RISK FACTORS FOR INDIAN KALA-AZAR

ALOK RANJAN, DIPIKA SUR, VIJAY P. SINGH, NIYAMAT A. SIDDIQUE, BYOMKESH MANNA, CHANDRA S. LAL, PRABHAT K. SINHA, KAMAL KISHORE, AND SUJIT K. BHATTACHARYA*

Rajendra Memorial Research Institute of Medical Sciences, Indian Council of Medical Research, Agamkuan, Patna, India; National Institute of Cholera and Enteric Diseases, Indian Council of Medical Research, Kolkata, India

Abstract. A case-control study was conducted to understand the risk factors associated with kala-azar in disease-endemic areas of Bihar, India. A total of 134 kala-azar cases treated at the Rajendra Memorial Research Institute of Medical Sciences in Patna and 406 healthy controls selected randomly from the neighborhoods of cases in their native villages were included in the study. Univariate analysis showed that education, a history of other diseases in the previous year, a history of kala-azar in the family, type of walls in houses, presence of a granary inside houses, presence of vegetation around houses, bamboo trees near houses, and irregular spraying around houses with DDT were risk factors. Multivariate analysis showed that a history of other diseases in the previous year (odds ratio [OR] = 3.6, P = 0.002), a history of kala-azar in the family (OR = 1.8, P = 0.03), mud-plastered walls in houses, (OR = 2.4, P = 0.0001), a granary inside houses (OR = 4.3, P = 0.0001), presence of bamboo trees around houses (OR = 2.3, P = 0.001), and houses not sprayed with DDT in the past six months (OR = 3.4, P = 0.0001) were significant risk factors for kala-azar. These results will be useful in developing kala-azar control programs for identifying intervention strategies such as better housing, regular and proper insecticide spraying, and promoting health awareness to the community residing in disease-endemic areas for reducing transmission and incidence of this disease.

INTRODUCTION

Indian kala-azar or visceral leishmaniasis (VL) is a parasitic diseases caused by Leishmania donovani and transmitted by the bite of the sand fly vector Phlebotomus argentipes. This disease has been one of the major health problems in the state of Bihar, India for many decades. Focal and sporadic cases of kala-azar have been occurring regularly in many districts since 1977. Presently, 28 of 37 districts in Bihar are endemic at various levels and nearly 67.5 million people are at the risk of this disease. More than 90% of all the cases in India are reported from Bihar alone. Considering the extent of under-reporting of kala-azar cases in Bihar, it has been estimated that the total number of cases would be 2–2.5 times higher than the actual reported incidence and may be even five times higher than officially reported figures. The increasing fatality rate observed during the past 10 years is a matter of serious concern among health care providers and policy makers. The persistence of perennial transmission of kala-azar in Bihar, India. They are situated in the Gangetic plain and all have the favorable ecologic factors for transmission of kala-azar such as alluvial soil, high sub-soil water, a monthly mean maximum temperature < 37°C, a monthly mean minimum temperature > 7.2°C, an annual rainfall ≥ 1,250 mm, a mean annual relative humidity ≥ 70%, abundant vegetation and an altitude < 600 meters. The climate of the study areas is similar with no wide variation. These conditions are highly suitable for an abundance of sand flies facilitating perennial transmission of kala-azar. Agriculture and its associated activities are the mainstay of the economy of these areas. The economy diversity in all study areas is not significant.

Study area. The study was based at the indoor ward of the Rajendra Memorial Research Institute of Medical Sciences RMRIMS in Patna, Bihar, India. A field study was undertaken in nearby disease-endemic villages in the districts of Patna, Vaishali, Muzaffarpur, Samastipur, and Nalanda (Figure 1). These districts are typical disease-endemic regions of kala-azar in Bihar, India. They are situated in the Gangetic plain and all have the favorable ecologic factors for transmission of kala-azar such as alluvial soil, high sub-soil water, a monthly mean maximum temperature < 37°C, a monthly mean minimum temperature > 7.2°C, an annual rainfall ≥ 1,250 mm, a mean annual relative humidity ≥ 70%, abundant vegetation and an altitude < 600 meters. The climate of the study areas is similar with no wide variation. These conditions are highly suitable for an abundance of sand flies facilitating perennial transmission of kala-azar. Agriculture and its associated activities are the mainstay of the economy of these areas. The economy diversity in all study areas is not significant.

