Oral manifestations of infections due to varicella zoster virus in otherwise healthy children

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Varicella zoster virus (VZV) causes varicella (or chickenpox) and establishes latency in nerve ganglia after the primary infection. The reactivation of virus later in life can cause mono- or polyneuropathy. The cranial nerves most commonly involved are five (herpes zoster or shingles), six, seven eight, nine and ten. In the present study we describe the oral lesions associated with VZV infections in normal children. In a 3 year period we examined 62 children, age 2 to 13 years old with diagnosed varicella and a 4 year old boy with herpes zoster at the 3rd branch of the trigeminal nerve. According to the clinical picture of varicella, the disease was defined as: (1) group A mild cases; (2) group B moderate cases; (3) group C severe. The manifestations of varicella were: mild varicella 19 children, moderate 26 children and severe 17 children. The results of the present study indicate that the prevalence of oral manifestations of varicella is related to the severity of the disease. In 17 severe cases, oral lesions were always present and the number was between 5 to 30. From 26 moderate cases, oral lesions were observed in 23 and the number was between 2 to 10. From 19 mild cases, oral lesions were present only in 6 cases and their number was 1 or 2. Often varicella's oral lesions resemble manifestations of other entities, and this may cause differential diagnostics problems.
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INTRODUCTION

Varicella-zoster virus (VZV) or human herpesvirus 3 (HHV-3) is a human pathogen, that has probably infected humans since prehistoric times.[1] VZV is a ubiquitous virus, that causes varicella, commonly known as chickenpox and establishes latency in sensory or/and occasionally in motor nerve ganglia after the primary infection.[2-4] VZV may re-emerge later in life, taking advantage of the decline in immune function that occurs with aging or with immunocompromised diseases.

VZV reactivation causes mononeuropathy or polyneuropathy. The cranial mono- or polyneuropathy can affect any cranial nerve and usually affects multiple nerves, causing central, cervical and peripheral effects. The cranial nerves, most frequently involved, are five (herpes zoster -known as shingles), six, seven (Ramsay Hunt's syndrome), eight, nine and ten.[3,6] Central nervous system infection due to VZV in AIDS has also been reported.[7] Moreover, there are many studies, in which recurrent aphthous ulceration is a possible clinical manifestation of reactivation of VZV infection.[8-10] However, the results of a recent study do not support a direct role for VZV in the pathogenesis of recurrent aphthous ulceration.[11]

Varicella is typically seen in children 5 to 9 years of age and adolescents.[12] Of 3 million cases of varicella per year in the U.S.A., more than 95% occur in children and adolescents.[13] In contrast, the incidence of the other VZV infections is very low in childhood. The reported estimated incidence for the herpes zoster (the most common VZV infection, except of varicella) is 0.74/1000 in the group under 9 years of age[13, 14] and 1/1000 in the group 10 to 15 years old annually.[15]

In otherwise healthy children, VZV infections are usually benign and self limited and serious complications, such as pneumonia, encephalitis, secondary bacterial infections, cerebellar ataxia, Reye's syndrome, etc, are unusual. In contrast, VZV infections are a significant cause of morbidity and mortality in immunocompromised patients.[16] These patients, with impaired

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Table 1. Categorization of 62 children with varicella, according to the severity of the disease, the number of patients with oral lesions, the number of the oral lesions that each one presents and the localization of oral lesions.

Varicella	Mild cases	Moderate cases	Severe cases
No of patients	19 (11g-8b)	26 (14g-12b)	17 (8g-9b)
No of patients with oral lesions	6 (4g-2b)	23 (13g-1Ob)	17 (8g-9b)
No of oral lesions	1-2	mean 5 (2-10)	mean 18 (5-30)
Location of oral lesions			
vermilion of lips	4	21	17
palate (hard-soft)	2	14	17
gingival	1		
cheek		3	6
lip mucosa		2	5
tongue		1	5

g: girl, b: boy

cell-mediated immunity, are slow to develop immunity and are prone to severe disease with dissemination of the virus to vital organs as the lungs, liver and brain.[17-20] Without effective antiviral therapy, death occurs in 7% to 20% of these patients.[18-21]

VZV infections are capable of producing lesions of the oral mucosa. In most cases, the clinical diagnosis is easy for the clinician, but, in many cases, it can be extremely difficult to distinguish between other entities and it is beneficial for all clinicians to have this in mind.

