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Study of immunoglobulins in patients with herpes virus infection

Olga A. Uspenskaya, Sania A. Spiridonova ✉, Ekaterina D. Apokina, Ekaterina N. Alyaseva

Privolzhsky Research Medical University, Nizhny Novgorod, Russian Federation

✉ saniyaspiridonova@mail.ru

Abstract

INTRODUCTION. Today, herpes virus infection is the leading cause of various clinical manifestations, high contagiousness, poor perinatal outcomes, and damage to all human systems and organs.

AIM. The purpose of this study is to examine the quantitative and qualitative composition of immunoglobulins in oral fluid and blood serum in patients with herpes virus infection.

MATERIALS AND METHODS. On the basis of the Department of Therapeutic Dentistry of the Privolzhsky Research Medical University (Nizhny Novgorod, Russian Federation), 25 patients suffering from herpes-virus infection of the oral cavity and the red border of the lips were examined. On the first day of the study and on the 14th day, the levels of secretory immunoglobulins, lysozyme, and the coefficient of local immunity factors were quantitatively determined.

RESULTS. When studying humoral immunity in the blood serum, there was a noticeably high level of IgG both on the 1st and 14th day of the study, which was also characteristic of IgM, and the concentration of IgA gradually increased by the end of the second week of the disease. The study of the content of immunoglobulin A in the oral fluid showed an increase in the titer by the end of the second week of the study, while the concentration of IgM was negligible, and the concentration of IgG slowly decreased by the 14th day.

CONCLUSIONS. When performing a correlation analysis between the groups of blood serum and oral fluid immunoglobulins, it was possible to trace similar changes in the ratio of data on their content, which allows us to use oral fluid indicators to assess the severity of herpes virus infection in the oral cavity and to monitor the treatment process.

Keywords: hematosalivary barrier, secretory and serum immunoglobulins, herpesvirus infection

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Изучение уровня иммуноглобулинов у пациентов с герпес-вирусной инфекцией

О.А. Успенская, С.А. Спиридонова ✉, Е.Д. Апокина, Е.Н. Алясева

Приволжский исследовательский медицинский университет, г. Нижний Новгород, Российская Федерация

✉ saniyaspiridonova@mail.ru

Резюме

ВВЕДЕНИЕ. На сегодняшний день герпес-вирусная инфекция занимает лидирующие позиции по развитию различного вида клинических проявлений, высокой контагиозности, ухудшению перинатального исхода, поражению всех систем и органов человека.

ЦЕЛЬ. Изучить количественный и качественный состав иммуноглобулинов ротовой жидкости и сыворотке крови у пациентов, страдающих герпес-вирусной инфекцией.

МАТЕРИАЛЫ И МЕТОДЫ. На базе кафедры терапевтической стоматологии Приволжского исследовательского медицинского университета выполнено обследование 25 пациентов, страдающих герпес-вирусной инфекцией полости рта и красной каймы губ. В первый день исследования и на 14 день выполняли количественное определение уровня секреторных иммуноглобулинов, лизоцима и коэффициента сбалансированности факторов местного иммунитета.

РЕЗУЛЬТАТЫ. При изучении гуморального иммунитета в сыворотке крови отмечался заметно высокий уровень IgG как в 1-й, так и на 14-й день исследования, что было характерно и для IgM, концентрация IgA увеличивалась постепенно к концу второй недели заболевания. Изучение содержания иммуноглобулина А в ротовой жидкости показало нарастание титра к концу второй недели исследования, концентрация IgM была ничтожно мала, а вот концентрация IgG медленно снижалась к 14-му дню.

ВЫВОДЫ. При выполнении корреляционного анализа между группами иммуноглобулинов сыворотки крови и ротовой жидкости удалось проследить аналогичные изменения в соотношении данных по их содержанию, что дает возможно нам использовать показатели ротовой жидкости для оценки тяжести протекания герпес-вирусной инфекции в полости рта, и контроля проводимого лечения.

Ключевые слова: гематосаливарный барьер, секреторные и сывороточные иммуноглобулины, герпесвирусная инфекция

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INTRODUCTION

In 1961, the concept of the hematosalivary barrier was first introduced, referring to a physiological mechanism involved in the selective regulation of substance exchange between the components of the salivary glands and the blood. It is important to note that the functional state of this barrier can be represented as a simple mathematical value, defined as the ratio of concentrations of various substances in the media on both sides of the barrier. This value is termed the distribution coefficient. Thus, when the concentration of substances in the blood increases, their content in saliva either slightly increases or remains unchanged, while the distribution coefficient rises, indicating a decrease in the permeability of the hematosalivary barrier. Conversely, when the concentration of substances in saliva increases, their content in the blood remains unchanged or slightly decreases, which is characterized by increased permeability of the hematosalivary barrier.