Study design. This was a case-control study. The cases were clinically and parasitologically confirmed kala-azar patients from the districts of Patna, Vaishali, Muzaffarpur, Samastipur and Nalanda admitted from April 2001 to September 2003 to the indoor ward of the Rajendra Memorial Research Institute of Medical Sciences in Patna. Field-based surveys were carried out in the native villages of kala-azar cases recruited into the study. For each index case, households having no kala-azar cases in the family were identified and a list of healthy controls matched for age and sex was made by the field workers. Three healthy controls from the list were randomly se-
lected. Multiple controls were selected for each case to increase the precision of the estimate. Serologic tests were not carried out to identify asymptomatic cases among the controls, which were selected primarily on the basis of the absence of clinical symptoms. Informed consent was obtained from all cases and controls before including them into study. The study was reviewed and approved by the Scientific Advisory Committee (SAC) and Institutional Ethical Committee.

Sample size. Since no prior quantitative information on various risk factors was available, a pilot study was conducted with 60 kala-azar cases and 182 healthy controls. The pilot study showed that education, type of house, presence of a granary, and vegetation were significant risk factors in univariate analysis. These variables were used to compute a final sample size of 134 kala-azar cases and 406 healthy controls.

Data collection. The potential socioeconomic factors for VL were included in a structured questionnaire given to kala-azar cases and healthy controls and are shown in Table 1. In the case of children, attendants or parents were requested to respond. Answers to questions relating to the nature and type of housing were checked and confirmed by field visits. Field visits were made to the native villages of kala-azar cases to verify the description of houses, facilities available, vegetation, and possession of household goods and other variables reported by the cases or attendants of cases at the time of the interview. Some of the stated descriptions in the questionnaire were later modified after actual observations made during the field visit. Statements of the subjects with regard to family income were not reliable because actual family income was difficult to estimate. Thus, a surrogate indicator for wealth, i.e., living standard index (LSI), was calculated on the basis of house type, availability of electricity, fuel used for cooking, presence of a lavatory facility, and possession of household consumer items including car, scooter/motorcycle, television, radio, sewing machine, electric fan, and bicycle. A score was assigned for each factor and the sum of scores for all factors for each household was taken as the LSI. On the basis of total score, the LSI was classified into three groups: low (total score < 9), medium (total score = 9–20), and high (total score > 20).

Data analysis. Forms were decoded and scrutinized for accuracy and consistency. Data were analyzed using Epi-Info version 6.2 (Centers for Disease Control and Prevention, At-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Variables used for data collection</th>
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<tbody>
<tr>
<td>Individual Information</td>
<td></td>
</tr>
<tr>
<td>Age, sex</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td></td>
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<tr>
<td>Number of the family members</td>
<td></td>
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<tr>
<td>Number of persons sleeping with index case</td>
<td></td>
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<tr>
<td>Family history of kala-azar</td>
<td></td>
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<tr>
<td>Ownership of selected consumer items such as TV, radio, liquid petroleum gas for cooking</td>
<td></td>
</tr>
<tr>
<td>Nutritional factors (types of foods consumed)</td>
<td></td>
</tr>
<tr>
<td>History of other diseases in last year</td>
<td></td>
</tr>
<tr>
<td>Congenital deformities</td>
<td></td>
</tr>
<tr>
<td>Household Information</td>
<td></td>
</tr>
<tr>
<td>General condition of the house</td>
<td></td>
</tr>
<tr>
<td>Structure of the house wall, roof, surface, and mosquito proofing in doors/windows</td>
<td></td>
</tr>
<tr>
<td>Presence of vegetation</td>
<td></td>
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<tr>
<td>Lavatory facility in the house</td>
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lanta, GA) and validated by logical and range checks with SPSS version 10.0 (SPSS, Inc., Chicago, IL). For each of the study factors, risk was estimated by calculating the odds ratio (OR) as an approximation of the relative risk with 95% confidence intervals (CIs) using Epi-Info version 6.2. The significance of the OR was analyzed with the Mantel-Haenszel chi-square test. On the basis of the OR in univariate analysis, variables that were statistically significant were included in the multiple logistic regression model. Stepwise multiple logistic regression was then applied for the identification of significant risk factors using SPSS version 10.0.