The purpose of the present study is to describe the oral lesions associated with VZV infections in otherwise healthy children.

PATIENTS AND METHOD

Patients

In a 3 year period (October 1997 to June 2000), we tried to locate normal patients infected with VZV during the age of childhood.

During this period, we examined 62 patients (33 girls and 19 boys, aged 2 to 13 years old mean age 6 years) with diagnosed varicella and one boy (4 years old) with diagnosed herpes zoster on the right side of the face at the 3rd branch of the trigeminal nerve.

The varicella was defined, according Kakourou *et al.*[14] as: **group A. mild cases:** children with fewer than 50 skin lesions and no fever; **group B. moderate cases:** children with 50 to 200 skin lesions; and **group C. severe cases:** children with more than 200 skin lesions and a fever of more than 38˚C.

None of the patients had been immunized with varicella vaccine and, also, none had taken any antiviral therapy.

Oral examination

Every child was clinically examined twice since the time of the appearance of the disease. The first examination was performed at the beginning of the disease (one or two days after the appearance of the rash) and the second examination during the duration of the disease (three to nine days afterwards). The examinations were performed by the same specialist in oral medicine, who recorded all the oral lesions.

RESULTS

Varicella patients

Group A. Nineteen children manifested mild varicella (11 girls - 8 boys). Six (4 girls - 2 boys) presented 1-2 oral lesions. In 4 cases the oral lesions appeared on the vermilion of the lips, in 2 cases at the palate (hard and soft) and 1 case on the gingiva.

Group B. Twenty-six children manifested moderate varicella (14 girls - 12 boys). Twenty-three (13 girls - 10 boys) presented 2 to 10 oral lesions (mean lesions 5). In 21 cases the oral lesions were located on the vermilion of the lips, in 14 at the palate, in 3 on the cheek, in 2 on the lip mucosa and in 1 on the tongue.

Group C. Seventeen children manifested severe varicella (8 girls - 9 boys) and all of them presented 5 to 30 oral lesions (mean lesions 18). All cases presented lesions on the vermilion of the lips and on the palate, 6 cases of the cheek, 5 on the lip mucosa and 5 on the tongue. The results of this study are summarized in Table 1.

Description of oral lesions

Each single oral lesion of the mucosa begins as a small vesicle (3mm to 4 mm) or blister (Figure 1), which quickly ruptures and the clinician usually finds slightly painful or painless, flat-based ulcers with erythematous halos and a white or whitish/yellow or brown ulcer bed (Figure 2 to 4). These ulcers often resemble a minor recurrent apthae. When multiple lesions are present, because of the vesicles collapsing together, they give the appearance of bigger lesions (Figure 5). New vesicles continue to erupt for 2 or more days. Old ruptured lesions, intermixed with fresh clear vesicles, can be observe on the moderate and severe varicella cases (Figure 6).

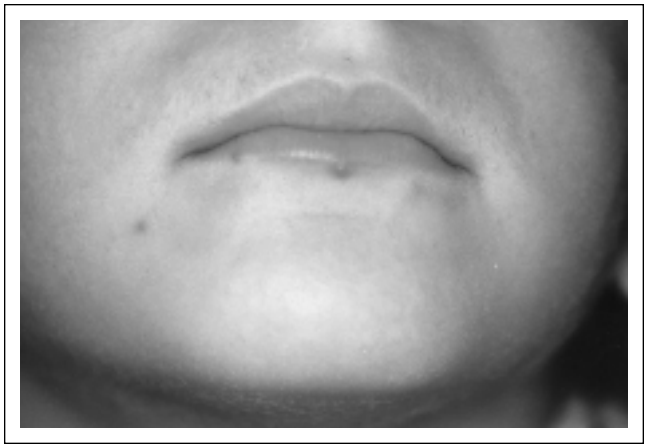

Figure 1. Two blisters on the vermilion of the lips, in a mild varicella case.

