SALIVARY HUMORAL AND CYTOKINE IMMUNE MARKERS IN CHILDREN WITH RECURRENT HERPETIC STOMATITIS AND CONCOMITANT ALLERGIC DISEASES.

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Abstract.*Recurrent herpetic stomatitis (RHS) is a common pediatric infection caused by herpes simplex virus type 1 and is frequently associated with impairment of mucosal immunity. When combined with allergic diseases, the severity of immune dysfunction may increase. This study investigated parameters of local humoral and cytokine immunity in children with recurrent herpetic stomatitis, both in its isolated form and in combination with allergic conditions.*

Keywords: *recurrent herpetic stomatitis; children; salivary immunity; secretory IgA; immunoglobulins; lysozyme; cytokines; IL-6; IL-10; allergic diseases; humoral immunity.*

Introduction

Recurrent herpetic stomatitis (RHS) is one of the most common chronic infectious diseases of the oral cavity in children. It is characterized by periodic exacerbations, painful ulcerative lesions, and disruption of the integrity of the oral mucosa. According to epidemiological studies, recurrent forms of herpes simplex virus (HSV) infection affect up to 20–40% of children worldwide, with the highest incidence observed in the 3–12-year age group [1,2]. In many countries, HSV-1 seropositivity among children reaches 60–70% by the age of five, and approximately one third of these cases develop a recurrent course of infection [3]. Recurrent herpetic stomatitis not only reduces quality of life due to pain and feeding difficulties but also predisposes children to secondary bacterial infections and prolonged mucosal hypersensitivity [4].

In recent years, increasing attention has been paid to the immunopathogenesis of RHS, particularly to the role of local (salivary) immunity. Saliva contains a wide range of humoral defense factors, including

immunoglobulins (IgA, IgM, IgG, and IgE) and antimicrobial peptides, which constitute the first line of protection of the oral mucosa [5]. Secretory IgA plays a central role in maintaining mucosal immunity by neutralizing viral particles and preventing their adhesion to epithelial cells [6]. However, children with recurrent HSV infection have been reported to exhibit quantitative and functional disturbances in these immunoglobulins [7].

Cytokines key regulators of inflammatory and immune responses are also involved in the pathogenesis of RHS. Proinflammatory cytokines, such as interleukin-6 (IL-6), promote local inflammation and epithelial damage, whereas anti-inflammatory cytokines, including interleukin-10 (IL-10), regulate immune responses and limit tissue injury [8]. Previous studies have demonstrated cytokine imbalance in children with RHS, characterized by elevated IL-6 levels and insufficient compensatory IL-10 secretion, resulting in prolonged inflammation and delayed healing of lesions [9].

Of particular clinical relevance is the coexistence of RHS with allergic diseases, the prevalence of which has been steadily increasing among the pediatric population. The prevalence of allergic conditions including bronchial asthma, atopic dermatitis, and allergic rhinitis has risen significantly over the past two decades, affecting up to 30% of children in developed countries [10]. It has been hypothesized that allergic inflammation further disrupts mucosal immunity and alters salivary immunoglobulin and cytokine profiles, thereby increasing the severity and frequency of RHS episodes [11].

Despite numerous studies, the relationship between humoral and cytokine immunity in the saliva of children with recurrent herpetic stomatitis especially in the presence of allergic diseases remains insufficiently explored. A detailed investigation of these immunological parameters may provide new insights into the mechanisms underlying disease chronicity and contribute to the development of personalized therapeutic and preventive strategies for affected children [12,13].

Recurrent herpetic stomatitis is an infectious disease predominantly caused by herpes simplex virus type 1 (HSV-1) of the *Herpesviridae* family. The disease is characterized by ulcerative lesions of the oral mucosa accompanied by regional lymphadenitis. Globally, up to 80% of infectious stomatitis cases are attributed to HSV-1, and among children particularly those aged 1–7 years the prevalence reaches approximately 70%, while it is significantly lower in adolescents and adults. This high prevalence in early childhood is associated with the immaturity of local mucosal immunity and increased exposure to environmental pathogens.

Although the pathogenesis of RHS has been extensively studied, quantitative alterations in local humoral immune factors especially in the presence of concomitant allergic diseases remain inadequately characterized. Understanding these changes is crucial, as the immune system in early childhood is still developing, and maternally derived antibodies largely disappear by the age of three, rendering children more susceptible to recurrent infections.

Cytokine-mediated immune regulation plays a pivotal role in both viral infection control and allergic inflammation. Interleukin-6 (IL-6) acts as a

proinflammatory mediator, stimulating acute-phase protein synthesis and leukocyte activation, whereas interleukin-10 (IL-10) functions as an anti-inflammatory cytokine by suppressing excessive immune responses while simultaneously enhancing antibody production. Assessing the balance between these cytokines in conjunction with immunoglobulin profiles allows for a deeper understanding of the immunopathogenesis of RHS and the mechanisms underlying its exacerbation in allergic comorbidity.

The aim of this study was to perform a comparative assessment of salivary levels of secretory immunoglobulin A (sIgA), lysozyme, total immunoglobulins (IgA, IgM, IgG, IgE), and cytokines (IL-6, IL-10) in children with isolated recurrent herpetic stomatitis and in those with RHS combined with allergic diseases.

