

REVIEW ARTICLE

ACUTE HERPETIC STOMATITIS: CLINICAL MANIFESTATIONS, DIAGNOSTICS AND TREATMENT STRATEGIES

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ABSTRACT

The aim: To evaluate the recent scientific articles concerning peculiarities of this oral pathology. The goal is to carry out a literature review by evaluating all signs and clinical symptoms related to this disease, so as to provide the clinician with a useful tool for an early diagnosis and treatment of the disease.

Materials and methods: The collection of relevant data were done using the scientific databases Pubmed, Google Scholar. A manual search on Dentistry and Pharmacological sources was also conducted for relevant studies published. The selected key words: ("Herpes virus" OR "HSV") AND ("oral" OR "oral lesions") were used for collecting the data.

Conclusions: The article presents clinical peculiarities of herpetic stomatitis depending on disease severity and course. Primary herpetic stomatitis appears as spherical clustered vesicles on the gingival and adjacent mucosa. Soon after eruption of elements of lesion they rupture forming painful halo like aphtae / ulcers. Typical symptoms are: pain from ruptured vesicles, lymphadenitis, fever etc. Early diagnosis of disease is important and treatment with antiviral medicaments can modify the course of the disease by reducing symptoms and potentially reducing recurrences. Management of acute herpetic stomatitis include antiviral medicaments intake, maintenance of fluids and electrolytes level in a body. The treatment principles based on etiologic, pathogenetic and symptomatic therapy are considered in manuscript.

KEY WORDS: herpes simplex virus, viral oral lesions, herpetic stomatitis

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INTRODUCTION

Herpes virus infections are among the most common and poorly controlled viral diseases. According to the Global Herpes virus Survey, the incidence and morbidity of humankind is increasing by more than 10 % year on year, and 90 % of adults and children in all countries of the world are infected with one or more serotypes of herpes viruses. Recurrent herpes virus disease affects from 2 to 12 % of population and need lifelong care [1, 2].

The virus can infect almost all human organs and systems, causing various clinical forms of infection: diseases of the central and peripheral nervous system, liver and other parenchymal organs, eyes, skin, mucous membranes of the gastrointestinal tract, genitals, mouth, and have certain significance in fetal pathology. Often there is a combination of different clinical forms of herpes infection [3, 4]. The main clinical forms of herpes infection diagnosed in domestic dental clinical practice are acute herpetic stomatitis (AHS) – primary herpetic infection, chronic recurrent herpetic stomatitis (secondary herpetic infection) and chronic recurrent labial herpes. The success of modern virology and its achievements allow improving the diagnosis and treatment of this pathology. However, in dental practice there are often difficulties in verifying and management of viral lesions [5, 6, 7].

One of the most common clinical forms of primary herpetic infection is acute herpetic stomatitis (AHS). The

disease is widespread in children from 6 months till 3 years old, which is associated with the disappearance at this age of antibodies obtained intra placental, immaturity of their own immune system (insufficient sIgA, lysozyme), age morphological features of oral mucosa structure (due to a thin epithelial layer with low glycogen and nucleic acids levels) as well as with frequent natural violations of the integrity of the mucous membrane as a result of teeth eruption and microtrauma [8, 9]. Currently, it is noted that AHS also affects newborns (from 2 to 43 days after birth), due to anti- and postnatal infection, while intrauterine infection is noted in 1/3 of cases [10].

A wide range of clinical manifestations allows us to talk about herpes infection as a medical and social problem. Thus, the problem solving of diagnosis and treatment of acute and recurrent forms of herpes infection with manifestations on the oral mucosa is one of the most important tasks facing practical medicine.

THE AIM

The purpose of this manuscript is to evaluate the recent scientific articles concerning peculiarities of this oral pathology. The goal is to carry out a literature review by evaluating all signs and clinical symptoms related to this disease, so as to provide the clinician with a useful tool for an early diagnosis and treatment of the disease.