The study of the hematosalivary barrier enables the development of new diagnostic approaches and allows prediction of the outcomes of various pathological conditions. Based on the biochemical composition of saliva and the characteristics of salivation, it is possible to assess the severity of oral diseases, predict their course, and evaluate the effectiveness of ongoing therapy [1; 2]. According to the literature, changes in salivary immunoglobulin levels have been observed in pregnant women with gingivitis associated with toxicosis; alterations in sIgA concentrations have been reported in celiac disease; and changes in specific IgA levels occur in acute respiratory viral infections. In children with frequent viral infections, alterations in salivary lysozyme and sIgA levels have been identified, and further investigation has revealed an imbalance in humoral and cellular immunity [3–5].

Currently, herpesvirus infection occupies a leading position in terms of the diversity of clinical manifestations, high contagiousness, adverse perinatal outcomes, and its ability to affect multiple systems and organs of the human body [6; 7]. A wide range of laboratory methods is available for detecting herpesvirus infections; the most commonly used include PCR diagnostics for identifying viral genomes and serological methods for detecting viral antigens [8–10]. The virus persists lifelong in sensory ganglia in a latent state; however, primary infection with herpesviruses – specifically herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), and cytomegalovirus (CMV) – primarily affects epithelial cells, including those of the salivary glands [2; 11]. An exception is the Epstein–Barr virus, which primarily targets B lymphocytes [12].

The first line of defense against herpesviruses in the oral cavity is the nonspecific immune system, where lysozyme, produced by the salivary glands, plays a key role [13; 14]. Lysozyme is involved in tissue regeneration, influences leukocyte phagocytosis, and activates the immune response through sIgA in combination with other immunoglobulins in the oral fluid [15, pp. 55–56; 16]. Concurrently, changes are also observed in serum immunoglobulin levels. A key difference between immunoglobulin content in blood serum and oral fluid is the high concentration of IgG and IgM and low IgA levels in serum, whereas in oral fluid, IgA predominates, with relatively low levels of IgG and IgM [17–19].

AIM

The aim of the study is to investigate the quantitative and qualitative composition of immunoglobulins in oral fluid and blood serum in patients with herpesvirus infection.

MATERIALS AND METHODS

A total of 25 patients with moderate herpesvirus infection of the oral cavity and vermilion border were examined at the Department of Therapeutic Dentistry of Privolzhsky Research Medical University (Nizhny Novgorod, Russian Federation). The recurrence rate was three or more episodes per year. Exclusion criteria included patient refusal to participate, pediatric age, use of immunomodulatory drugs, and inability to attend follow-up visits. For each patient, a dental record form (043/U) was completed, informed consent for participation and personal data processing was obtained, and a clinical oral examination was performed using a dental mirror and probe. All patients received identical oral medications.

On day 1 and day 14 of the study, quantitative assessment of secretory immunoglobulins, lysozyme levels, and the coefficient of balance of local immunity factors was performed. Unstimulated mixed saliva was collected by expectoration into sterile tubes. The level

of sIgA was determined using a solid-phase enzyme-linked immunosorbent assay (ELISA) with reagent kits designed for biological fluids. Serum IgG and IgM levels were also measured using solid-phase ELISA with appropriate reagent kits. Serum IgA, IgG, and IgM concentrations were additionally assessed using the Mancini radial immunodiffusion method in gel.

Reference values for serum immunoglobulins were as follows: IgA 1.39–2.61 g/L, IgG 8.35–14.6 g/L, and IgM 0.72–1.26 g/L; for oral fluid: IgA 0.069 ± 0.028 g/L, IgG 0.042 ± 0.017 g/L, IgM 0.055 ± 0.011 g/L, and sIgA 0.14–0.55 g/L. Lysozyme activity was assessed using the nephelometric method described by Dorofeychuk [20]. The coefficient of balance of local immunity factors (Ksb) was calculated according to the formula proposed by Tolkacheva [21]. Data interpretation followed the recommendations of Lukinykh: 0.1–1.0 indicates a favorable condition; 1.1–2.0 indicates a borderline state (risk group); ⩾2.1 indicates reduced protective function (disease group) [22].

