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RISK FACTORS FOR ONSET OF CUTANEOUS AND MUCOCUTANEOUS LEISHMANIASIS IN BOLIVIA

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Abstract. A survival analysis was performed on data from an endemic area of Bolivia where two populations, natives and highland migrants, were living, to investigate risk factors for onset of cutaneous leishmaniasis (CL) and its mucosal form (MCL). In a first data set (703 subjects with 242 CL patients), significant risk factors for CL were gender, native/migrant status, activity, and home-forest distance. The instantaneous risk of CL increased until adolescence in both populations, and rapidly decreased thereafter. This risk was 3–10 times higher in migrants than in natives until 20 years of age, and became similar thereafter. Environmental and behavioral factors did not seem sufficient to explain this contrast between the two populations, and this evolution with age may suggest differences in the mechanisms involved in the development of individual protection during childhood. In a second data set (446 CL patients with 34 mucosal forms) the native/migrant status was the main factor associated with the onset of mucosal form.

Mucocutaneous leishmaniasis (MCL) caused by *Leishmania braziliensis braziliensis,*[1] also known as *L. (Viannia) braziliensis,*[2] is endemic in many regions of Central and South America,[3] and is the predominant form of leishmaniasis in Bolivia.[4] In this country, the disease extends into the majority of the tropical Amazonian lowlands, including the high endemicity areas of Alto Beni and neighboring part of Beni.[5] In addition to the native population that had inhabited the area for several centuries, these areas are also colonization zones where high-altitude populations regularly migrate from the Andean highlands, an area free of MCL, for economic reasons (e.g., ending of tin mining activities in the highlands following the decrease in metal prices), and a government policy of relocation.

Mucocutaneous leishmaniasis occurs in two stages after the infected sand fly bite: a primary cutaneous lesion, followed in some cases by a secondary mucosal involvement generally resulting in severe facial deformities.[6] Cross-sectional studies and case series have shown an increase in the prevalence of cutaneous leishmaniasis (CL) where behavioral factors lead to frequent contacts with the habitat of infected sand flies.[7–9] The same kind of behavioral factors, such as entering forests after sunset, hunting, and lumbering, were recently found to increase the risk of *Leishmania* infection, defined by leishmanin skin test conversion, in a longitudinal study from Colombia.[10] In this work, it was also noted that subjects 10–30 years of age had the greatest risk of leishmanial lesions, whereas older adults experienced the greatest risk of infection. Since the peak of incidence for CL at approximately 20 years of age was also found in prior studies on CL,[11–14] it is especially appropriate to investigate risk factors influencing the age of CL. Therefore, our first goal was to study time to onset of CL using survival analysis methods that allow 1) investigations of environmental and behavioral factors influencing the instantaneous risk of being infected, i.e., the probability of being affected by CL in a given time interval knowing that one has not been affected in the preceding intervals, also denoted as hazard function), 2) quantifying the variation of this instantaneous risk with age, and 3) the search for possible influence of the native/migrant status, taking advantage of the presence of two population groups. Furthermore, since little is known about environmental factors influencing the development of mucosal form of the disease,[4,15] the second goal of our study was to investigate factors influencing the time to onset of the mucosal form among a sample of CL-affected patients.

SUBJECTS AND METHODS

Study area. The study area, already described in a previous report,[4] will be briefly summarized. The region of Alto Beni (Department of La Paz) and the regions of Rurrenabaque, Yucumo, and San Borja (Department of Beni) were covered by the study. Alto Beni is situated at the foot of the Andes (altitude = 400–700 m), while Beni lies in the plain. This zone, covered by tropical rain forest, extends between Sararia and Covendo (west to east) and between Rurrenabaque and Caravani (north to south) and encompasses approximately 2,400 km^2. As mentioned in the Introduction, the population consists of two main groups. The first is the native group composed of two tribes of Amazonian Indians: Chimanes (3,000 persons) and Mosetenes (1,200 persons). The second is the migrant group that consists of Highlands Indians (Quechua and Aymara) comprising approximately 50,000 persons who after initially clearing forested land, have engaged in agriculture. Although the operational area is crossed by a single, unpaved road and by various rivers, its uneven topography makes access difficult and the majority of settlements have to be visited on foot. In addition to the presence of two distinct populations (native and migrant), this area was chosen because the prevalence of CL is reported to be the highest in the country,[5] and there is only one parasite species, *L. (V.) braziliensis,* that causes tegumentary leishmaniasis.[16]

