

Epidemiologic aspects of recurrent herpes labialis among Jordanian university students

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ABSTRACT

الأهداف: دراسة الخصائص الوبائية لهربس الشفاه المتكرر (RHL) عند عينة من السكان الشباب البالغين وتقييم العلاجات لدى المصابين منهم.

الطريقة: أجريت دراسة مقطعية على عينة عشوائية تتكون من 1000 طالب يدرسون في الجامعة الأردنية، عمان، الأردن، خلال الفترة من مايو وسبتمبر 2009م. تمت معاينة الطلبة وسؤالهم عن كافة الأمور المتعلقة بهذا المرض والسيطرة. تم استخدام اختبار T، واختبار المربع تشاي لمقارنة الاختلافات بين المجموعات.

النتائج: كان مدى انتشار المرض اللحظي يساوي 2.3%، والسنتوي 17%، والعمرى 26.4%. تأثر مدى الانتشار إحصائياً بمكان السكن، والدخل العائلي، وكلية الطالب ولم يتأثر بجنس الطالب، الحالة الاجتماعية، والحالة الصحية، والتدخين، والتقرح القلاعي المتكرر. أكثر المناطق المصابة كانت الطرف الأيسر من الشفاه السفلية والوعكة الصحية، والضغط النفسي، والحالة الجوية كانت أكثر العوامل المحفزة على ظهور هربس الشفاه. كان معدل بداية ظهور المرض منتصف العقد الثاني من العمر. تكرر المرض مرتين على الأقل في العام عند 51.2% من مجموع الأشخاص المصابين، و61.7% من العينة أقروا بإصابة أحد أفراد العائلة. ما يقارب نصف الأشخاص المصابين بالمرض حاولوا علاج الإصابة و18.2% منهم فقط استخدموا مضادات الفيروسات. استخدم البعض أحمر الشفاه، أو الفازلين، أو معجون الأسنان، أو الطحينية لتغطية مكان الإصابة. كان معظم المصابين يطلبون النصيحة العلاجية من المعارف، والأصدقاء وطلب 26.3% فقط النصيحة من المختصين في القطاع الصحي.

خاتمة: كان انتشار هربس الشفاه المتكرر (RHL) في هذه العينة كبيراً. هنالك حاجة لتعريف المرضى بالعلاجات الطبية المناسبة لهذا المرض لتخفيف معاناتهم، وتحسين نوعية الحياة لديهم.

Objectives: To study the epidemiologic aspects of recurrent herpes labialis (RHL) in a young adult population and to evaluate treatments used by affected patients.

Methods: A cross-sectional survey conducted on a random sample of 1000 students of The University of Jordan, Amman, Jordan between May and

September 2008. Subjects with RHL were identified and asked to describe their disease and its management. Chi-square and t-test were used to compare differences between groups.

Results: The point prevalence of RHL was 2.3%, annual prevalence was 17%, and lifetime prevalence was 26.4%. The prevalence was related to the place of living, income, and college, but not to gender, marital status, medical history, smoking, or aphthous stomatitis. Eruptions occurred mostly on the left side of the lower lip and systemic upset, stress, and cold weather were the main triggering events. The mean age of onset was approximately 15 years. Of the cases, 51.2% reported at least 2 recurrences annually and 61.7% had positive family history. Nearly one-half of cases have treated the lesions and only 18.2% have used antiviral therapies. Some used lipstick, vaseline, tahini, or toothpaste to cover lesions. Treatment was recommended mostly by relatives and friends, only 26.3% sought treatment advice from medical practitioners.

Conclusion: A high prevalence of RHL among this population was found. There is a need to educate patients with RHL on treatment options available to reduce their distress and to improve their quality of life.

