American Cutaneous Leishmaniasis in Eastern Minas Gerais: veiled reality of a neglected disease

Leishmaniose Tegumentar Americana no Leste de Minas Gerais: realidade velada de uma doença negligenciada

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INTRODUCTION

American Cutaneous Leishmaniasis (ACL) is an anthropozoonosis, defined by the World Health Organization (WHO) as one of the six most important infectious diseases of the world, both for its magnitude and for its ability to produce deformities, with repercussions in social and economic fields. Included in the group of neglected diseases, it represents a major public health problem in Brazil, since the disease is present in all federative units. It is an infection caused by different species of protozoa of the genus Leishmania and is transmitted through the bite of female hematophagous vectors from the Psychodidae family. The disease’s transmission cycles present variations in different regions of the country since they depend on a diversity of vector species, parasites, reservoirs, and hosts. Besides, there is a great influence of socioeconomic factors, since deforestation, precarious housing, and lack of basic sanitation favor the increase in the vector’s population. Then, the occupation of deforested areas and the rural exodus resulted in two distinct epidemiologic patterns, one related to the expansion of agricultural frontiers and the other to the growth of peri-urban regions, with possible adaptations of the parasite to

Methods: a combined study was carried out as a cross-sectional and an ecological approach of time series type, using notified and confirmed ACL cases, from 2007 to 2020. Primary and secondary data were used. Data were analyzed using descriptive and inferential statistics (simple linear regression, T-test, Mann-Whitney, chi-square (χ2) at a 5% significance level).

Results: a total of 219 cases were reported with a decreasing temporal trend, with a higher frequency observed for the cutaneous form (82.6%), age group 40 to 59 years (32.1%), black race (56.4%), and completed elementary school (47.7%). Individuals with the mucosal clinical form had lesions for a longer time, a greater chance of not progressing to cure, and used more vials of meglumine antimoniate when compared to patients with the cutaneous form.

Conclusions: different correlations were observed between the variables studied and the profile of involvement described in the scientific literature, with the clinical form predominantly cutaneous and with a good prognosis.

Keywords: Epidemiology; Cutaneous Leishmaniasis; Mucocutaneous Leishmaniasis; Neglected Diseases; Public Health.

Resumo

Objetivo: analisar os casos notificados e confirmados de LTA em um município do leste de Minas Gerais, no período de 2007 a 2020. Métodos: foi realizado um estudo combinado com abordagem transversal e ecológica do tipo série temporal, utilizando casos notificados e confirmados de LTA, de 2007 a 2020. Foram utilizados dados primários e secundários. Os dados foram analisados por meio de estatística descritiva e inferencial (regressão linear simples, teste T, Mann-Whitney, qui-quadrado (χ2) com nível de significância de 5%). Resultados: foram notificados 219 casos com tendência temporal decrescente, com maior frequência observada para a forma cutânea (82.6%), faixa etária de 40 a 59 anos (32.1%), raça negra (56.4%) e ensino fundamental completo (47.7%). Indivíduos com a forma clínica mucosa apresentaram maior tempo de lesão, maior possibilidade de não evoluir para cura, e usaram mais ampolas de meglunina antimoniate quando comparados a pacientes com a forma cutânea. Conclusões: foram observadas diferentes correlações entre as variáveis estudadas e o perfil de acometimento descrito na literatura científica, com a forma clínica predominantemente cutânea e com bom prognóstico.

Palavras-chave: Epidemiologia; Leishmaniose Cutânea; Leishmaniose Mucocutânea; Doenças Negligenciadas; Saúde Pública.
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ACL can present different clinical forms depending on the parasite’s species involved and the immunological response developed by the host. The two main manifestations are cutaneous and mucosal. The first one is characterized by painless lesions with a rounded or oval shape, an erythematous base, infiltrated with a firm consistency, well-delimited and elevated edges, reddish base, and coarse granulations. The second one is characterized by infiltrative ulcers, affecting the larynx, nasopharynx, and oral cavity. Laboratory diagnosis, especially by serology, is a challenge, considering that it has low sensitivity and specificity values. The association between clinical and parasitological diagnoses is useful in public health services and is often used to confirm the disease.

In the 1960s, ACL was first diagnosed at Vale do Rio Doce, Minas Gerais. Researchers detected infected individuals reporting little or no contact with forested areas, different from what was observed in other areas where the disease occurs in Brazil. For the main city in the region, Governador Valadares, the first record took place in 2001 with the publication of a descriptive study covering the period from 2001 to 2006, with 241 cases recorded, of which 46.1% were registered in 2006. A predominance of infected individuals living in urban areas was observed. Evidence of the disease urbanization may be related to environmental modifications caused by changes in the population’s lifestyle and the environment enabling the occurrence of the transmission cycle.

The objective of this study was to perform an analysis of notified and confirmed cases of ACL in a municipality East of Minas Gerais, from 2007 to 2020.