Study design. From May 1990 to July 1991, active case detection for MCL was carried out in this area by the Instituto Boliviano de Biologia de Altura. This case detection was carried out as part of a rural campaign for diagnosis and treatment of MCL in Bolivia, of which practical details are provided in a previous report.[4] During this screening campaign, 12,000 inhabitants of these regions were clinically examined, and 480 CL and MCL cases were recorded. From each case, a familial study was conducted based on the presence and the examination of siblings and parents to identify

nuclear families. Familial data could be collected for 242 cases (some of them being related to one another) that belong to 118 nuclear families totaling 703 subjects and constituting our first data set (set 1). Forty-one of these families were of native origin, and 77 were migrants. This family sample was primarily selected to investigate genetic factors involved in the development of CL, but it also provided useful information in the search for other factors influencing the onset of CL.

The second data set (set 2) contained all 480 cases (446 CL and 34 MCL), including the previous 242 cases with familial data and the remaining 238 patients for whom no family data were available because of unknown parents or siblings, or relatives living far away. To ensure maximal reliability, a comparison was made between our case registration and the one of the local health centers. The discrepancy was low, but some missing cases were identified and examined. After the purpose of the study had been explained, informed consent was obtained from the study subjects. The use of human subjects was approved by the Ethical Committee of the Instituto Boliviano de Biologia de Altura (La Paz, Bolivia).

Diagnosis of tegumentary leishmaniasis. The primary diagnosis of CL was exclusively clinical because it was not difficult to make in this area as long as patients were examined by trained clinicians.[11] The typical active lesion is a deep, rounded, well-circumscribed ulcer with raised borders, which is not cured with antibiotics.[16] In the presence of such a lesion, the patient was sent to the nearest health center for further investigation, final diagnosis, and treatment. Past cases of CL were identifiable by the characteristic scars detected during the physical examination. Therefore, study subjects were classified as 1) affected when presenting with either an active lesion or characteristic scar(s), and 2) unaffected when healthy with no scars. Mucosal lesions were suspected in the presence of nasal blockage or perforation, a history of epistaxis, and the presence of a typical skin scar. The patient was then sent to the health center for further investigation, final diagnosis (approximately 10% of them being parasitologically confirmed), and treatment. Patients with a doubtful diagnosis such as a scar with a history of trauma to the site were excluded from the study.

Recorded explanatory variables. For the analysis performed on data set 1, the trait under study was the time to onset of CL. The start of the follow-up was birth for natives and date of the arrival in the endemic area for migrants. Endpoint was the date of onset of CL for affected subjects and the date of the last clinical examination for unaffected subjects. Recorded time-independent covariates were gender, area of residence (plain or plateau), and native/migrant status. Time-dependent covariates were current and previous logarithm of home-forest distances in meters (when subjects have moved during their follow-up), and current and previous activities (when subjects have changed their activity during the follow-up) divided into three classes of exposure according to the time spent in the forest each day. The high risk class corresponded to more than 4 hr a day spent in the forest (hunting, fishing, lumbering, farming), the medium class corresponded to between 2 and 4 hr (carpenter, half-time farmer), and the low class corresponded to less than 2 hr (child in school, housewife, nurse, teacher).