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After the primary infection, which usually occurs in childhood, herpes simplex virus type 1 (HSV-1) is thought to remain latent in sensory ganglia for the life of the host.¹ Periodic recurrences, manifested usually as recurrent herpes labialis (RHL), are usually triggered by a variety of endogenous or exogenous factors, including cold weather, sunlight, infection, trauma, and stress.²

Recurrent herpes labialis, or cold sores, is a self-limiting infection that causes pain and well-localized blistering on the mucocutaneous junction of the lips.³ Fever and constitutional symptoms are rare and healing is usually complete in 7-10 days without scarring. Most people have no warning of the recurrent attack, but some experience a recognizable prodrome.¹ Prompt treatment with oral or topical antiviral medications can shorten the duration of eruptions and palliate symptoms. Prophylactic treatment with antiviral medications might help prevent relapses.⁴ In addition, any counteracting triggers can greatly reduce symptoms from a recurring cold sore outbreak. For example, simple application of sunscreen or lip balm may prevent an outbreak of RHL.³ Prevalence of HSV-1 infection is high worldwide, but varies markedly by country and population subgroup.⁵ Herpes simplex virus type 1 seroprevalence was particularly high (80%) among young adults in some Middle East countries.⁶ The epidemiology of recurrent herpetic infections has been relatively neglected. In addition, the reported prevalences in these studies may refer to lifetime reported disease occurrence (lifetime prevalence [LTP]), or to one-year reported disease occurrence (annual prevalence, [AP]), or to the proportion of subjects presenting with clinically apparent lesion (point prevalence [PP]).⁷⁻¹⁷ No data on RHL epidemiological aspects were available for Jordan or other Arab countries in the region. To allow a better understanding of the burden of infection, the present study was designed to examine the prevalence and clinical characteristics of RHL in a Jordanian population and to describe treatments used by patients to encounter this infection.

Methods. Face-to-face interviews were conducted with randomly selected students studying at the University of Jordan, Amman, Jordan in the period between May and September 2009. Systematic random sampling of students leaving lecture rooms in the medical, scientific, and humanitarian hall complexes in the university was conducted. The study sample consisted of 1000 students. Included in the sample were students who were studying at that period at the University of Jordan, and were randomly selected. We excluded non-Jordanian students and few students who were uncertain on the history of RHL, and could not decide if they had positive history or not. The students were given sufficient details on RHL and showed pictures of typical cases of the disease. They were also informed and showed pictures of recurrent aphthous stomatitis (RAS) to prevent mistaking it for RHL. Students who agreed to participate were subsequently asked if they have RHL at the present time (PP), if they had RHL in the last 12 months (AP), or if they have ever had RHL (LTP).

Patients who had RHL at time of survey were clinically examined to confirm its presence. With reference to the last episode of RHL, the patients were asked on their chief complaint, to point to the exact location of lesions, and to mention what they think as RHL precipitating factors. The students who had RHL or history of RHL were also asked on their age at first episode, duration of lesions to heal, annual recurrence rate, family history of RHL, and if they have treated the latest episode. If the answer was yes concerning treatment, the students were then asked on the nature of treatment used, the person who recommended the treatment, and if they have found this treatment helpful in reducing their distress. Data on demographic characteristics were collected for each student.

Statistical analysis was performed using SPSS for Windows release 16.0 (SPSS Inc., Chicago, IL, USA). Frequency distributions were obtained and mean values for continuous variables (\pm value of standard deviation) were calculated. Chi-square test and t-test were used to compare differences between groups. Statistical significance was set at $p < 0.05$.

Results. The sample was composed of 1000 students, 373 men and 627 women, and their ages ranged from 17-29 years (mean = 20.3 ± 1.79 years). Of the recruited students, 23 (2.3%) had PP, 170 (17%) had AP, and 264 (26.4%) had LTP of RHL. Age of the students had no significant effect on prevalence of RHL. Other characteristics of the students and their associations with PP, AP, and LTP are summarized in Table 1. Annual prevalence and LTP of RHL were significantly higher in students whose families were living outside the capital city of Amman far from the university. Interestingly, PP of RHL was highest in students studying at humanitarian colleges, followed by scientific colleges, and least in health colleges such as dentistry and medicine ($p = 0.03$, χ^2 test). A relation with income was found, LTP of RHL decreased significantly as the household monthly income increased ($p = 0.04$, χ^2 test). On the other hand, the prevalence of RHL was not significantly affected by gender, marital status, medical history, or smoking history of the students. In addition, no significant association was found between LTP of RAS and PP, AP, or LTP of RHL. The complaints during the last attack of RHL for those who had history of RHL (264 students) was pain and discomfort in 92 (34.8%) students, poor aesthetic in 85 (32.2%), pain and poor aesthetic in 78 (29.6%), while 9 (3.4%) had no complaints. The location of the RHL lesions during the last episode of infection is shown in Table 2. Lesions developed on the lower lip in 51.9% of cases and on the upper lip in 46.2% of cases and were more common on the left side (45.8%) than the right side (29.9%). Eight

