

Epidemiologic, clinical findings and risk factors of recurrent herpes labialis in healthy adult patients: a case-control study

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ABSTRACT

Objectives: Herpes labialis is a common viral infection and characterized by recurrent vesicular lesion primarily on the lips and perioral skin. The aim of this study was to determine the epidemiological, clinical characteristics and trigger factors associated with recurrence herpes labialis in adult patients.

Methods: This case-control study was conducted with the participation of one hundred adult patients and the same number of control. Data collected about demographics, clinical, as well as trigger factors from individuals who met inclusion criteria.

Results: Seventy-four percent of cases and 34% of controls were female that showed significant difference ($p < 0.001$). Mean body mass index of patients was significantly higher than controls ($25.9 \pm 2.9 \text{ kg/m}^2$ versus $22.0 \pm 2.9 \text{ kg/m}^2$, $p < 0.001$). The most common location of the lesions during the last episode of infection was upper lip (65%). The number of lesions was single in 58% and multiple in 42% of patients. The frequency of episodes per year was more than two attacks each year in most patients (83%). Positive family history of recurrence herpes labialis was found in 50% and 20% of cases and controls respectively ($p < 0.001$). Emotional stress (61%), sunlight exposure (54%) and flu (37%) were the main triggering factors reported by the patients.

Conclusions: This study revealed that recurrence herpes labialis is more common in women and on the upper lip. Family history of recurrence herpes labialis was positive significantly in patients. The most common trigger factors were stress, sunlight exposure, flu. Higher body mass index was a probable risk factors for recurrence herpes labialis.

Keywords: Recurrence herpes labialis, adult, epidemiology, trigger factors

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Recurrence herpes labialis (RHL) is one of the most prevalent and clinically common viral infectious diseases in general population [1]. It is caused by the reactivation of latent infection of herpes simplex virus-1 (HSV-1). About 45% to 98% of the world population are infected by HSV-1 and 15 to 40% of infected people may develop RHL [2]. The primary HSV-1 infection typically occurs in early



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childhood and is asymptomatic or can cause herpetic gingivostomatitis. After the primary infection, the virus ascends the sensory nerve axons and establishes chronic, latent infection in the trigeminal ganglion [3]. Recrudescence is a consequence of centrifugal migration of the reactivated virus from the trigeminal ganglion to the periphery and its local replication. Recurrent lesions are common on the mucocutaneous junction of the lips and less common intraorally [4].

Most patients experience prodromal symptoms prior to the appearance of lesions which is associated with pain, itching, burning, tingling and paresthesia. After about 24 hours lesions appear and are characterized by erythema, papules and blisters. The lesions crust over and heal without scarring over a period of 1-2 weeks [5]. The diagnosis of RHL is based on the history, classic location and clinical appearance of the lesions [6].

RHL varies in severity from patient-to-patient. In some individuals, infection is infrequent and considered a minor problem. But in others, episodes of recurrences are frequent and may be painful, long-lasting, disfiguring and negatively affect the patient's quality of life [7, 8]. The factors that trigger the outbreak of RHL are not completely understood. The most important are stress, fever, dental manipulation, upper respiratory tract infections, ultraviolet light, menstruation, trauma and immune incompetence [9].

Studies about RHL in adults have been equivocal in identifying some of the risk factors. The present study was designed to examine epidemiological and clinical characteristics of the disease in a group of adult patients and comparing findings of patients with a control group. Another aim of the study was to evaluate some risk factors associated with RHL.

METHODS

This case-control study was conducted from February 2016 to May 2017 in Semnan, Iran. All adult patients (≥ 18 years) with diagnosis of RHL who were visited in Dermatology and Infectious diseases clinics of Semnan University of Medical Sciences were considered for participation in the study. RHL was defined as at least one episode during the recent year.

Control groups were selected from adult individuals without history of RHL by the systematic

sampling. Subjects with history of connective tissue disorders, receiving immunosuppressive drugs and those with non-ascertainable clinical status were excluded.

A structured data collection sheet was used to obtain information about demographics, clinical, as well as trigger factors from individuals who met inclusion criteria. Basic data collected included age, gender, blood group and body mass index (BMI). During the visit patients were clinically examined to confirm its presence and the location of lesion. Also, participants were asked to indicate the age at first episode of RHL, perceived precipitating factors, number of lesions (single or multiple), duration of lesions to heal, annual recurrence rate and family history of RHL. A short verbal stress rating scale was used for measuring the perception of stress [10]. Sunlight exposure was defined as being outdoors more than one hour for three days before the appearance of lesions.

Informed consent was obtained from all participants before enrollment. The study protocol was approved by the Research Council and Ethical Committee of the Semnan University of Medical Sciences.

Statistical Analysis

Data were analyzed by Kolmogorov-Smirnov, Chi Square, student's *t* tests and logistic regression analysis using SPSS 18.0. A *p* value less than 0.05 was considered statistically significant.