For the analysis performed on data set 2, the trait under study was the time to onset of mucosal lesions. The start of the follow-up was the date of onset of CL. The endpoint was the date of onset of mucosal leishmaniasis for MCL-affected subjects and the date of last clinical examination for others. Only time-independent covariates were used for this analysis. In addition to the covariates previously described, we considered age of CL in years, number of initial cutaneous lesion(s) (single or multiple), duration of initial cutaneous lesion(s) (more or less than six months), localization(s) of initial cutaneous lesion(s) (above or below the waist as suggested by Llanos-Cuentas and others[15]), and treatment in terms of being correct (at least 20 mg/kg/day of meglumine antimoniate for 20 days by intramuscular injections)[4] or incorrect (less than 20 mg/day or less than 20 days).

To collect both of these data sets, we used a questionnaire written in Spanish that could be translated, if necessary, into the local dialect (needed mostly for the native populations) by one of the interviewers. Recall bias did not seem to be a problem since interviews were conducted in the presence of all family members, clearly decreasing the risk of false information. Moreover, the population easily recognized the lesion.

Statistical analysis. The Cox proportional hazards model[17] was used to analyze these data and estimate relative risks (RRs). This model specifies a loglinear relationship between the hazard function (i.e., instantaneous risk of developing the disease) and covariates, and measures the effects of these covariates in terms of RR. For data set 1, analysis was first performed considering all individuals independently and in a second time using a stratification by family. Within a family, individuals are not independent (for example, in terms of genetic background or residence location). To take into account these dependencies between relatives, we used a well-known statistical-specific method called stratification. The stratification has to be done on the factor that introduces dependence between individuals (here the family). The stratification is not needed in data set 2 since the subjects are no longer relatives. To assess the evolution of the instantaneous risk of CL with age among natives and migrants, the Cox model was not appropriate[18] because for most subjects (in particular all natives), age was confounded with time of follow-up. In this case, the piecewise exponential model (PEM) was used.[19] In this model, the hazard is estimated within mutually exclusive intervals and is assumed to be constant within these intervals. In a given interval, the hazard can be computed as the ratio between the number of cases occurring during this interval and the number of exposed individuals in terms of person-years. In the present study, six age intervals (years) were considered (0–4, 5–9, 10–14, 15–19, 20–24, and ≥ 25) with estimation of the six corresponding hazards ($\lambda^1, \lambda^2, \ldots, \lambda^6$). As an example, a native 12 years old will contribute to an estimation of λ^1, λ^2, and λ^3, whereas a migrant of the same age who arrived in the endemic area at the age of seven years will only contribute to the estimation of λ^2 and λ^3. All statistical analysis was performed using SAS software (SAS Institute, Cary, NC).

RESULTS

Risk factors for CL. Distributions of time to onset of CL among natives and migrants are shown in Figure 1. The