MATERIALS AND METHODS

The collection of relevant data were done using the scientific databases Pubmed, Google Scholar. A manual search on Dentistry and Pharmacological sources was also conducted for relevant studies published. The selected key words: ("Herpes virus" OR "HSV") AND ("oral" OR "oral lesions") were used for collecting the data.

REVIEW AND DISCUSSION

The term "herpes" (from the Greek "herpo" - to crawl) was first described by the Roman physician Herodotus around 100 BC. Mentions of it are found in the treatises of Hippocrates, Avicenna and Paracelsus. Herpes virus was first isolated in 1912 by W. Griitter, who experimentally developed keratoconjunctivitis in rabbits after the introduction of fluid from the human herpes vesicle into the scarified eyelid. In 1921, Lipschütz described acidophilic intranuclear inclusions ("Lipschutz bodies") visible in an ordinary light microscope, which Cowdry (1934) defined as the inclusion of the herpes simplex virus. There is about 90 members of the family of herpes viruses, 8 of which are routinely infects only humans. These are herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (that causes chickenpox and shingles), Epstein-Barr virus, cytomegalovirus, human herpes viruses types 6, 7 and Kaposi's sarcoma virus or human herpes virus 8 [8, 11, 12].

Herpesviruses belong to the family Herpesviridae (DNA genomic viruses) and according to their biological properties are divided into 3 subfamilies:

- Alphaherpesvirinae: herpes simplex virus (HSV) types 1 and 2: Herpes simplex virus-1, -2 (HSV-1, HSV-2). Chickenpox / shingles are caused by - Varicella-Zoster virus (VZV).
- Betaherpesvirinae: cytomegalovirus - Cytomegalovirus (CMV). Herpes virus type 6 - Human herpesvirus-6 (HHV-6). Herpes virus type 7 - Human herpesvirus-7 (HHV-7).
- Gammaherpesvirinae: Epstein-Barr virus (EBV). Herpes virus type 8 - Human herpesvirus-8 (HHV-8, Kaposi's sarcoma human virus associated - KSHV) [1, 12].

Viruses of the Herpesviridae family are spherical formations with a diameter of 100-300 nm with a complex structure in which there are at least 4 structural components:

- nucleotide - central part of the virion, represented by two strands of DNA wound on a cylindrical protein rod;
- capsid (from the Latin "capsa" container, case) - protein capsule in which the nucleotide is enclosed; the capsid has the form of a correct polyhedron, assembled from hundreds of identical protein prismatic hollow capsomeres;
- inner shell (in English "tegumen" - cover) - a super-capsid structure, which is a three-layer membrane with irregular outlines;
- outer shell (in English 'envelope' case, cover, envelope) - lipoprotein structure of irregular shape with outward-facing protrusions, covering one or more nucleocapsids of herpes with their individual inner shells [13].

Herpes viruses are obligate intracellular genetic parasites that reproduce in the nucleus of infected cells, causing their rapid degeneration and death.

ETIOLOGY AND PATHOGENESIS OF HERPETIC STOMATITIS

Herpes simplex virus causes lesions in almost every individual. Infection can occur both in childhood and in adulthood. The source of infection is an infected person (sick or virus carrier).

Ways of spreading infection: air-drop, contact (direct and indirect), transplacental, transfusion. Herpes simplex virus (HSV) enters the body through oral mucosa, nasopharynx, eyes, genitals, and infects the skin. The initial reproduction of the virus occurs at the entrance gate of infection, and then penetrates into the regional lymph nodes (lymphadenitis). If the body's defenses do not cope with the pathogen, then in the incubation period there is a primary viremia (i.e. an entrance into the bloodstream), and then into organs and tissues. Settling there, the pathogens multiply rapidly, and cause tissue damage by type of necrosis. Secondary viremia is characterized by the appearance in the blood of a large number of viruses that occur in the prodromal period and the first days of the disease [9,10].

After the primary infection (latent or acute), up to 70 % of the population become lifelong infected with the herpes virus.

