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Post-treatment Clinical Outcomes of Cutaneous Leishmaniosis in the Bam Area, South Eastern Iran: Analysis of over 9,000 Cases

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SUMMARY

Background: Knowledge about risk or protective factors for post-treatment outcomes in Cutaneous Lishmaniosis are rare, especially in endemic areas such as Iran. The present study aimed to evaluate the association between the outcome of infection, clinical manifestation, and treatment with adverse post-treatment outcomes in Cutaneous Lishmaniosis patients.
Methods: This was a cross sectional study based on recently collected data of 9077 Cutaneous Lishmaniosis patients (4585 female and 4492 male) from March 2003 to March 2011 in the Bam area, Iran. Multivariable multinomial logistic regression was applied to assess the effect of outcome of infection, clinical manifestation and treatment on relapse, treatment after interruption, treatment failure and clinical resistance.
Results: Head lesions were strongest risk factor for relapse (Odds Ratio, OR=4.21; CI 95%: 3.56-4.98), treatment after interruption (2.00; 1.70-2.35), treatment failure (6.61; 5.17-8.45) and clinical resistance (2.62; 2.00-3.44). Family occurrence (yes vs. no), intra lesion therapy method, treatment duration (>3 v. ≤ 3 week) and source of detection by Surveillance (active vs. passive), were the most protective factors for relapse (OR=0.58; CI 95%: 0.46-0.74), treatment after interruption (0.36; 0.31-0.42) treatment failure (0.24; 0.20-0.29) and clinical resistance (0.24; 0.09-0.67).
Conclusion: Head lesions and treatment variables (e.g. therapy method and duration) could predict the occurrence of adverse post-term outcomes of Cutaneous Lishmaniosis. Further longitudinal studies have to clarify cause and effect relationships.

1. Introduction

Cutaneous leishmaniasis (CL) is the most common form of the leishmaniosis.[1] It is estimated that the majority of CL cases is restricted to some tropical and sub-tropical countries, including Iran.[2] Zoonotic Cutaneous Leishmanias (ZCL) and Anthroponotic Cutaneous Leishmaniasis (ACL) are occurring in different parts of Iran, ZCL in central,[3] north, north-east,[4] ad south-west,[5] while ACL is endemic in large cities including Tehran, Shiraz, Mashhad, Kerman and small cities like Bam.[6] The Kerman province, especially the city of Bam, was one of the known old focal points of ACL in Iran.[7] There is clear evidence that *leishmania tropica* species is the causative parasite of ACL in urban areas that is transmitted by the bite of the infected sand-fly (*Phelebotomus sergenti*). After the 2003 earthquake in the Bam area, the prevalence of CL significantly increased.[8] CL usually produces ulcers on the exposed parts of the body, such as the face, arms and legs. These lesions may persist for a long time (6-15 months).[9]

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Many different therapeutic interventions, including topical, systemic and nonpharmacological treatments, have been introduced, such as paromomycin ointments, thermotherapy, intralesional pentavalent antimonials and cryotherapy; systemic treatment consists of pentavalent antimonial salts at a daily dose of 20/mg/kg Sb^{5+} of pentavalent antimony.[10] In Iran, specific treatment for cutaneous leishmaniosis is meglumine antimoniate compound.[11]

Due to a large number of lesions and permanent scars, prolonged duration of treatment (several months) is required in some cases.[12] Unfortunately, there are unwanted side effect according to type of treatment, e.g. pain at the injection site in the case of interlesional or cardiac and pancreatic toxicity, toxicity-related mortality in systemic administration, which may be the reason for non-adherence and non-compliance.[9] Subsequently, studies have shown that as a result, clinical resistance,[13] failure[14] and consequently disease relapse can occur.[15,16] Not only does the occurrence of relapse and/or treatment failure depend on the quality of the treatment program, but also the clinical manifestation of CL may be important.

It should be emphasized that in CL the epidemiologic relationship between the vector and the human reservoir host still remain a major challenge. Therefore effective control is not a realistic goal.[1] Nevertheless, reducing the burden of disease by focusing on the outcomes of infection, clinical manifestation and treatment can be achieved. However, there is very little evidence regarding the characteristics of CL patients, particularly in Iran. Hence, the objectives of the present study were to describe the post event pattern in CL and to identify determinant risk factors of adverse outcomes following treatment in south eastern Iran.