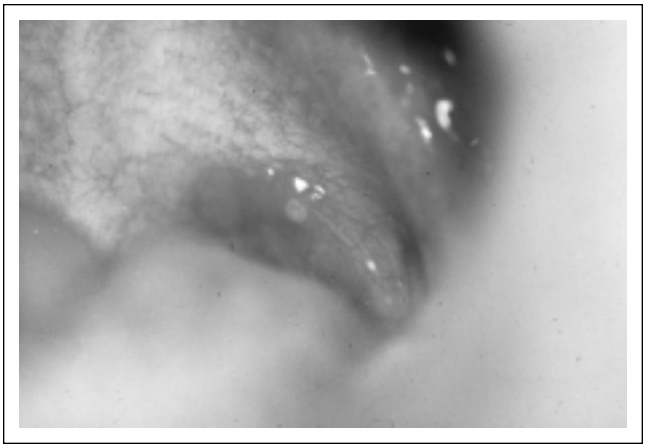

Figure 2. Solitary oral ulcer resembling minor recurrent apthae on the soft palate, in a mild varicella case.

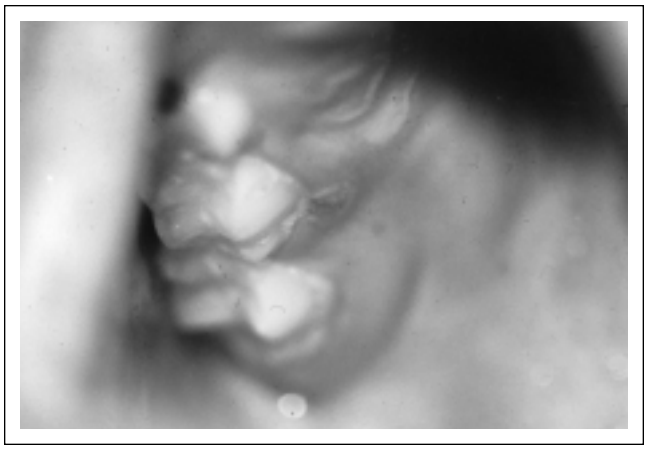

Figure 3. Oral ulcer with brown bed on the hard palate, in a mild varicella case.

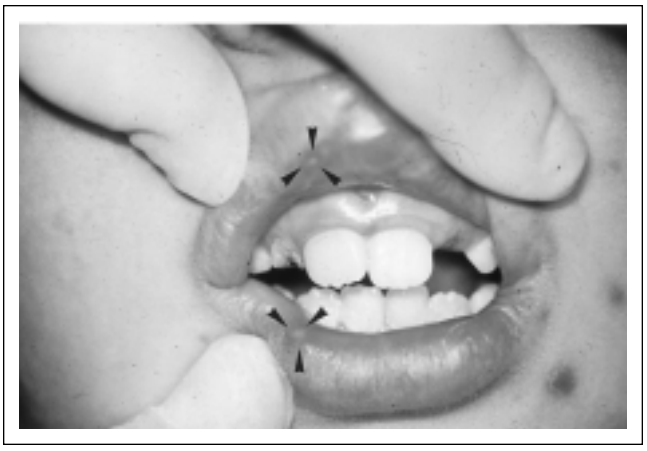

Figure 4. Two ulcers on the vermilion of the lips, in a moderate varicella case.

Trigeminal herpes zoster patient

A 4 year old, otherwise healthy boy developed herpes zoster on the right side of the face, at the 3rd branch of the trigeminal nerve (Figures 7, 8). Except for the appearance of a skin rash on the face and on the oral mucosa, we observed few vesicles and blisters on the body skin also (Figure 9).

No one in his household had been infected with varicella or any other VZV infection after his birth and his mother had not been exposed to varicella or any other VZV infection during pregnancy.