(3%) of the students with positive LTP of RHL had bilateral lesions and 56 (21.2%) had midline lesions with involvement of the nostrils in 4 cases. There were no age or gender differences in site distribution of RHL lesions. According to the students, the duration of the lesions (last episode) ranged between 3 and 15 days (mean 7.15 ± 3.1 days). When asked about the factors they thought were associated with the development of their lesions, associated illness was reported by 80 students (30.3%), stress by 57 (21.6%), weather changes, particularly cold conditions, by 40 (15.2%), certain types of food such as chocolate, hummus, falafel, and salty food by 29 (11%), trauma by 9 (3.4%), dryness of the lips by 4 (1.5%), hormonal factors by 3 (1.1%), and acne drugs by one student (0.4%). In 41 cases (15.5%) no specific predisposing factors were determined. Precipitating factors were not significantly different between men and women although stress was reported more in women and weather changes more in men. Of the 264 students with positive RHL history, 216 (81.8%) recalled the onset of their lesions. The first attack of RHL occurred between the ages of 4 and 22 years with mean age of 14.6 ± 3.8 years (median 15 years) and without significant effect of gender. The onset occurred before the age of 20 years in 95.4% of the students.

Positive family history of RHL was found in 163 cases (61.7%). As shown in Table 3, once per year was the most frequent recurrence rate reported by the subjects (98 students, 37.1%), but in 77 students (29.2%) it was twice per year, and in 58 students (22%) it was 3 or more attacks per year. Recurrence was infrequent (less than once/year) in 31 students (11.8%). As shown in Table 3, approximately 548 episodes of herpes labialis were experienced by the 1000 student each year (total disease burden of herpes labialis). Of the 264 students with history of RHL, 137 (51.9%) have used products to treat the last episode of the infection. The tendency to treat RHL or not was not significantly affected by age of the student, gender, place of living, marital status,

Table 2 - Location of recurrent herpes labialis lesions in 264 students with positive history of the disease.

Location	Upper lip		Lower lip		Upper & lower lips		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Right side	29	(11.0)	48	(18.2)	2	0.8	79	(29.9)
Midline	42	(15.9)	13	(4.9)	1	0.4	56	(21.2)
Left side	48	(18.2)	71	(26.9)	2	0.8	121	(45.8)
Bilateral	3	(1.1)	5	(1.9)	-	-	8	(3.0)
Total	122	(46.2)	137	(51.9)	5	1.9	264	(100)

Table 1 - Demographic variables of the students and its relation to prevalence of recurrent herpes labialis.

Variable	Total		PP		P-value	AP		LTP		P-value
	n	(%)	n	(%)		n	(%)	n	(%)	
<i>Gender</i>					0.12					0.61
Women	627	(62.7)	11	(1.8)		107	(17.1)	169	(27.0)	
Men	373	(37.3)	12	(3.2)		63	(16.9)	95	(25.5)	
<i>Place of living</i>					0.49					0.003
Amman	797	(79.7)	17	(2.1)		124	(15.6)	194	(24.3)	
Other regions	203	(20.3)	6	(3.0)		46	(22.7)	70	(34.5)	
<i>Marital status</i>					0.49					0.89
Single	980	(98.0)	23	(2.3)		169	(17.2)	259	(26.4)	
Married	20	(2.0)	0	(0)		1	(5.0)	5	(25.0)	
<i>College</i>					0.032					0.08
Health	295	(29.5)	2	(0.7)		47	(15.9)	80	(27.1)	
Science	395	(39.5)	9	(2.3)		58	(14.7)	90	(22.8)	
Humanitarian	310	(31.0)	12	(3.9)		65	(21.0)	94	(30.3)	
<i>Household income JD/month</i>					0.27					0.04
<250	44	(4.4)	2	(4.5)		9	(20.5)	16	(36.4)	
250-1000	662	(66.2)	16	(2.4)		116	(17.5)	181	(27.3)	
>1000	294	(29.4)	5	(1.7)		45	(15.3)	67	(22.8)	
<i>Smoking</i>					0.22					0.20
No	670	(67.0)	15	(2.2)		122	(18.2)	184	(27.5)	
Ex-smoker	28	(2.8)	2	(7.1)		7	(25.0)	10	(35.7)	
Yes	302	(30.2)	6	(2.0)		41	(13.6)	70	(23.2)	
<i>Medically fit</i>					0.23					0.45
Yes	905	(90.5)	23	(2.5)		154	(17.0)	242	(26.7)	
No	95	(9.5)	0	(0)		16	(16.8)	22	(23.2)	
<i>History of RAS</i>					0.62					0.26
No	470	(47.0)	12	(2.6)		79	(16.8)	132	(28.1)	
Yes	530	(53.0)	11	(2.1)		91	(17.2)	132	(24.9)	