Once, the herpes simplex virus enters the nerve endings and spreads into the nerve ganglia, from where it periodically migrates to the periphery, causing recurrences of the disease. This can be result of such factors as avitaminosis, overheating or hypothermia, physical or psycho-emotional stress, inflammatory processes, bad habits and others.

CLINICAL MANIFESTATIONS OF ACUTE HERPETIC STOMATITIS

In the course of the disease, as with any other infectious illness, there are five periods: incubation, prodromal, period of development/progression of the disease (catarrhal and rash of the lesion elements), attenuation (epithelization) and clinical recovery (convalescence).

The incubation period of AHS lasts from 2 to 26 days (average 6-12 days). Depending on the severity of intoxication and local manifestations in the oral cavity, the disease can occur in mild, moderate and severe forms. The severity of AHS is assessed on the basis of a combination of symptoms of general (degree of intoxication) and local (severity of lesions of the oral mucosa) symptoms.

After being infected, virus replication begins in the epidermal cells of the skin and in the oral mucosa epithelium. Regardless of the presence of local clinical manifestations of the disease, the replication of the virus occurs in a volume sufficient for the virus to enter the sensitive or autonomic nerve endings. It is believed that the virus or its nucleocapsid spreads through axons to the body of a nerve cell in the ganglion.

After HSV enters the patient's body, it reproduces in the cells of local tissue and adjacent lymphatic formations, so the appearance of elements of the lesion in the oral cavity is preceded by lymphadenitis of varying severity. The process usually involves the lymph nodes of the mandibular area,

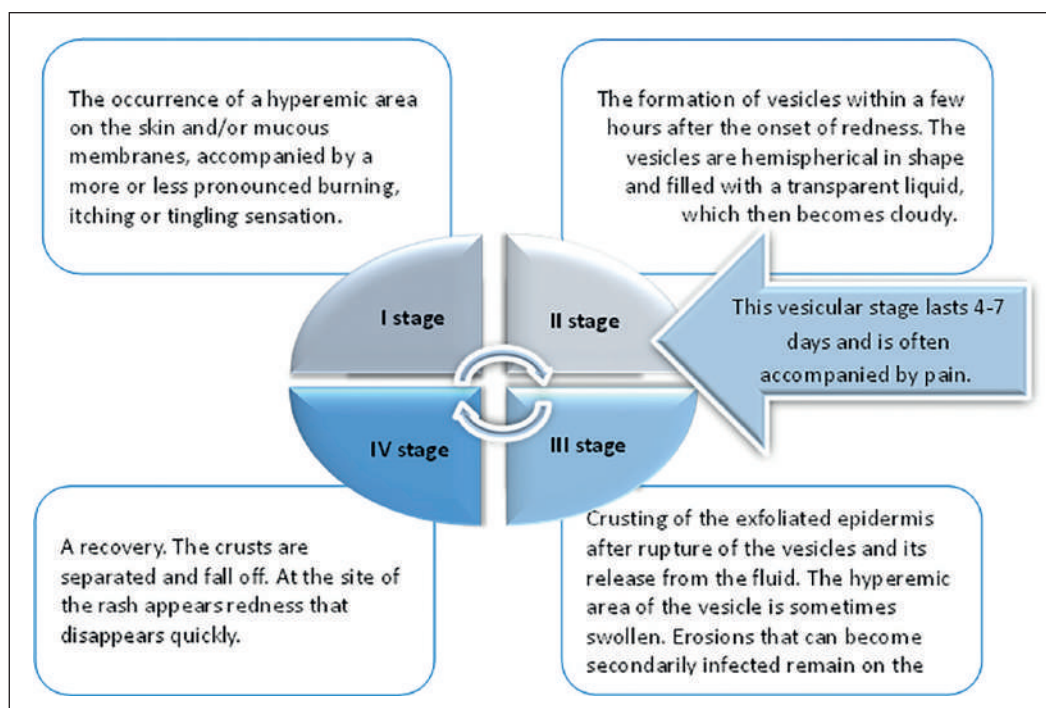


Fig. 1. Stages of herpetic vesicle life cycle.

and sometimes other areas. Lymphadenitis is preceded by a rash and accompanies the entire period of the disease.