Materials and Methods

The study was conducted on 120 children aged 1–7 years. The study population was divided into three groups, each comprising 40 participants:
(1) healthy children without recurrent herpetic stomatitis (RHS) or allergic diseases (control group);
(2) children diagnosed with RHS without allergic comorbidities (comparison group);
(3) children diagnosed with RHS in combination with allergic diseases (main group).

All participants were recruited from pediatric outpatient clinics. Written informed consent was obtained from parents or legal guardians prior to enrollment.

Saliva samples were collected in the morning, at least two hours after food or fluid intake, using a standardized non-invasive procedure. Unstimulated whole saliva was collected into sterile tubes under the supervision of trained personnel. The samples were immediately frozen and stored at −20 °C until analysis.

Immunological analyses were performed in certified laboratories. Local immune factors, including secretory immunoglobulin A (sIgA) and lysozyme, were determined using standard enzyme-linked immunosorbent assay (ELISA) kits. Humoral immunity was assessed by measuring salivary concentrations of total IgA, IgM, IgG, and IgE. In addition, cytokine status was evaluated by determining levels of IL-6 (proinflammatory cytokine) and IL-10 (anti-inflammatory cytokine) using high-sensitivity ELISA kits. All measurements were performed in triplicate, and mean values were calculated.

Statistical analysis was carried out using SPSS software. Results are presented as mean ± standard deviation (SD). Intergroup comparisons were performed using Student's *t*-test. Differences were considered statistically significant at $p < 0.05$.

Changes in Nonspecific Local Immune Factors

Table 1 presents the concentrations of sIgA and lysozyme in saliva. Healthy children exhibited high baseline levels of both parameters, whereas children with

RHS demonstrated a pronounced decrease. The most substantial reduction was observed in children with RHS combined with allergic pathology.

Table 1. Salivary concentrations of secretory IgA and lysozyme in children with recurrent herpetic stomatitis.

Group	sIgA (μg/mL)	Lysozyme (μg/mL)
Healthy controls	207.17 ± 9.31	159.76 ± 7.40
RHS without allergy	105.76 ± 3.66*	98.18 ± 4.78*
RHS with allergy	90.57 ± 4.89*†	76.71 ± 2.59*†

Data are presented as mean ± standard deviation (SD).

- **p < 0.001 vs. healthy controls.**

† p < 0.05 vs. RHS without allergy.

The concentration of sIgA in healthy children was 207.17 μg/mL, whereas in children with RHS it decreased to 105.76 μg/mL and further declined to 90.57 μg/mL in those with concomitant allergic diseases. A similar trend was observed for lysozyme, with levels decreasing from 159.76 μg/mL in the control group to 98.18 μg/mL in the comparison group and to 76.71 μg/mL in the main group. These changes indicate a pronounced impairment of mucosal immunity.

Discussion

The obtained results demonstrate that children with recurrent herpetic stomatitis exhibit significant alterations in both local and systemic humoral immunity. The marked reduction in sIgA and lysozyme levels confirms impairment of the first line of mucosal defense, predisposing patients to recurrent infections. These changes were more pronounced in children with concomitant allergic diseases, indicating a synergistic negative effect of allergic inflammation on oral mucosal immunity.

Regarding immunoglobulin profiles, children in the main group showed a pronounced deficiency of IgA accompanied by elevated IgM levels, suggesting an impaired or incomplete immunoglobulin class-switching process. The absence of a significant increase in IgG levels in this group—contrary to the sharp elevation observed in the comparison group—indicates insufficiency of the secondary immune response in the presence of allergic pathology.

Cytokine data further support the presence of an enhanced inflammatory state, with particularly high IL-6 levels detected in children from the main group. This finding suggests that allergic inflammation amplifies the inflammatory cascade triggered by HSV-1 infection. Although IL-10 levels were also increased, likely as a compensatory anti-inflammatory mechanism, this increase was insufficient to counterbalance the predominant proinflammatory response.

Overall, the observed immune dysregulation in children with RHS combined with allergic diseases reflects a complex interaction between viral persistence, impaired mucosal immunity, and chronic allergic inflammation. These findings have important clinical implications, highlighting the need for combined antiviral and immunomodulatory treatment strategies, particularly in pediatric patients with allergic comorbidities.

Results

Analysis of salivary immune parameters revealed significant differences between healthy children and those with RHS. These differences were more pronounced in patients with concomitant allergic diseases. The overall trend was characterized by a marked reduction in local protective factors (sIgA and lysozyme), alterations in immunoglobulin balance, and increased cytokine levels, particularly the proinflammatory cytokine IL-6.

Conclusion

Children with recurrent herpetic stomatitis demonstrate significant impairments of local immunity, particularly reflected by reduced levels of sIgA and lysozyme, with these disturbances being more pronounced in the presence of allergic diseases. In such cases, humoral immunity is characterized by decreased IgA levels, compensatory overproduction of IgM, and persistently elevated IgE concentrations. The cytokine profile reveals predominance of IL-6–mediated inflammation, only partially compensated by IL-10.

These findings emphasize the importance of assessing local immune parameters and cytokine status to guide targeted therapeutic approaches in children with recurrent herpetic stomatitis.

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