RESULTS

Finally, 100 patients with diagnosis of RHL met inclusion criteria and were enrolled. Same numbers of controls were selected. The mean age of patients was 37.1 ± 13.4 years and for the controls was 28.2 ± 7.2 years ($p < 0.001$). Seventy-four percent of cases and 34% of controls were female that showed significant difference ($p < 0.001$). Mean BMI of patients was significantly higher than controls (25.9 ± 2.9 kg/m² versus 22.0 ± 2.9 kg/m², $p < 0.001$). The most common blood group among the patients and controls was A (44% and 55% respectively). But distribution of ABO blood groups in the patients with RHL was not significantly different from the control group ($p = 0.109$). Basic characteristics of cases and controls are

Table 1. Distribution of basic characteristics in individuals with and without recurrent herpes labialis

Characteristics	Study Group		p value
	Patients (n = 100)	Control (n = 100)	
Age (year)			< 0.001
< 40	22	14	
40-59	9	1	
≥ 60	69	85	
Gender			< 0.001
Male	26	66	
Female	74	34	
Body Mass Index (kg/m²)			< 0.001
< 18.5	0	9	
18.5-24.9	37	76	
25-29.9	58	13	
≥ 30	5	2	
Family History			< 0.001
+	50	20	
-	50	80	
Blood Group			0.109
A ⁺	44	55	
B ⁺	15	16	
AB ⁺	20	20	
O ⁺	21	9	

given in Table 1.

The number of lesions was single in 58% and multiple in 42% of patients. The location of the RHL lesions during the last episode of infection are listed in Table 2. The mean duration of suffering from RHL in patients was 12.10 ± 11.03 years. The mean duration of each episode was 7.24 days. The mean interval between attacks was 12.04 ± 9.37 months. The frequency of episodes per year was more than two

attacks each year in most patients (83%). Positive family history of RHL was found in 50% and 20% of cases and controls respectively ($p < 0.001$).

The most common trigger factors reported by participants were stress, sunlight exposure and flu (Table 3). The results of logistic regression analysis showed that BMI (OR=2.1, 95% CI:1.16-2.8, $p < 0.001$) was significantly higher in patients with RHL.

Table 2. Distribution of herpes labialis lesions at the time of examination

Location	Percentage
Upper lip	65
Lower lip	40
Nose	13
Cheek	1

Table 3. Perceived triggers for the episode of herpes labialis among the patients

Trigger	Percent
Stress	61
Sunlight exposure	54
Flu	37
Fever	33
Trauma	2
Menstruation (in women)	9

DISCUSSION

Recurrence herpes labialis is a very common disease worldwide. The relationship between some risk factors and the occurrence of the disease is somehow complex. Also, the prevalence of predisposing factors may vary between different populations which has led to discordant findings among studies.

A striking finding in our study was the significantly higher BMI in patients with RHL compared with controls. Based our knowledge no previous study evaluated this variable. Obesity has some effects on the immune response through a variety of immune mediators. It has been suggested that the adipose tissue participates actively in inflammation and immunity by releasing a variety of proinflammatory and anti-inflammatory factors. This leads to dysregulated immune response and may leads to susceptibility or reactivation of infections in individuals with high BMI [11]. Several studies in adult suggest that BMI was associated with the risk of some infections including skin, respiratory, urinary tract and nosocomial infections [12]. Bernstein *et al.* [13] reported that having a larger BMI was associated with higher human herpes virus type 8 infections.

According to our results, RHL was more common in females. Similarly, this sex difference has been reported in some other studies [14-16]. In contrast in Embil *et al.*'s study [17] RHL prevalence was found to be higher among men than among women. On the other hand, some other researcher reported that RHL was not statistically significant difference between two genders [18, 19].

In the present study the lesions were more common on the upper lip than lower lip that showed comparable pattern with some other studies [20, 21]. The results of the Sawair *et al.* [22] study showed a slight higher occurrence of the lesions on the lower lip (51.9%) than upper lip (46.2%).

Information from our patients indicated that most individual experienced more than two episodes of herpes labialis per year. Similarly, Axell *et al.* [21] reported more than two episodes per year. This finding is in contrast with most previous reports stated that majority of patients experienced ≤ 2 episodes of herpes labialis per year [18, 23, 24]. One probable explanation for this difference is that patients with one

or two episodes may not seeking medical care for their problem.

Studies in adults about the trigger factors of RHL showed different results. The most common factors reported by the participants in this study were stress, sunlight, flu and fever. Similarly, a higher level of perceived stress was the most common associated risk factors of RHL [18, 25] or one of more common trigger factors in some studies [20, 22]. Suggested biologic mechanism is the association between changes in stress and immune and neuroendocrine markers especially the modulations of T-lymphocyte function that can leads to virus reactivation [26, 27]. Psychological stress, through its suppression of both innate and adaptive immune responses, especially CD8+ T cell control of latent HSV-1 infections may be an important factor in the reactivation of herpes infections [28]. Other studies reported different trigger as the most common provocative factors of RHL [16, 23]. The difference in these findings might at least partly be explained by differences in the study design, patients' selection, and number of samples.

According to the patients, the mean duration of each episode was 7.24 days that is in accordance with Sawair *et al.*'s study [22] (mean 7.15 ± 3.1 days). A shorter healing time was reported by Axell *et al.*'s study [21] in most cases. Positive family history of RHL was significantly more common in patients. Most previous studies confirmed this finding [18, 22, 23].

Limitations

Our study has several limitations that should be taken into account in interpreting the findings. First, the eligible patient number is relatively small in this study. Second, we assessed patients in university affiliated hospital, so that referral bias may be occurred. Third, because of the difficulty in remembering past events, the likelihood of recall bias is present.

CONCLUSION

Our study revealed that RHL is more common in women and on the upper lip. Family history of RHL was positive significantly in patients. The most common trigger factors were stress, sunlight exposure,

flu and fever. Higher BMI was a probable risk factors for RHL. Controlling of stress, sunlight exposure, fever and BMI may lead to reducing episode of the diseases.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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