Description of the oral lesions

At the time of the clinical examination, intraoral lesions were observed. The oral mucosa of the child demonstrated unilateral swelling and scattering of small painless, vesicles (3mm to 4mm) and flat-based ulcers (broken vesicles) on the right side of the tongue, cheek and chin. The enanthema appears on an erythematous base, along the course of the involved nerve. There were no other (except cutaneous lesions) clinical manifestations (pain, fever, lymphadenitis or neurological changes). The patient did not receive any antiviral therapy. During 15 days of follow up, marked improvement was observed. The number of lesions decreased markedly and the existing lesions dried.

DISCUSSION

In the bibliography, it is mentioned that oral lesions occur in small numbers (usually 1 to 7) in varicella.[12] The results of the present study indicate that the prevalence of oral manifestations of varicella relates to the severity of the disease. In cases where the clinical picture of the disease is severe, oral lesions are always present. From 17 cases of the present study (group C - severe cases), oral manifestations were always present and the number of oral lesions was between 5 to 30. In contrast, in cases of moderate clinical picture, the number and the prevalence of oral lesions are decreased. From the 26 cases that we examined and categorized to group B (moderate cases), oral manifestations were observed in 23 cases and in these cases the oral lesions

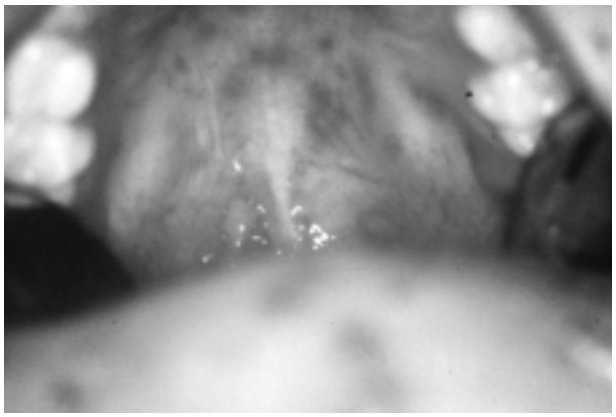

Figure 5. Ulcers and multiple vesicles which collapse together on the palate, in a severe varicella case.

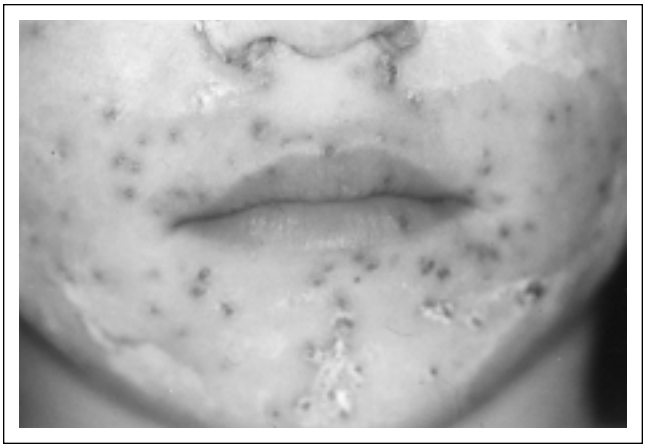

Figure 6. Old ruptured lesions intermixed with fresh blisters, in a severe varicella case.

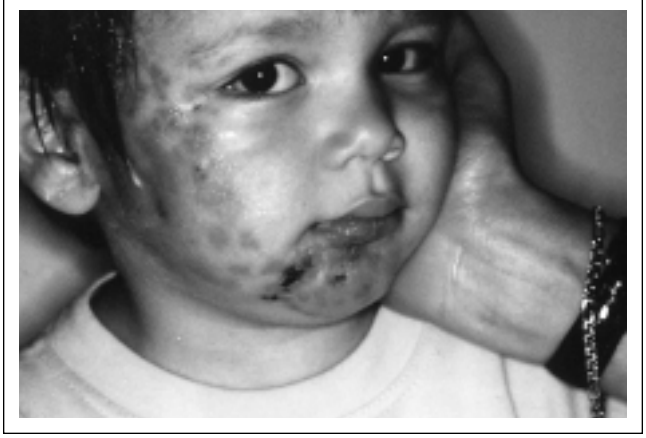

Figure 7. Herpes zoster of the 3rd branch of trigeminal nerve in a 4 years old child.

were between 2 to 10. From the 19 cases of group A (mild cases), oral manifestations were present only in 6 cases, where the number of lesions was between 1 to 2.