RESULTS

The distribution of the cases and controls by age, sex, family size, and LSI is shown in Table 2. Differences in the proportion in each age group (P = 0.35), sex (P = 0.12), average family size (P = 0.11), and LSI (P = 0.86) of cases and controls were not statistically significant. The LSI indicated that most of the cases and controls belonged to low socioeconomic strata of the community. This result indicated that primary socioeconomic and demographic characteristics were similar in both cases and controls.

The unadjusted ORs of risk factors for individual and family characteristics is shown in Table 3. The results showed that education, history of other diseases (tuberculosis, jaundice, and gastrointestinal infections in the past year), history of kala-azar in family, type of walls, presence of a granary inside the house, presence of vegetation around the house, bamboo trees near house, and irregular spraying with DDT around the house were significant risk factors by univariate analysis.

The results of multiple logistic regression analysis are shown in Table 4. The significant risk factors on the basis of adjusted ORs for kala-azar in multivariate analysis were identified. Some factors, which were significant in univariate analysis, were not significant risk factors in multivariate analysis. The adjusted ORs and 95% CIs for each significant variable are shown in Table 4. A history of other diseases in the past year was significantly associated with kala-azar (OR = 3.6, 95% CI = 1.6–7.8, P = 0.002). A history of kala-azar in any family member in the past year was also a risk factor (OR = 1.8, 95% CI = 1.0–3.1, P = 0.03). Mud-plastered walls in houses was a significant risk factor for kala-azar (OR = 2.4, 95% CI = 1.5–3.8, P = 0.0001) compared with cement-plastered houses. The presence of a granary, an earthen pot made of hard mud that is commonly used for storing grains in rural areas of Bihar, inside houses was a also significant risk factor (OR = 4.3, 95% CI = 2.7–6.8, P = 0.0001).

The presence of vegetations such as small creepers, herbs, and bushes in the vicinity of houses was a significant risk factor in univariate analysis but, did not show significance in multivariate analysis. However, presence of bamboo trees in the vicinity of houses was significantly associated with kala-azar (OR = 2.3, 95% CI = 1.4–3.8, P = 0.001). The lack of spraying on houses with DDT in the past six months significantly increased the risk of kala-azar (OR = 3.4, 95% CI = 2.1–5.5, P = 0.0001). All combinations of two-way interactions of the risk factors were examined, but only the combinations of houses not sprayed with DDT and mud-plastered walls (OR = 5.4, 95% CI = 2.8–10.1, P = 0.0001) and houses not sprayed with DDT and granaries (OR = 4.7, 95% CI = 2.1–10.4, P = 0.0001), were significant.

DISCUSSION

This study is probably the first attempt to assess the association of various socioeconomic and environmental factors with occurrence of kala-azar using a case-control design approach. The LSI showed that 84% of the cases had very low standards of living, but this was not significant in univariate analysis. It was previously reported that most kala-azar patients had incomes less than $1 per day (45 Indian Rupees). Such poverty may not be a risk factor for kala-azar, but it can lead to malnutrition, poor housing conditions, lack of preventive measures in the form of sanitation and bed nets, and illiteracy. Thus, poverty could be a major determinant for continued transmission of Kala-azar in Bihar and other parts of India.

A history of other diseases such as tuberculosis, hepatitis, or viral fever in the past year has a significant impact on the occurrence of kala-azar because these diseases may reduce the immune status of the host. The low immunity of the host increases the risk of being infected with L. donovani. Multiple cases of kala-azar in a family have been reported from Bihar. In this study, it was observed that the risk of kala-azar was higher among cases with a history of kala-azar among the family members in the past year compared with those cases with no history of kala-azar among family members. The presence of kala-azar cases in the family might aid the transmission of this disease in the presence of sand fly vectors and other conditions favorable for completion of transmission cycle within the house.

The use of mud for wall construction or for plastering walls was found to be significantly associated with kala-azar, a finding previously reported in other studies. Phlebotomus argentipes sand flies are commonly found in cracks and crevices of mud walls, mud-plastered walls, or unplastered brick walls in rural areas of Bihar. These endophagic sand flies usually breed inside cowsheds and human dwellings, especially inside cracks and crevices of walls where optimum temperature and humidity are available. Mud walls can retain moisture for many months after the rainy season, which further increases favorable conditions for sand fly breeding and resting. Filling of cracks and crevices in walls with a mixture of lime and mud has been advocated as an ecologic approach for the control of P. argentipes inside houses.

