiple sclerosis and in 90% of individuals in the control group. Although overall seropositivity rates did not differ significantly, IgM antibodies indicative of viral reactivation were identified exclusively in the multiple sclerosis group, where five patients demonstrated positive IgM responses. This finding suggests a higher frequency of herpes simplex virus reactivation among patients with multiple sclerosis, even in the absence of overt clinical symptoms.

Seropositivity for varicella-zoster virus was significantly higher in the multiple sclerosis group compared with controls, reaching 71% versus 50%, respectively ($p = 0.04$). This difference may reflect either increased susceptibility, altered immune response, or more frequent viral reactivation in the context of chronic immune dysregulation.

All patients with multiple sclerosis in the present cohort were seropositive for Epstein–Barr virus, whereas seropositivity in the control group was 83%, a statistically significant difference ($p = 0.034$). Moreover, 14% of patients with multiple sclerosis demonstrated serological markers suggestive of Epstein–Barr virus reactivation. Notably, none of these patients reported a history of clinically apparent infectious mononucleosis, underscoring the likelihood of subclinical or unrecognized primary infection and reactivation episodes.

In contrast, cytomegalovirus IgG antibodies were more frequently detected in the control group than in patients with multiple sclerosis, with seropositivity rates of 90% and 79%, respectively. This difference did not reach statistical significance ($p = 0.17$). Antibodies to human herpesvirus type 6 were found with comparable frequency in both groups, with no significant intergroup differences.

Quantitative analysis of antibody titers revealed pronounced differences. Mean titers of Epstein–Barr virus nuclear antigen IgG antibodies in patients with multiple sclerosis were 3.3 times higher

than those observed in healthy controls. IgG titers to herpes simplex virus types 1 and 2 were elevated 3.6-fold, while varicella-zoster virus IgG titers were increased approximately twofold in the multiple sclerosis group. Conversely, cytomegalovirus IgG titers were 1.5 times lower in patients with multiple sclerosis, and human herpesvirus type 6 IgG titers did not differ significantly between groups.

Table 1. Seroprevalence of Herpesvirus Infections in Patients with Multiple Sclerosis and Healthy Controls

Virus	Multiple Sclerosis, % (n=120)	Control Group, % (n=30)	p-value
HSV-1/2 IgG	94	90	>0.05
HSV-1/2 IgM	4.2	0	–
VZV IgG	71	50	0.04
EBV IgG	100	83	0.034
CMV IgG	79	90	0.17
HHV-6 IgG	Comparable	Comparable	>0.05

Table 2. Relative Mean IgG Antibody Titers in Multiple Sclerosis Compared with Controls

Virus	Relative IgG Titer in MS Group
EBV (EBNA IgG)	3.3-fold higher
HSV-1/2 IgG	3.6-fold higher
VZV IgG	2.0-fold higher
CMV IgG	1.5-fold lower
HHV-6 IgG	No significant difference

Discussion. The results of this study demonstrate that patients with relapsing–remitting multiple sclerosis exhibit a distinct serological profile of herpesvirus infections compared with healthy individuals. While overall exposure to herpesviruses is common in the general population, the magnitude of immune response and frequency of viral reactivation appear to differ substantially in multiple sclerosis.

The universal seropositivity for Epstein–Barr virus observed in our patient cohort is consistent with previous international studies and further supports the hypothesis that Epstein–Barr virus plays a central role in multiple sclerosis pathogenesis [1,5]. Elevated titers of EBNA IgG antibodies likely reflect sustained immune stimulation by latent viral antigens. Mechanistically, Epstein–Barr virus may contribute to disease development through infection of B lymphocytes, promoting their survival, antigen-presenting capacity, and migration into the central nervous system [6]. These infected B cells may serve as a reservoir for chronic immune activation and intrathecal antibody production, a hallmark of multiple sclerosis.

The absence of a reported history of infectious mononucleosis in seropositive patients with signs of Epstein–Barr virus reactivation is noteworthy. This observation aligns with data suggesting that delayed or asymptomatic primary infection may be more relevant for multiple sclerosis risk than clinically manifest mononucleosis, or that recall bias limits the reliability of patient history [7].

Increased seroprevalence and elevated IgG titers to varicella-zoster virus and herpes simplex viruses further indicate a broader dysregulation of antiviral immunity in multiple sclerosis. Reactivation of these viruses, even if clinically silent, may enhance systemic and central nervous system inflammation through cytokine release, activation of autoreactive T cells, and disruption of the blood–brain barrier [8].

The finding of lower cytomegalovirus IgG titers in patients with multiple sclerosis is intriguing and has been reported in other studies. Some authors have proposed a potential protective effect of cytomegalovirus infection against autoimmune diseases, possibly mediated by expansion of regulatory T-cell populations or immune exhaustion mechanisms [9]. However, this hypothesis remains controversial and requires further investigation.

Human herpesvirus type 6 did not show significant differences between groups in our study. Although experimental data suggest its potential involvement in demyelination, clinical and serological studies have yielded inconsistent results [10]. It is possible that tissue-specific viral

activity within the central nervous system is not adequately reflected by peripheral blood antibody levels.

From a clinical perspective, the demonstrated high prevalence of herpesvirus markers and increased antibody titers in multiple sclerosis patients, even with relatively short disease duration, suggests that chronic viral persistence and reactivation may accompany the disease from early stages. This observation has potential implications for monitoring, risk stratification, and therapeutic decision-making, particularly in the context of immunomodulatory and immunosuppressive treatments that may further influence viral dynamics.

Conclusion. This study demonstrates that patients with relapsing–remitting multiple sclerosis exhibit a higher prevalence and increased serological activity of several herpesvirus infections compared with healthy individuals. Universal seropositivity for Epstein–Barr virus, significantly elevated IgG antibody titers to Epstein–Barr virus, herpes simplex viruses, and varicella-zoster virus, as well as evidence of viral reactivation, support the concept of persistent herpesvirus involvement in multiple sclerosis. These findings, obtained in a regional cohort from Uzbekistan, reinforce the role of chronic viral infections as important environmental factors in multiple sclerosis and underscore the need for further longitudinal and mechanistic studies integrating virological, immunological, and clinical data.

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