In cases where the clinical picture of the disease is severe, we observed that the oral lesions were present for 5 to 10 days and new vesicles continued to erupt for 2 or more days. Old ruptured lesions, intermixed with fresh clear vesicles, can be observed. In cases of moderate clinical picture, the duration of the presence of oral lesions was decreased from 3 to 8 days, and in cases of mild clinical picture from 1 to 3 days.

The multiple oral mucosal vesicles and ulcers (in groups B and C), that resemble lesions seen in primary herpes simplex virus infection, are also common. Often, the vesicles collapse together, giving the appearance of bigger lesions. The clinical appearance of skin lesions and the co-existence of other clinical manifestations of the disease (fever, malaise, lymphadenitis, etc) make the diagnosis of varicella relatively easy. Contrary to that, the small number of oral lesions (group A), which resemble minor recurrent apthae, and the small number of skin lesions (commonly 3 to 5) and the possible absence of other general clinical manifestations, are possible may create differential diagnostic problems.

Today, a vaccine against varicella is available. Clinical trials of the vaccine were introduced for both normal and immunocompromised children, and a protective, but not completely preventive effect against varicella infection was reported.[22] Those who do develop varicella after vaccination have milder symptoms, with fewer skin and mucosal lesions. Moreover, development of herpes zoster is rarely observed among healthy children following vaccination.[23, 24] Taking in consideration that today vaccination against varicella is widely used, resulting in the decrease of the moderate and severe cases, many cases, which present a mild clinical picture, create differential diagnostic problems.

As far as the localization of oral lesions is concerned, we observed that in the three groups the vermilion of lips was the main area of clinical appearance (41 cases), followed by the palate (33 cases) and any other oral site. The appearance of oral lesions is more common in ceratosic areas of the oral mucosa.

It has been mentioned that oral lesions sometimes were developed prior to the skin lesions.[12] In the present study, we were unable to observe this, because the first oral examination of the children took place after the diagnosis of varicella. In a relative question to the parents and to the older patients, none were able to give us a credible answer, concerning the time of the first examination that took place prior to the beginning of the disease (one to two days after appearance of the disease).

Treatment of the oral lesions in general is not necessary, since they are painless or slightly painful.[12]

After primary infection (varicella), VZV becomes latent in nerve ganglia. It is estimated that 0.3% to 0.50 o of the population suffers from herpes zoster, which is due to VZV reactivation.[25] The herpes zoster of the head represents the 5% of the total cases.[26] When herpes zoster

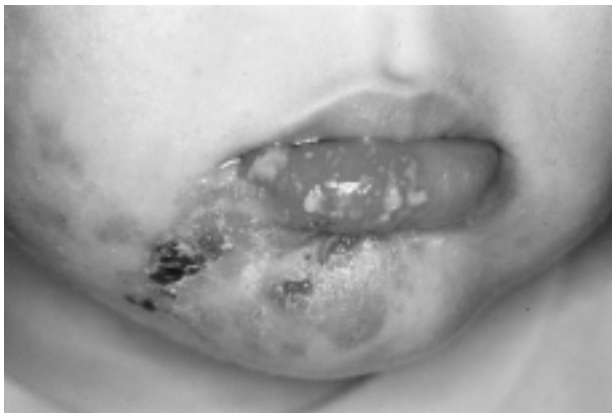

Figure 8. Magnification of the case of the fig. 7, where in details we observed a unilateral skin and oral mucosa lesions.

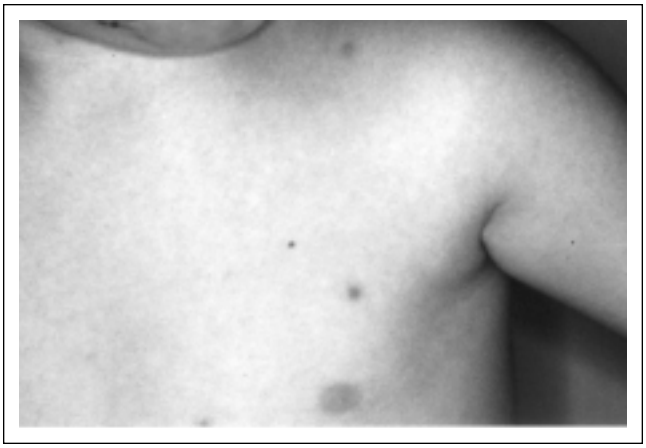

Figure 9. Body skin lesions of the same (fig. 7, 8) 4 years old patient.