In the incubation period, there is primary viremia, i.e. penetration of the virus into the bloodstream. Penetrating through the capillary barrier by diapedesis, HSV is deposited in the liver, spleen and other organs and multiplies rapidly. Tissue lesions by a type of necrosis develop.

It is described four stages of herpetic vesicle life cycle as given in Figure 1.

Mild form of acute hermetic stomatitis. *The incubation period* is not clinically evident. It lasts an average of 6-12 days with a range of 2 to 26 days.

The prodrome stage begins suddenly with a slight increase in body temperature to 37-37.5° C. The general state of the patient health is quite satisfactory and as usual patient wellbeing does not suffer great. The patient sometimes has minor symptoms of catarrhal inflammation of the mucous membrane of the nasal cavity, upper respiratory tract.

Erythema and slight swelling of the gingival margin (catarrhal gingivitis) are visible in the oral cavity. The duration of this period of the disease is 1-2 days. Sometimes the clinical picture of AHS is limited to gingivitis, followed by a period of remission of the disease (catarrhal type of AHS).

The stage of development/progression of AHS is called the period of rashes: on the background of hyperemic oral mucosa appears single (1-2) or clustered elements of the lesion (vesicles) in the form of 3-5 foci of superficial epithelial necrosis. The vesicle stage is usually seen by parents and the doctor, these vesicles rupture within 24 hours, resulting in shallow, painful, small aphthae/ulcerations. In most cases, on the background of mouth redness, there are single or grouped elements of the lesion, the number of which usually does not exceed 6. The rash appears single time. The duration of this stage of disease is 1-2 days.

The attenuation period of the disease is longer. Within 1-2 days, the elements of lesion starts to have from gray to white center, their edges and center are blurred, it is ringed by red rim of erythema and they take the form of ordinary aphthae. These lesions are less painful. After epithelialization of the lesion elements, during 2-3 days, the phenomena of catarrhal gingivitis persist, especially in the area of the anterior teeth of the upper and lower jaw.

Patient with this form of the disease have no changes in the blood formula, as a rule; only by the end of the disease there is a slight lymphocytosis sometimes. Natural immunity in the mild form of stomatitis suffers slightly, and in the period of clinical recovery the protective forces of the patient's body are almost at the level of those in healthy, i.e. in the mild form of AHS clinical recovery means complete recovery of the body's protective forces [14-18].

Natural immunity in a case of mild stomatitis suffers slightly. Clinical recovery in the mild form of acute herpetic stomatitis is accompanied by complete recovery of the body's impaired protective forces.

The moderate-severe form of AHS is characterized by quite pronounced symptoms of intoxication and lesions of the oral mucosa in all periods of the disease. In the prodromal period, the patient's temperature rises from 37.5 to 39° C; it is very difficult to decrease the temperature, it lasts 2-3 days. The general condition of patient worsens, appears fatigue, the patient becomes capricious, with loss of appetite. In the oral cavity there are signs of acute respiratory disease and catarrhal sore throat.

As the disease progresses, during the development of the disease (phase of catarrhal inflammation) the temperature rise up to 38-39° C, there are headache, nausea and pale skin. At the peak of temperature rise, the increased hyperemia and the expressed swelling of a mucous membrane,

elements of lesion both in an oral cavity, and quite often, on skin of a peri-oral area appears. In the oral cavity there is usually from 10 to 20-25 elements of the lesion. During this period salivation increases, saliva becomes viscous. There is a pronounced inflammation and bleeding of gums.