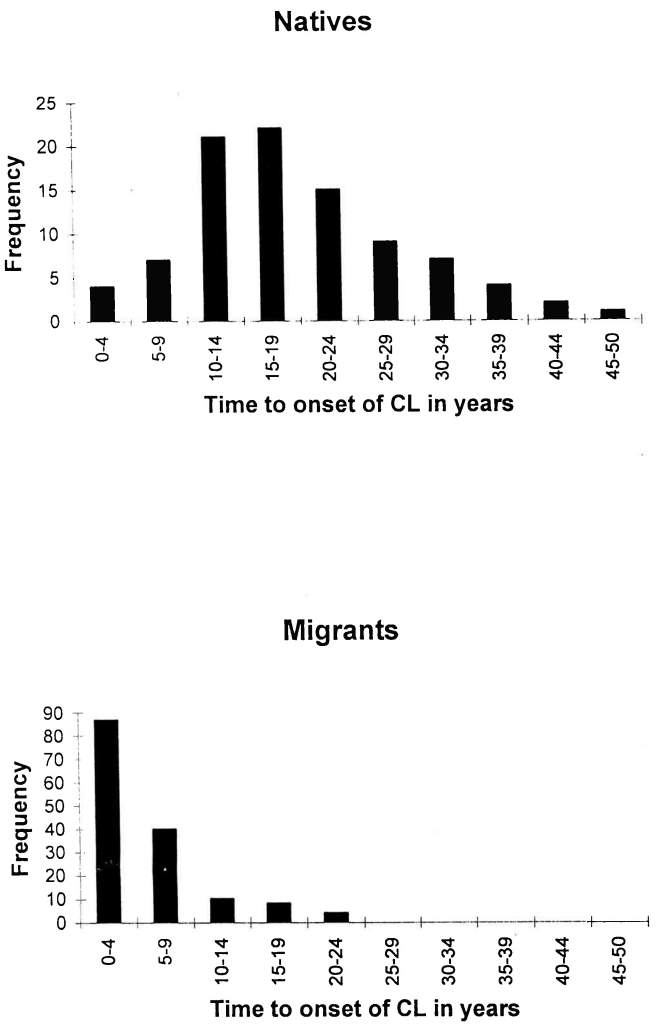

FIGURE 1. Time to onset of cutaneous leishmaniasis (CL) among natives and migrants.

mean (SD) time to onset was higher among natives, 18.7 (9.6) years than among migrants, 5.3 (4.9) years. Univariate analyses showed that gender, native-migrant status, area of residence, and activity were highly associated with onset of CL whereas home-forest distance was not significant. The RR (95% confidence interval [CI]) of developing CL was 1.86 (1.41–2.45) for males versus females, 3.07 (2.30–4.11) for migrants versus natives, 1.74 (1.35–2.25) for individuals living in the plateau versus the plain, and 4.82 (3.37–6.89) for high exposure versus low exposure subjects. Multivariate analysis was performed since certain of these factors are not independent and the results are shown in Table 1. Native-migrant status and activity remained strongly associated with onset of CL ($P < 0.0001$). The RR was 2.77 for migrants versus natives, 2.1 for medially exposed subjects versus lowly exposed ones, and 2.75 for highly exposed subjects versus lowly exposed ones. Gender was of less influence ($P = 0.02$) with an RR of 1.44 for males versus females, whereas home-forest distance reached significance ($P = 0.01$) with an RR of 0.71 for subjects living 100 m from the forest versus subjects living only at a distance of 10 m. Multivariate analyses were also performed stratifying by family, and provided very similar results.

TABLE 1
Multivariate analysis of risk factors for cutaneous leishmaniasis

Covariates	P*	Relative risk		95% CI†
Gender	0.02	Female	1	–
		Male	1.44	1.05–1.97
Native/migrant status	0.0001	Native	1	–
		Migrant	2.77	1.94–3.94
Area of residence	NS	Plain	1	–
		Plateau	0.83	0.61–1.14
Activity	0.0001	Low	1	–
		Medium	2.10	1.41–3.11
		High	2.75	1.85–4.09
Log home-forest distance	0.01	10 meters	1	–
		100 meters	0.71	0.62–0.81

* NS = not significant.
† CI = confidence interval.

Variation of the instantaneous risk of CL with age. Table 2 shows the data used to estimate the instantaneous risks, i.e., the distribution of CL cases, exposed individuals, and person-years at risk by age group and native/migrant status. Results of PEM analysis are shown in Figure 2 and are expressed in terms of RR, with the instantaneous risk reference value being that of natives in the first age class (0–4 years). As an example, the risk of developing CL for natives 10–15 years of age is 9.4 times higher than between 0 and 4 years. Evolution of the RR was qualitatively the same among natives and migrants with a peak around adolescence, and then rapidly decreasing. Quantitatively, the risk of CL was 10 times higher for migrants than for natives during the first five years of life, approximately three times higher from 5 to 20 years of age, and becoming similar thereafter.