involves the trigeminal nerve, the ophthalmic branch is most commonly involved. Approximately 15% to 20% of the cases of herpes zoster of the trigeminal nerves affect either the 2nd and the 3rd branch.[25]

The most important etiological factors for herpes zoster outbreak are increased age or a compromised immune system.[27] The greatest percentage of varicella's cases is observed in children, with the highest incidence at 5 to 9 years of age. For this reason, the appearance of herpes zoster in younger children is extremely rare.[28] As we have already stated, in individuals less than 9 years of age, there is an estimated incidence of 0.74/1000[13, 14] patients and in individuals 10 to 15 years of age the incidence is 1/1000 patients, annually.[15] Terrada *et al.*[29] found that, in children less than 7 years of age, the involvement of cranial nerve dermatomes was 25%. In children older than 7 years of age 78.9% involved the thoracic dermatomes. The estimation for the trigeminal herpes zoster is even less. Kakourou *et al.*[14] in a 3 year study in healthy and immunosuppressed children, found 21 children with herpes zoster. Thirteen of them with immunodeficiency and 8 were normal. From those 21 children, 4 presented trigeminal herpes zoster and 3 of them belonged to the healthy group.

In the present study only 1 case was found with herpes zoster of the 3rd branch of trigeminal nerve, at the age of 4 years old. In this case, except for the skin rash and the oral mucosa manifestations at the 3rd branch of the trigeminal nerve, we observed few vesicles and blisters on the body skin also.

In the present case, it is not established that the child had been affected previously by VZV. The possibility of a patient developing herpes zoster without previous varicella requires the following conditions: 1) the mother developed varicella or zoster during pregnancy and the first exposure to VZY was in the uterus. The rate of varicella transmission from mother to fetus is close to 24% during pregnancy;[30] 2) the mother is VZV immune and he/she was exposed to varicella during the first few months of life, when transplacental antibodies were still present; 3) after vaccination;[23, 24] 4) subclinical or mild development of varicella without diagnosis. The first two situations usually occur under the age of 2 years.[24] The child of the present case had not been vaccinated. Due to these two reasons, we believe that, in this case, the child must belong to the fourth situation.

The clinical diagnosis of herpes zoster at the trigeminal nerve is relatively easy. If oral mucosa and skin are involved, the herpes zoster has the appearance of unilateral scattering small painful vesicles, blisters and ulcers. In some cases the lesions affect only the oral mucosa.[26]

In the present case, except of the observed lesions in oral mucosa and head skin, we also observed a few non-localized vesicles on his body skin.

Many patients report an intensely painful period of 2 to 3 days before the skin eruption. The pain is described as dull, nagging, nonspecific, non-localized and affecting the entire distribution of the involved nerve. Sometimes the infection has been presenting the picture of an acute pulpitis.[27] These findings are common in adults, but in children herpes zoster is a painless process.[14, 28] Also, in children, post-infection pain or hypnoanesthesia are not usually observed but they are observed in adults.[26]

According to the review of the available literature and the clinical experience of Rothe *et al.*[31] treatment of herpes zoster in normal children is not recommended, as it is relatively benign. Contrary to that, other authors suggest the treatment of the disease with the use of acyclovir.[12-14, 26] The efficacy of acyclovir for the treatment of primary and recurrent VZV infections in children has reduced the morbidity and mortality of these illnesses in immunocompromised children dramatically.[32] In children, acyclovir appears to be better tolerated than adults.[31] Possible side effects are nausea and vomiting, which occur in less than 8% of adults and 3% of the

pediatric population, respectively.[13]

The introduction of varicella vaccine for immunization of healthy children is expected to have a gradual impact on the incidence of VZV infections in the population.[32]

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