The rash often recurs, so that when examining the oral cavity you can see the elements of the lesion, which are at different stages of clinical and cytological development. After the first rash of the elements of the lesion, the body temperature usually drops to 37.0-37.5° C. However, subsequent rashes are usually accompanied by a rise of temperature to the previous level. The patient does not eat, sleeps poorly, the symptoms of secondary toxemia increase.

ESR raises up to 20 mm / h, more often there is leukopenia, sometimes minor leukocytosis. The level of rod-shaped neutrophils and monocytes is usually within the upper limits of normal, lymphocytosis and plasmacytosis are detected.

The duration of the period of attenuation of the disease depends on the degree of resistance, the presence of carious and damaged teeth, and the rationality of therapy. Epithelialization of the elements of the lesion is delayed up to 4-5 days. Gingivitis, pronounced bleeding of gums and lymphadenitis last the longest [14-18].

Severe form of AHS is much less common than moderate – severe form. In the prodromal period, the patient has all signs of the onset of acute infectious disease: apathy, adynamia, headache, musculoskeletal hyperesthesia, arthralgia and others. Frequent symptoms of cardiovascular disease: brady- or tachycardia, muffled heart sounds, hypotension. Some patients have nosebleeds, nausea and vomiting, pronounced lymphadenitis not only of submandibular but also of cervical lymph nodes.

During the development of the disease, the temperature rises up to 39-40° C. The patient has a sad expression of face; attention is drawn to the suffering look of eyes. There may be a mild runny nose, cough, slightly swollen and hyperemic conjunctiva. Lips are dry, erythematous, with crusts. The mucous membrane of the oral cavity is swollen, brightly hyperemic with pronounced gingivitis.

In 1-2 days in the mouth begin to appear elements of the lesion (vesicles) - up to 20-25. Often rashes in the form of typical herpetic blisters occur on the skin around the mouth, eyelids, conjunctiva, earlobes, on fingers in the type of paronychia. Rash in the mouth recur and therefore in the disease progress in a seriously ill patient there are about 100 of vesicles.

The elements of lesion merge to form large areas of mucosal necrosis. Not only the lips, cheeks, tongue, soft and hard palate are affected, but also the gingival margin. Catarrhal gingivitis turns into ulcerative-necrotic. There is a sharp putrid odor from the mouth, profuse salivation with blood. Inflammatory phenomena on the mucous membrane of the nasal cavity, respiratory tract, eyes are worsening. Blood streaks are also found in the secretion from the nose and larynx, and sometimes nosebleeds are noted. In this condition, patient needs active treatment by a dentist, in connection with which it is advisable to hospitalize the patient in a hospital or specialized infectious diseases hospital.

In the blood - leukopenia, shift of the formula to the left, eosinophilia, single plasma cells, young forms of neutrophils, sometimes with toxic granularity. During rashes the content of sIgA, IgA, IgG, IgM increases. Then, during the remission of the disease and recovery, the level of IgG continues to raise, IgA and sIgA decreases, and the level of IgM normalizes. Humoral factors of the body's natural defenses during the development of the disease are sharply reduced. In the urine - protein or its traces is visualized.

The period of attenuation of the disease depends on the timeliness and correctness of treatment and the presence in the patient's history of comorbidities. Despite the clinical recovery of a patient with severe AHS, during convalescence there are profound changes in homeostasis [14-18].

DIAGNOSIS OF HERPES VIRUS INFECTION

The diagnosis of AHS is established on the basis of anamnestic and epidemiological data, typical clinical symptoms, as well as cytological-morphological studies. All patients under observation are given a set of clinical, laboratory and instrumental tests (clinical blood tests, immunological tests, etc.).

The diagnosis of oral mucosa pathology, diseases of red border of the lips and facial skin with the etiological role of herpes infection should be established using modern research methods.

Polymerase chain reaction (PCR) is one of the most modern molecular biological tests that can detect virus replication and its phase, determine and identify the DNA of virus nuclei. The PCR method is highly sensitive even to trace fragments of the virus, so a positive test does not mean the existence of an inflammatory process at present. The biological material that must be taken to diagnose a viral infection is also important.