PP - point prevalence, AP - annual prevalence, LTP - lifetime prevalence, P-value by Chi-square test, JD - Jordanian Dinar (1 JD= ≈1.4\$), RAS - recurrent aphthous stomatitis

Table 3 - Number of episodes of recurrent herpes labialis experienced by each student in the 1000 sample in the last year.

Number of herpetic episodes in last year	n	(%)	Total†
0	736	(73.6)	0
<0.5	10	(1)	3*
0.5	21	(2.1)	11.5
1	98	(9.8)	98
2	77	(7.7)	154
3	20	(2)	60
4	17	(1.7)	68
5	10	(1)	50
6	1	(0.1)	6
7	3	(0.3)	21
10	4	(0.4)	40
12	3	(0.3)	36
Total	1000	(100)	547.5*

†equals recurrence rate per year multiplied by number of students who had this recurrence rate. ‡assumption. *the estimated total number of herpetic episodes experienced by the 1000 students in the last year (the total disease burden)

Table 4 - Medicines/products used in the treatment of recurrent herpes labialis.

Nature of treatment	n	(%)
Conventional medicines (n=100)		
Topical antivirals	48	(35.0)
Antibiotics	8	(5.8)
Solcoseryl	7	(5.1)
Topical anesthetic/analgesic	5	(3.7)
Topical steroid	3	(2.2)
Others (fluconazol, antihistamine, panoxyl, iodoforn, chlorhexidine)	5	(3.7)
Unidentified medical cream/ointment	24	(17.9)
Alternative treatments (n=37)		
Vaseline	11	(8.0)
Lipstick	10	(7.3)
Tahini	5	(3.7)
Lip moisturizers	4	(2.9)
Toothpaste	3	(2.2)
Others (lemon, cumin, ice, olive oil)	4	(2.9)
Total	137	(100)

Table 5 - Studies conducted to investigate the prevalence of recurrent herpes labialis.

Authors	Country	Year	Sample study		PP	AP	LTP
			n	Age (years)			
Ship et al ⁷	USA	1960	1788		-	-	38.2
Embil et al ⁸	21 countries	1975	8976		-	14.8	30.3
Young et al ⁹	USA	1988	446		-	-	32.9
Crivelli et al ¹⁰	Argentina	1988	846	4-13	5.2	-	-
Axell & Liedholm ¹¹	Sweden	1990	20333	≥15	3.1	17.4*	-
Kovac-Kavcic & Skaleric ¹²	Slovenia	2000	555	25-75	-	-	16.0
Lowhagen et al ¹³	Sweden	2002	5000	0-60	-	19.4*	26.6
Shulman ¹⁴	USA	2004	10032	≤17	1.4	14.8	-
Lorette et al ¹⁵	France	2006	9342	≥18	-	14.8	-
Malvy et al ¹⁶	France	2007	2796	35-65	-	-	38.3
Mathew et al ¹⁷	India	2008	1190	2-80	0.6	-	-
Sawair et al (present study)	Jordan	2010	1000	17-29	2.3	17.0	26.4