The coefficient was calculated using the following formula:

$$Ksb = \frac{\text{IgG} \times 40}{\text{IgA} \times 0.6 \times \text{Lysozyme}}.$$

Statistical data processing was performed using Microsoft Office (Excel) and the statistical software packages Statgraphics v.7, Stadia, and Statistica 7.0.

Normality of data distribution was assessed using the Shapiro–Wilk, Kolmogorov–Smirnov, and Lilliefors tests. The arithmetic mean (M) and standard deviation (SD, σ) were calculated for all studied parameters.

Pairwise and multiple comparisons between variables, as well as correlation analyses, were conducted. For normally distributed data, the significance of differences between mean values was assessed using Student's *t*-test. For multiple comparisons, Student's *t*-test with Bonferroni correction was applied.

Relative frequencies were calculated for qualitative variables. A 95% confidence interval for frequencies was determined using the Wald method. To test hypotheses regarding differences between independent samples, the Mann–Whitney U test and Pearson's chi-square (χ^2) test were used (including assessment of distribution normality at the selected level of significance). In addition, Fisher's exact two-tailed test was applied to evaluate the significance of differences in binary and categorical data. Correlation analysis was performed using Spearman's rank correlation coefficient.

A p-value ⩽ 0.05 was considered indicative of statistically significant differences between groups.

RESULTS

The study included 13 women and 12 men aged 25 to 40 years. All participants were diagnosed with chronic herpetic stomatitis of moderate severity. Medical history analysis revealed that 34.7% of patients had been affected for 1 to 3 years, 22.7% for more than 5 years, 17.3% for 7 years, and 25.3% for more than 7 years.

The analysis of humoral immunity in blood serum (Table 1) revealed a markedly elevated level of IgG on day 1 of the study (19.61 ± 1.87 g/L), which remained high on day 14 (26.87 ± 2.12 g/L) ($p < 0.05$). These findings indicate an adequate immune response to the viral agent.

An increased level of IgM was also observed on day 1 (1.59 ± 0.044 g/L), with a further rise by day 14 (3.7 ± 0.039 g/L) ($p < 0.01$). The elevation of IgM titers reflects the exacerbation stage of the disease.

The IgA level on day 1 was 3.5 ± 0.029 g/L and increased to 3.72 ± 0.00 g/L by day 14 ($p < 0.01$), indicating a gradual rise over the course of two weeks. Overall, consistently high levels of IgG and IgM were observed on both day 1 and day 14, while IgA concentration demonstrated a progressive increase toward the end of the second week of the disease.

The analysis of immunoglobulins in oral fluid (Table 2) revealed the following changes: on day 1, the IgA level was 0.036 ± 0.0013 g/L, decreasing to 0.028 ± 0.0094 g/L by day 14 ($p < 0.001$). Regarding sIgA, the level on day 1 was 0.164 ± 0.021 g/L, which decreased to 0.097 ± 0.051 g/L by day 14 ($p < 0.001$). The elevated sIgA level at the onset of the disease can be explained by a high viral load, which declines by day 14.

Table 1. Parameters of humoral immunity in the blood serum of patients with chronic herpetic stomatitis of moderate severity

Таблица 1. Показатели гуморального иммунитета в сыворотке крови пациентов с хроническим герпетическим стоматитом средней степени тяжести

Immunoglobulin classes	Reference values (Norm)	Day 1 of the study, M ± SD	Day 14 of the study, M ± SD
IgG, g/L	8.35–14.6	19.61 ± 1.87*	26.87 ± 2.12*
IgM, g/L	0.72–1.26	1.59 ± 0.044*	3.7 ± 0.039**
IgA, g/L	1.39–2.61	3.5 ± 0.029*	3.72 ± 0.00**

* $p < 0.05$, ** $p < 0.01$

Table 2. Levels of immunoglobulins in the oral fluid of patients with chronic herpetic stomatitis of moderate severity

Таблица 2. Уровень иммуноглобулинов в ротовой жидкости пациентов с хроническим герпетическим стоматитом средней степени тяжести

Immuno-globulin classes	Reference values (Norm)	Day 1 of the study, M ± SD	Day 14 of the study, M ± SD
IgG, g/L	0.042 ± 0.017	0.067 ± 0.0025*	0.044 ± 0.0011*
IgM, g/L	0.055 ± 0.011	0.0028 ± 0.00077*	0**
IgA, g/L	0.069 ± 0.028	0.036 ± 0.0013*	0.028 ± 0.0094*
sIgA, g/L	0.14–0.55	0.164 ± 0.021	0.097 ± 0.051*
Lysozyme, %	50.70	39.133 ± 3.7*	37.13 ± 2.2*