2. Materials and Methods

This cross sectional study using pre-existing data from epidemiologic surveillance systems was conducted from March 2003 to March 2011 in the Kerman province including Bam and Normashir. 9,077 individuals infected by CL caused by *L.tropica* were included in the study. Definitive cases were confirmed microscopically by smear or culture from cutaneous lesions.[11]

To achieve the study objective, these variables were included: demographic variables (age, sex and nationality) and outcome of infection, clinical manifestation and treatment including source of detection of cases (passive or active surveillance), previous scar, family occurrence, scar covering, comorbidity, therapy duration, therapy method (intramuscular, local and cryotherapy), body region involved, scar duration and number of healed lesions. We classified the participants into five case types: a) patients presenting with active lesion(s) and receiving CL treatment for the first time classified as *new case*, b) patients who have been declared cured of CL in the past by a physician, after one full course of systemic or local treatment, and returned because of the reactivation of apparently cured lesion(s) classified as *Relapse*, c) patients who interrupt systemic and local treatment for 10 and 7 days or more, and return to the health service with active lesion, classified as *treatment after interruption*, d) patients who had active lesion after 4 to 6 months despite complete systemic or local treatment, classified as *treatment failure*, e) patients with relapse or treatment failure who had active lesion 6 weeks after completing at least 2 rounds of systemic treatment, classified as *clinical resistance*.[17]

Distribution of continuous and ordinal variables were assessed by Histogram plot and Kolmogorov-Smirnov test. According to normality of data, the Kruskal Wallis H test was used to compare outcome of infection, clinical manifestation, and treatment among case types. In addition, the Chi-squared test was used to assess the association between categorical variables. Multivariable multinomial logistic regression (adjusted by age, sex and nationality) by new cases as a baseline comparison group was used to model case types as a nominal dependent variable and infection, clinical manifestation and treatment as independent variable. Odds ratios (OR) with 95% confidence intervals (CI 95%) were calculated. To avoid over-parameterization, we excluded some variables because of low sample sizes: e.g. back and abdomen categories. If there are more parameters to estimate than observations in the dataset, then the model is over-parameterized and there is not enough information to yield valid parameter estimates.

A multivariable multinomial logistic regression model including all explanatory variables was constructed to calculate the probability of each adverse post-term treatment outcomes to assess the discriminant power of all explanatory variables assessed by the Receiver Operating Characteristic curve (ROC curve). In a ROC curve, the true positive rate (Sensitivity) is plotted as a function of the false positive rate (100-Specificity) for different cut-off points of a parameter. Area under the Curve (AUC) measures discrimination, i.e, the ability of the test to correctly diagnosis each post-treatment outcomes. Statistical analyses were conducted using Stata software, version 11 (Stata Corp, College Station, TX, USA). The level of statistical significance for all tests was $p \leq 0.05$.

3. Results

Median (IQR) age was 21[28] years (range 1 to 110). The cases detected by passive surveillance in female and male subjects was 94.8 and 95%, respectively. The proportion (%) of new, relapse, treatment after interruption, treatment after failure and chronic cases in CL patients was 72, 9, 10, 5 and 4, respectively. Age-sex distribution of the outcomes showed that the proportion of adverse post-treatment outcomes for male was higher than for female subjects, except for clinical resistance. Most new reported cases and relapses were aged under 10 years and between 20 and 40 years, as shown in Figures 1 and 2. A cross tabulation outcome of infection, clinical manifestation and treatment of CL patients by case type in detail is presented in Table 1.

Table 2 presents the adjusted prevalence odds ratios (POR) for all study variables by adverse outcomes after treatment. Multivariable multinomial logistic regression after adjusting age, sex and nationality showed that the occurrence of scar on head (face, ear and neck) had the strongest effect size on relapse, treatment after interruption, treatment failure and clinical resistance cases (OR= 4.21, 2, 6.61 and 2.62 respectively, $p \leq 0.001$). In the case of compared intramuscular (IM) injection, as result of intra leshional

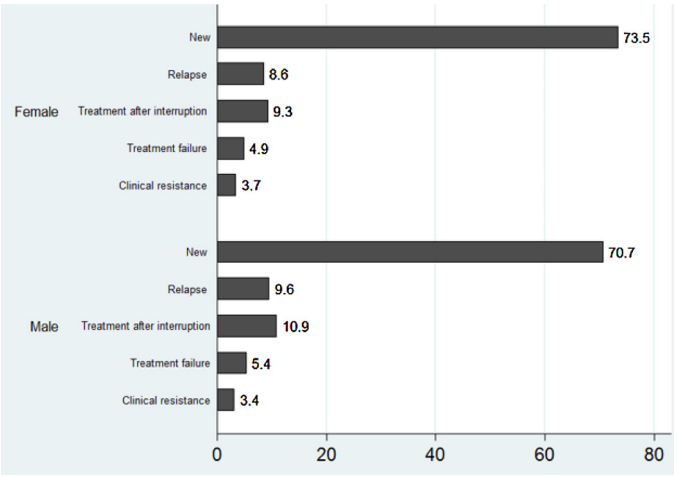

Figure 1. The proportion of cutaneous leishmaniosis patients by gender (2003-2011).