PP - point prevalence, AP - annual prevalence, LTP - lifetime prevalence, *2-year prevalence

college, or his/her smoking history. However, household monthly income had significant effect; 57.4% of those with >500 Jordanian Dinars (JDs)/month had used products to treat RHL compared with 39.5% of those with ≤500 JDs ($p=0.007$, χ^2 test). Treatment is shown in Table 4. There were 100 subjects (73%) who used conventional medicines and 37 (27%) who used only alternative treatments (ATs). Topical antivirals were used by only 18.2% of the students who had history of RHL and represented 48% of the conventional medicines used. Of the 37 subjects who used ATs, 14 used lipstick or moisturizers, 11 used vaseline, 5 used Tahini, and 3 used toothpaste to cover the lesions. Treatment was significantly affected by smoking history; 43.2% of current smokers who treated the RHL lesions used ATs compared to 21.1% of ex-smokers and 20% of non-smokers ($p=0.03$, χ^2 test). Alternative treatments were used less frequently by students studying at health colleges and by those with high income but the difference between groups did not reach statistical significance. Treatment was recommended mostly by relatives and friends (32.1%), followed by medical practitioners (26.3%), and pharmacists (20.4%). The treatment was self-trial in 14.6% of the cases. Only 6.6% sought treatment advice from dentists. Interestingly, healthcare providers recommended 8.1% of the ATs and 14% of the conventional treatments were recommended by ordinary people. When asked whether they have found the treatment useful, 112 (81.8%) subjects responded positively, with no significant difference between those who used conventional or ATs.

Discussion. One of the study limitations, as in similar studies, was measuring the exact annual and LTP of RHL because patients may not provide reasonably accurate data. This particularly important in case of patients who have not experienced a lesion for >2 years who may forget to report. However, we think that the prevalence measured in the present study were

reliable since recurrent herpetic lip lesions are clinically distinct and can be easily differentiated from other lesions. In addition, the sample selected were young educated students who were expected to provide rationally accurate data. Mistaking these lesions for other common recurrent oral lesions such as RAS was prevented by showing the students colored images of both lesions. Since almost all students had the onset of RHL before age 20 years, studying this age group may reflect the extent of this disease in the entire population. However, it is unknown if the incidence of RHL predisposing factors is different in this subpopulation from other groups, and therefore, it will be of interest to conduct future studies recruiting nationally representative samples for comparison. Additionally, it is important to conduct similar studies in other Arab countries for comparison. To compare the prevalence of RHL between different studies, one should take into consideration if PP, AP, or LTP is being measured and variations between samples in age, gender, professions, and socioeconomic status (Table 5). In a study conducted on health sciences students in the United States, the LTP rate of RHL was 38.2%.⁷ This high prevalence in North America was then confirmed by a multinational (21 countries) study conducted on samples of university students of health professions from 6 continents.⁸ Although the average LTP rate in all countries was 30.3%, the LTP reported in North America was the highest (40.2%).⁸ In comparison with the LTP rate (17.6%) for some Asian countries reported in that multinational study,⁸ the rate found in this Middle Eastern Arab population (26.4%) is considerably higher and comparable to that reported in Africa (30.2%) and Europe (31%).⁸ In line with these findings, the present LTP rate was very close to that reported in Sweden (26.6%)¹³ and the present PP rate (2.3%) was approximately 4 times higher than that found in India (0.6%).¹⁷ Since recurrent herpetic lesions are observed in nearly one-third of HSV-1 infected individuals,² the seroprevalence of HSV-1 in this population is expected to be approximately 80%, a seroprevalence rate exactly similar to that reported in Syria.⁶ Although the PP prevalence of RHL found in the present study was relatively higher in men, the difference was not statistically significant and no significant gender differences in AP and LTP were found, a finding supported by previous reports.^{7,8} This could be attributable to insignificant gender difference in the seroprevalence of HSV-1.¹⁸ However, some studies have found higher prevalence of RHL in women,^{13,15} but the findings was explained by the possibility that women were more likely to take notice of herpetic lesions than men. The finding that RHL was more prevalent in students from regions outside