* $p < 0.001$, ** $p < 0.0001$

The IgG concentration in oral fluid was 0.067 ± 0.0025 g/L on day 1 and decreased to 0.044 ± 0.0011 g/L by day 14 ($p < 0.001$). Notably, the IgM level in oral fluid was negligible: 0.0028 ± 0.00077 g/L on day 1 and 0 g/L on day 14 ($p < 0.0001$). Overall, a trend toward a decrease in IgA and IgG levels by day 14 was observed, while IgM concentrations remained extremely low throughout the study period.

Assessment of lysozyme levels in oral fluid (Table 2) demonstrated a significant decrease compared to normal values (39.133 ± 3.7% on day 1 and 37.13 ± 2.2% on day 14, $p < 0.001$), with a further downward trend by day 14.

The coefficient of balance of local immunity factors (Ksb) proved to be a valuable indicator for predicting disease severity, identifying patients with reduced protective function, and enabling timely preventive interventions aimed at enhancing host defense mechanisms. On day 1, 60% of patients had a Ksb ⩾ 2.1, indicating reduced protective function of the oral fluid; 24% had values between 1.1 and 2.0, corresponding to a risk group; and 16% had values between 0.1 and 1.0, considered normal. By day 14, 49.3% of patients had Ksb values between 1.2 and 2.0, 32% between 0.1 and 1.0, and 18.7% ⩾ 2.1.

DISCUSSION

The salivary glands are well vascularized due to a large number of arteriovenular anastomoses equipped with sphincters. Their constriction leads to increased capillary pressure and facilitates the transfer of metabolites from the capillary lumen into the cells of the secretory epithelium involved in saliva formation. According to the literature, the development of inflammation is associated with increased permeability of the hematosalivary barrier and enhanced passive transport through the oral mucosa, which was confirmed in our study of secretory immunoglobulin levels [23]. Analysis of the cytokine profile of oral fluid has demonstrated that changes in the levels of major immunoglobulin classes and their ratios in blood and saliva correlate not only with each other but also with the severity of the inflammatory process [24].

The protein composition of saliva is generally similar to that of blood serum; however, the proportions of immunoglobulins differ significantly. Determination of sIgA levels in saliva is one of the key indicators of local immunity, reflecting adaptive mechanisms to environmental changes [25]. The synthesis of sIgA involves plasma cells and a secretory component produced by epithelial cells of the salivary glands. According to Lobeyko et al. [26], both acute and chronic inflammatory processes in the oral cavity are characterized by decreased sIgA levels in saliva, which is consistent with our findings: sIgA levels were below normal on day 1 and continued to decline by day 14.

Immunoglobulins enter the oral fluid primarily through transudation across the inflamed mucosa, which is most permeable to IgG, less so to IgA, and least permeable to IgM [27]. Our findings confirm the low permeability of the mucosa for IgM: its level was below the normal range on day 1 and approached zero by day 14. A decrease in IgM levels indicates a deficiency in humoral immunity. In contrast, IgG and IgA exhibit a higher capacity for transudation; however, their levels were below normal on day 1 and showed a decreasing trend by day 14, suggesting a reduction in antigenic load.

Regarding serum immunoglobulins, all fractions were elevated above normal values on both day 1 and day 14. It is well established that IgM is one of the first immunoglobulins produced in response to acute infection and is responsible for preparing infected cells for complement-dependent cytolysis, which is consistent with our results, as IgM levels were elevated on day 1 and increased further by day 14. According to the literature, herpesviruses can stimulate lymphocytes to produce IgA. Elevated IgA levels and their progressive increase indicate an acute viral infection and possible immune system exhaustion. As for IgG, a marked increase was observed on day 1 compared to normal values, with a continued upward trend by day 14, reflecting the chronic nature of the disease and corresponding to the resolution phase of clinical manifestations [28].

Lysozyme is a natural antiseptic present on the surface of the mucous membrane, produced by epithelial cells and serving as a major component of neutrophil granules. It exerts antiviral activity by binding viral DNA and inhibiting viral replication. Lysozyme functions in close interaction with biologically active molecules. In combination with IgA, it neutralizes damaging components of the immune response and limits IgG production. An increase or predominance of IgG over IgA indicates усиление антигенного воздействия. The results of the present study demonstrated a decrease in lysozyme levels on day 1 compared to normal values, with a slight further reduction by day 14, indicating suppression of the immune system [29].