Risk factors for developing the mucosal form among CL-affected patients. Univariate analysis showed that only native/migrant status, age of onset of CL, and duration of the initial lesion(s) had a significant effect with P values between 0.03 and 0.05. The RR of developing a mucosal form of the disease was 2.31 for CL-affected migrants versus CL-affected natives (95% CI = 1.15–5.05), 1.32 for each of 10 years of the age of CL (95% CI = 1.02–1.74), and 0.44 for a duration of the cutaneous lesion(s) > six months versus ≤ six months (95% CI = 0.19–0.98). Results of multivariate analysis are shown in Table 3. Effects of native/migrant status and duration of initial cutaneous lesion(s) remained sig-

TABLE 2
Distribution of cutaneous leishmaniasis (CL) cases, exposed individuals, and person-years at risk by age group and according to the native/migrant status

	Age range (years)					
	0–4	5–9	10–14	15–19	20–24	≥25
Native						
Cases of CL	4	7	21	22	15	23
Exposed individuals	269	255	227	177	133	102
Person-years	1,325	633	948	792	625	1,405
Migrant						
Cases of CL	11	14	35	37	12	40
Exposed individuals	157	168	165	117	70	147
Person-years	400	471	612	381	286	2,339

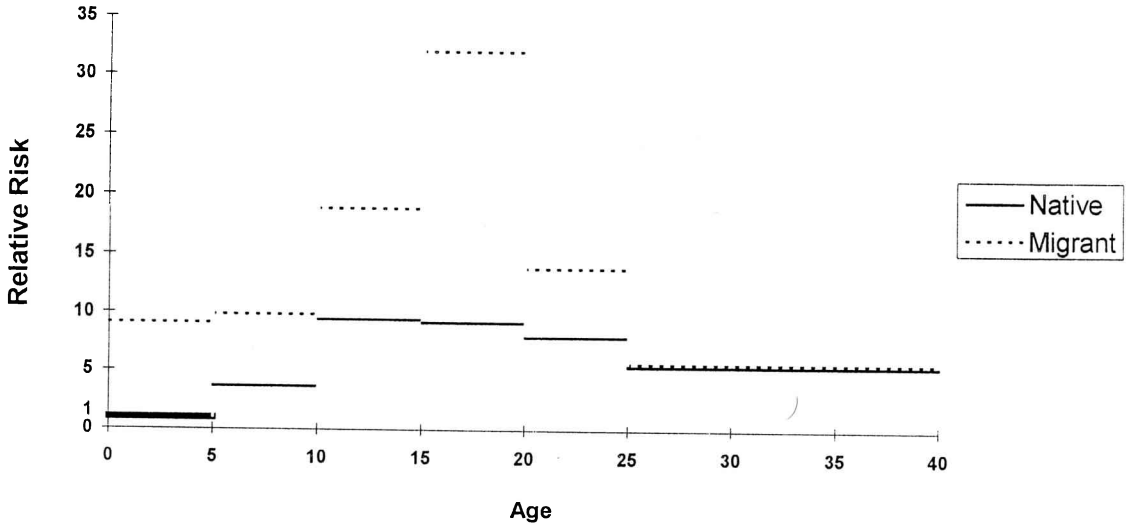

FIGURE 2. Variation with age of the relative risk of cutaneous leishmaniasis among natives (**bold lines**) and migrants (**dotted lines**). Six age groups are considered: 0–4 years, 5–9, 10–14, 15–24, and ≥ 25. The baseline level is the risk of a native between 0 and 5 years of age.

nificant with RRs very similar to those observed by univariate analysis, but age of CL was no longer significant.