the capital city of Amman could be explained by the variation in socioeconomic status that was reported¹⁰ to be a factor that affects the prevalence of RHL. However, in the present study, factors other than income may be responsible for this association as the link between LTP of RHL and income was statistically weak and was not maintained in case of AP and PP of RHL. Unlike what had been reported that the prevalence of RHL was significantly lower among smokers, and especially among pipe smokers,^{11,19} no such association was found. Interestingly, in the current study, although the number was small and the difference was not statistically significant, we noticed a higher prevalence of RHL in ex-smokers. A similar observation of increased recurrence of aphthous ulcers following cessation of smoking was reported²⁰ and was explained by increased stress following cessation of smoking. Besides systemic illness, stress was thought to be the second most important predisposing factor of RHL in the current study. Although we thought that students of health sciences will have the highest prevalence of RHL due to higher psychological stress, they had the lowest PP and students of humanitarian sciences had the highest. The reasons for this difference are unknown; however, it is possible that health care students were more aware of RHL and, therefore, prevent recurrences by avoidance of predisposing factors of viral reactivation and timely use of prophylactic medications. Although some studies have shown a significant association between RHL and RAS,^{8,9} no such association was found in the current study. The investigators who found such association thought that a similar underlying pathological process or unknown cofactor might be involved in both lesions.⁸ The results showed a slight higher occurrence of RHL on lower lip compared with upper lip and higher chance of occurrence on the left side. It is possible that lower lip is influenced more by RHL triggering factors such as sun exposure and lip biting secondary to emotional stress. A French study have also shown a higher occurrence of recurrent herpes on the lower lip compared with the upper lip and linked the location of orofacial herpes with the severity of the disease;¹⁵ when less than 6 episodes per year were reported by subjects, lesions were mainly located on lips, whereas those reporting at least 6 episodes per year had significantly higher chance to have lesions on other facial locations such as cheeks, ear, within nose, forehead, or more than one location. This is the first study reporting side predilection of RHL and the reasons to explain this finding are unknown. This is the first study to calculate the total disease burden of herpes labialis. Recently, Harmenberg et al²¹ reviewed previous studies on RHL and utilized mathematical modeling

using the cumulative distribution function equation to estimate RHL total disease burden in Swedish population. The model suggested that approximately 600,000 episodes of RHL occur in a population of 1,000,000 every year.²¹ The total disease burden of RHL in a population of 1000 students calculated in the present study was approximately 548 episodes per year. Our number calculated using every patient's history of recurrence of the disease in the last year was very close to that estimated using mathematical modeling by Harmenberg et al²¹ and both data support that there are a very large number of herpes labialis episodes in any given population. The results indicated the need for patient education on RHL treatment. Periodic recurrences of herpes were associated with decreased well-being, including diminished general and mental health, physical impairment, and degradation in daily activities.¹⁵ In the present study, 96.6% of the subjects thought that RHL lesions were causes of discomfort and/or poor aesthetic. Poor aesthetic is an expected social barrier particularly in this cohort. Therefore, effective therapy has the potential to affect the lives of many subjects, particularly those with frequent recurrent episodes. In the present study, 51.2% of those with a positive history of RHL reported at least 2 recurrences per year. Early treatment may reduce the frequency and severity of recurrent attacks by speeding up healing of lesions and by reducing pain.²¹ In the present study, only one-half of those with positive history of RHL attempted treating the lesions and only 18.2% used antiviral agents. In comparison, 92.1% of French people who treated RHL lesions used antiviral therapy.¹⁵ Some patients were using topical agents that may alter the healing of RHL lesions such as lipstick and toothpaste. Smokers showed higher tendency to use these inaccurate remedies. Some subjects were using antifungal and even topical steroids indicating lack of understanding of the nature of RHL. This could be attributable to the finding that a significant proportion consulted relatives and friends or conducted self-experiments to treat RHL lesions.

In conclusion, the results indicated that RHL is a significant health problem among university students. The prevalence is higher than that reported in some Asian countries. Therefore, there is a need to educate patients with RHL on the treatment options available to reduce their distress and to improve their quality of life. The treatments employed by the subjects indicated lack of knowledge on the infectious nature of the disease and the potential of viral spread to other sites or other individuals. The patients should be aware on the presence of potential triggers that they should avoid and the importance of timely application of herpes medications.

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