It is well established that the functional state of any biological barrier is characterized by a value reflecting the ratio of a given substance concentration on either side of the barrier [30]. The permeability of the hematosalivary barrier is assessed by comparing the levels of substances in blood serum and oral fluid. Based on our findings, an increase in sIgA and IgA levels in oral fluid is associated with enhanced permeability of the hematosalivary barrier, which acts as a protective interface preventing harmful agents from entering the bloodstream, where a decrease in IgA levels was observed. In contrast to IgA, IgG predominates in blood serum, as confirmed by our results, reflecting an increased antigenic load. However, several studies have reported the pathogenic role of excessive immune complexes containing IgG, which may stimulate reaginic reactions. The low IgM level in oral fluid is explained by the low permeability of the hematosalivary barrier to this immunoglobulin [31].

Thus, the hematosalivary barrier plays a critical role in the multifactorial mechanism of homeostasis. In response to viral invasion, it redistributes immunoglobulin levels between blood and saliva by modulating its permeability and functional activity.

Analysis of the relationship between IgA, IgG, and IgM levels in blood serum and oral fluid revealed the following: an increase in IgA levels in oral fluid was associated with a decrease in serum IgA ($r = -0.546$); an increase in serum IgG was accompanied by a marked decrease in salivary IgG ($r = -0.824$); and an increase in serum IgM corresponded to a near-zero level of IgM in oral fluid ($r = -0.943$). These findings indicate a strong inverse correlation between immunological parameters in blood serum and oral fluid.

CONCLUSION

The obtained results demonstrated multidirectional dynamics of immune parameters in blood serum and oral fluid in chronic recurrent herpetic stomatitis of moderate severity. This reflects the physiological mechanism of the hematosalivary barrier and provides a rationale for the use of oral fluid parameters, obtained via a non-invasive sampling method, for assessing disease severity in oral herpesvirus infection, monitoring therapeutic efficacy, and predicting clinical outcomes.

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INFORMATION ABOUT THE AUTHORS

Olga A. Uspenskaya – Dr. Sci. (Med.), Associate Professor, Head of the Department of Therapeutic Dentistry, Privolzhsky Research Medical University, 10/1 Minin and Pozharsky Square, Nizhny Novgorod 603005, Russian Federation; https://orcid.org/0000-0003-2395-511X

Sania A. Spiridonova – Cand. Sci. (Med.), Associate Professor, Department of Therapeutic Dentistry, Privolzhsky Research Medical University, 10/1 Minin and Pozharsky Square, Nizhny Novgorod 603005, Russian Federation; https://orcid.org/0000-0002-7233-446X

Ekaterina D. Apokina – Resident of the Department of Therapeutic Dentistry, Privolzhsky Research Medical University, 10/1 Minin and Pozharsky Square, Nizhny Novgorod 603005, Russian Federation;

Ekaterina N. **Alyaseva** – Resident of the Department of Therapeutic Dentistry, Privolzhsky Research Medical University, 10/1 Minin and Pozharsky Square, Nizhny Novgorod 603005, Russian Federation;

ИНФОРМАЦИЯ ОБ АВТОРАХ

Успенская Ольга Александровна – д.м.н., профессор, заведующий кафедрой терапевтической стоматологии, ФГБОУ ВО «Приволжский исследовательский медицинский университет», 603005, Российская Федерация, г. Нижний Новгород, пл. Минина и Пожарского. д. 10/1; https://orcid.org/0000-0003-2395-511X

Спиридонова Сания Ахмедовна – к.м.н., доцент кафедры терапевтической стоматологии, ФГБОУ ВО «Приволжский исследовательский медицинский университет», 603005, Российская Федерация, г. Нижний Новгород, пл. Минина и Пожарского. д. 10/1; https://orcid.org/0000-0002-7233-446X

Апокина Екатерина Дмитриевна – ординатор кафедры терапевтической стоматологии, ФГБОУ ВО «Приволжский исследовательский медицинский университет», 603005, Российская Федерация, г. Нижний Новгород, пл. Минина и Пожарского. д. 10/1

Алясева Екатерина Николаевна – ординатор кафедры терапевтической стоматологии, ФГБОУ ВО «Приволжский исследовательский медицинский университет», 603005, Российская Федерация, г. Нижний Новгород, пл. Минина и Пожарского. д. 10/1

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