Immunological methods for detecting herpesvirus antigens: IFR - immune fluorescence reaction; DIM - direct immunofluorescence method; ELISA - enzyme-linked immunosorbent assay; MFA is a method of fluorescent antibodies.

The presence of herpesvirus is determined by culturing the virus.

Histomorphological method - detection of vacuolar, ballooning dystrophy, spongiosis, "giant" multinucleated cells.

Cytological method in smears-prints determine "giant" multinucleated cells

Clinical blood test: lymphocytosis, monocytosis, atypical mononuclear cells, increased ESR.

Laboratory studies make it possible to make a differential diagnosis of diseases caused by different families of viruses, given that some enteroviruses (Coxsackie viruses) are also able to cause vesiculosis and the clinical manifestations on oral mucosa, similar to lesions caused by herpesviruses. [5].

HERPETIC STOMATITIS ADOPTED THERAPY

Treatment of herpes virus infections includes 3 stages:

Stage I - treatment in the acute period (antiherpetic drugs, drugs of interferon and its inducers, natural antioxidants, immunoglobulins, probiotics)

Table I. Treatment strategy of acute herpetic stomatitis

Stage of disease	Direction of treatment	Object of influence	Group of drugs	The application of drugs	
				local	general
development/ progression	etiotropic	VHS-1, VHS-2	antiviral agents (ideally during the first 3 days of symptomatic infection)	+	+
		immunodeficiency	immunotherapy/ immune strengthening	+	+
		dehydration	drink a lot (heavy drinking), rehydration		+
	pathogenetic	intoxication	drink a lot (maintenance of fluids and electrolytes), detoxification		+
		fever	antipyretics		+
		inflammation of oral mucosa (alteration, exudation)	non-steroidal anti-inflammatory drugs	+	
		pain when eating	rational diet, topical anesthetics	+	
	symptomatic	gums bleeding	antiseptics, hemostatic agents	+	
	pathogenetic	inflammation of oral mucosa (proliferation)	epithelization agents	+	
attenuation	symptomatic	pain during food intake	rational diet, topical anesthetics	+	
		gums bleeding	antiseptics, hemostatic medications	+	

Stage II - therapy in remission (immunomodulators, adaptogens, thymus hormones, probiotics). In the second stage of treatment, an in-depth examination of the patient by certain specialists for determining the general state of health is done.

Stage III is associated with dynamic monitoring and rehabilitation of patients.

Treatment of herpetic stomatitis, as well as any other infectious disease, should have an etiotropic, pathogenetic and symptomatic directions. The doctor's tactics in the treatment of patients with acute herpetic stomatitis should be determined by the severity of the disease and the period of its development.

Local therapy for acute herpetic stomatitis has the following objectives: to relieve or alleviate painful symptoms in the mouth; to prevent recurrent rashes of elements of lesion (reinfection); promote their epithelialization.

General treatment depends on the age, clinical condition of the patient and includes the use of drugs: detoxification therapy; hyposensitizing drugs (in severe forms

corticosteroids according to the scheme); antiviral drugs; immune-modulate drugs; analgesics, antipyretics and anti-inflammatory drugs; antioxidants; probiotics.

Summarizing the results of scientific research and practical work of dentists, we offer a strategy for the treatment of acute herpetic stomatitis (Table I) [8-10, 19-21].

For the prevention of acute herpes it is necessary to promote drive strict sanitary control with the use of individual hygiene products and dishes, cleanliness control of hands, a ban on kissing a patient, regularly ventilate room installation, etc.

CONCLUSIONS

In conclusion, it should be noted that acute herpetic stomatitis, of any form, is an acute infectious disease and requires in all cases the attention of a general physician and dentist together: to provide comprehensive treatment, to exclude contact with healthy patients, to take measures to prevent this disease in patients.

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The Authors declare no conflict of interest.

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