DISCUSSION

In the first analysis, the major risk factors for developing CL were activity patterns and native/migrant status, whereas gender and home-forest distance, although significant, were less strong determinants of the risk of CL. The increased risk associated with high-risk activities and male gender are consistent with previous reports.[5, 7–12, 20] Home-location has also been shown to be a risk factor for the infection,[21, 22] but an RR quantifying the decrease of the risk with the distance from the house to the forest was not estimated previously. In our study, the discordance between univariate and multivariate analyses results concerning the home-forest distance effect is easily explained by the confounding effects of the migrant/native status. Migrants, who settled later in the area, live further from the forest than natives. Since migrants have a higher risk of being affected, the home-forest effect is underestimated if the native-migrant status is not taken into account in the analysis. The main result of this first survival analysis on CL is certainly the major effect of the migrant-native status, with a three-fold increased risk of CL in the migrant population. This difference could be explained by the way these two populations interact with the forest in their agricultural practices, with the migrants exposing themselves more to transmission by sand flies (Llanos-Cuentas A, Campos M, unpublished data). As an example, migrants are involved in the activity of deforestation whether during their settling-down period or their agricultural activities, while natives have a less aggressive activity towards the forest. Furthermore, natives generally light a smoky fire by burning plants during the night to keep blood-sucking insects away; this habit is unknown among migrants. However, the results in Figure 2, which show that the difference in risk between the two groups tends to disappear in adults, while behavioral factors remain similar, argues against the environmental hypothesis. The higher risk of CL among migrants could also reflect the role of a genetic component influencing the onset of CL as suggested by several reports,[23–25] and we are investigating this hypothesis in an ongoing analysis.

TABLE 3
Multivariate analysis of risk factors for the mucosal form in patients with cutaneous leishmaniasis (CL)

Covariates	P*	Relative risk		95% CI†
Native/migrant status	0.03	Native	1	–
		Migrant	2.29	1.05–5.27
Duration of the cutaneous lesions	0.04	≤6 months	1	–
		>6 months	0.44	0.19–0.97
Gender	NS	Female	1	–
		Male	1.19	0.49–2.86
Area of residence	NS	Plain	1	–
		Plateau	2.15	0.85–5.46
Number of cutaneous lesions	NS	Unique	1	–
		Multiple	0.79	0.23–2.62
Age at onset of CL	NS	10 years	1	–
		20 years	1.23	0.88–1.67
Treatment of the cutaneous lesions	NS	Correct	1	–
		Incorrect	1.22	0.44–3.35

* NS = not significant.
† CI = confidence interval.

The variation of the instantaneous risk of CL with age among natives and migrants showed that this risk increased through adolescence in both populations, and rapidly decreased thereafter. This evolution is consistent with the one observed for the incidence of CL with age in other countries,[11, 13, 14] since the evolution of an annual incidence is similar to that of a discrete instantaneous risk with a one-year interval.[26] Furthermore, this incidence peak around adolescence is also observed in other infectious diseases such as leprosy.[27] Infection intensities for schistosomiasis display the same pattern in endemic areas, with maximum levels of infection intensity between 10 and 20 years of age, and this evolution has been related to the age-dependent evolution of immunity[28, 29] and appears to depend mainly on the susceptibility/resistance status of the individuals.[29–32] In experimental mouse leishmaniasis, the host's innate and acquired re-

sistance has been shown to play a major role in response to infection,[33] and a recent investigation in humans has provided evidence for a genetic component in susceptibility to clinical leishmaniasis, influencing severity of disease and resistance to disease among healthy individuals.[25] This component could account in part for the evolution of incidence with age since individuals affected at an early age were found to be genetically more susceptible. In the present study, the observation that the RR of CL between natives and migrants decreases with age suggests that the differences between the two groups could be associated with mechanisms involved in the development of individual protection during childhood.

The second analysis showed that the risk of developing a mucosal form of the disease was increased among migrants with an RR of 2.29 versus natives, but we found no strong effect of factors related to the primary cutaneous lesion as reported by Llanos-Cuentas and others.[15] However, the low number of MCL cases in our study reduced the power of our analysis, and a larger sample is needed to assess the role of these latter variables.

Further studies combining genetic and immunologic approaches should provide useful information about the relationships between immunity, genetic susceptibility/resistance, and the evolution of leishmaniasis infections. However, information and prevention remain of major importance, and our findings clearly indicate that young migrants who have the higher risk of developing CL should be a primary target for such efforts. To ensure maximum efficiency, education and prevention should be done as early as possible (ideally preceding migration) since the delay between settling in an endemic area and CL is very short. Such efforts should also involve the native population. To provide early detection and treatment of cases, extensive education of the area population would certainly be beneficial. Since the peak of incidence increases around adolescence, it would be interesting to start this information campaign during school time.

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