The presence of granaries inside houses was found to be significantly associated with kala-azar because they are usu-
ally kept in bedrooms. It is the usual practice in rural areas to
frequently clean the outer surface of the granary with water.
The mud cracks and crevices on the outer side of granaries
retain the moisture and thus provide sufficient dampness for
breeding and resting of sand flies. Empty granaries also pro-
provide suitable places for breeding of sand flies because of
easier access. Immature sand flies (larvae) have also been
detected in soil collected inside granaries. Dampness as a risk
factor has also been reported in west Bengal and Nepal.12,13

In rural areas of Bihar, houses are usually surrounded by
moderate-to-high density vegetation such as seasonal crops,
bananas, bamboo trees, small creepers, climbers, and herbs.
The presence of vegetation was significantly associated with
kala-azar in univariate analysis, but not in multivariate analy-
sis. The presence of vegetation as a risk factor of kala-azar has
also been previously reported.6

In this study, bamboo trees near houses was found to be a
significant risk factor for kala-azar. It has been reported that
some plants such as *Amaranthus spinosa* (*Amaranthaceae)*,
*Musa sapientum*, and *Croton sparciflorous* are very rich
source of fructose and thus attract *P. argentipes*.14,15

<table>
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<th>TABLE 4</th>
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| Risk factors for Kala-azar by multivariate analysis using a logistic
regression model* |

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of other diseases</td>
<td>1.27</td>
<td>0.40</td>
<td>3.6</td>
<td>1.6–7.8</td>
<td>0.002</td>
</tr>
<tr>
<td>History of kala-azar in family</td>
<td>0.60</td>
<td>0.28</td>
<td>1.8</td>
<td>1.0–3.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Mud-plastered wall</td>
<td>0.87</td>
<td>0.24</td>
<td>2.4</td>
<td>1.5–3.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Granary inside house</td>
<td>1.46</td>
<td>0.24</td>
<td>4.3</td>
<td>2.7–6.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Presence of bamboo tree near house</td>
<td>0.85</td>
<td>0.25</td>
<td>2.3</td>
<td>1.4–3.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Household not sprayed with DDT</td>
<td>1.24</td>
<td>0.24</td>
<td>3.4</td>
<td>2.1–5.5</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* ref = referent; VL = visceral leishmaniasis.
booy trees. Bamboo trees also provide shade and consequently produce dark and humid surroundings around the vicinity of the houses, creating suitable resting sites for sand flies. Two rounds of DDT spraying in disease-endemic areas has been one of the control strategies of the Kala-azar Control Program in India since 1991. In the present study, the risk of kala-azar was higher among the family members residing in houses not sprayed with DDT compared with those living in houses spayed with DDT. This is a very significant finding in the context of kala-azar control. However, spraying with DDT as a long-term control measure may have serious consequences such as harmful and long-lasting effects on the environment. Malathion paint, a slow-release emulsified suspension, has been shown to be a suitable alternative for vector control in terms of toxicity, effectiveness, and operational cost.

Thus, the socioeconomic characteristics identified as risk factors of VL in this study could help strengthen existing control strategies. Better housing and improved living conditions in disease-areas of Bihar could reduce the transmission of the disease by eliminating conditions suitable for breeding of sand flies inside the houses. Proper implementation of existing health awareness programs could help people in rural areas modify their behavioral patterns by keeping granaries outside their bedrooms and minimizing vegetation around houses that supports sand flies. The main emphasis on targeting intervention would be enhancing community awareness in areas susceptible to kala-azar through dissemination of appropriate information. Since local government (Panchayati Raj) in the rural areas of India is a strong forum, its involvement in these programs is essential. Women groups and local non-governmental organizations should also be actively involved in awareness programs. These findings have important practical implications because they suggest that these measures, along with appropriate vector control and improved treatment facilities in rural areas, may be particularly effective in reducing the incidence of kala-azar and its transmission of infection by sand fly vectors.

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Reprint requests: Sujit K. Bhattacharya, Rajendra Memorial Research Institute of Medical Sciences, Indian Council of Medical Research, Agamkuan, PO Gulzarbagh, Patna 800 007, Bihar, India.

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