Methods

Study Area

The municipality of Governador Valadares, located in the eastern region of the state of Minas Gerais, Brazil, has a territorial area of 2,342 km², determined in 2018. Projections from the Ministry of Health estimate that in 2020 the municipality had 281,046 inhabitants. According to the United Nations Development Programme (UNDP), the Municipal Human Development Index (IDHM) is 0.727 and is the largest city in terms of population in the eastern region of Minas Gerais. It has the Reference Center for Endemic Diseases and Special Programs Dr. Alexandre Castelo Branco (CREDEN-PES), with regional assistance and continued monitoring of people with leprosy, tuberculosis, and leishmaniasis and supports the conduction of scientific studies.

Data collection

A combined cross-sectional, analytical and ecological study of the historical series of confirmed and autochthonous cases of ACL in the municipality of Governador Valadares. The study's population covered all the notified and confirmed patients for ACL according to the criteria of the Ministry of Health between January 1st, 2007, and December 31st, 2020.

The data were gathered in two stages: 1. Secondary data: notified cases in the Notified Diseases Information System (SINAN), made available by the Municipal Health Department of Governador Valadares and by the Health Department of Minas Gerais (Portal for Health Surveillance) from 2007 to 2020; and 2. Primary data (complementary to the secondary data): a review of the records and medical charts from patients assisted at the Reference Center for Endemic Diseases and Special Programs by Dr. Alexandre Castelo Branco (CREDEN-PES) from 2007 to 2018.

Non-probabilistic linkage was performed between the primary and secondary data, relating the nominal records from SINAN and CREDEN-PES through the pairing of the following variables: “patient’s name”, “mother’s name”, “age” and "date of diagnosis”.

Data analysis

Frequency and proportion analyses were made for the following categories: 1. Sociodemographics (sex, age, race/color, scholarly); 2. Type and clinical evolution (cutaneous or mucosal; cure, deaths by ACL, abandonment, or deaths from other causes); 3. Confirmation criteria (clinical-laboratory or clinical-epidemiological); 4. Therapy criteria (Pentavalent antimonate, Amphotericin B, Pentamidine, total number of vials); 5. Entry type (new case or relapse); 6. Times of injury and resolution. The coefficient of detection for ACL cases was calculated by the ratio between the number of diagnosed and the resident population, multiplied by 100 thousand by year. Given the difficulties to get the number of individuals exposed to the risk of contract ACL, the annual resident population estimated by the Brazilian Institute for Geography and Statistics was used.

For analysis of time trends, a simple linear regression model was used at a significance level of 5%, with the detection coefficient for ACL as the dependent variable and the year of notification as the independent variable. The model was chosen because it best explained the behavior of the indicators over time, taking into account the analysis of the scatterplot, the value of the coefficient of determination ($R^2$), and the analysis of residuals. The trends found were classified as increasing, stable or decreasing.

Regarding the statistical analysis, T-test for independent samples or Mann-Whitney were used to analyze the numerical variables and the categorical variables were compared by the chi-square test ($\chi^2$), and the effect size was evaluated from the calculation of the Cramer’s V. A value of p<0.05 and a 95% confidence interval (95% CI) indicated statistical significance. Logistic regression analysis was used to identify variables that were independently associated, using the Stepwise method.

For data analysis, Microsoft Office Excel 2007, JASP version
Ethics Statement

The study was conducted with the approval of the Ethics Committee of Research with human beings of the Federal University of Juiz de Fora under the number 2.751.396. The national and international normative in research ethics were strictly followed with nominal data, ensuring information protection and data secrecy.

RESULTS

In the period between 2007 to 2020, 219 cases of ACL were reported in residents of the city of Governador Valadares, of which 98 (44.7%) were female and 121 (55.3%) were male. There was a prevalence of 17.4% of the mucosal form of ACL, totaling 36 cases. However, most cases are cutaneous, represented by 183 individuals (82.6%) (Table 1). Cases were predominant in the 40-59 age group (32.0% of cases). Approximately 60.0% of the cases were over 40 years old. There was also a predominance of the cutaneous form in all age groups. Regarding the cutaneous/mucosal ratio, it was higher in the age group below or equal to 19 years, resulting in 15.5. Calculating the Odds Ratio to verify the predominance of the cutaneous form over the mucosa according to age group using less than or equal to 19 years as a reference, the results were positive in all age groups, and for people over 60 years old equal to 5.17 (CI 1.10 - 24.21), with a value of p=0.02 (Table 1).

For the race variable, cases were predominant in the black race, with 123 cases (56.4%). However, there were 72 cases (33.0%) in white individuals. The cutaneous form was more prevalent in both groups (Table 1). Almost half of the cases (47.7%) occurred in people with up to elementary school education. Only 10 cases were observed in individuals with complete higher education and 2 cases registered for illiterates. The cutaneous form was predominant in individuals with all levels of education, with a higher cutaneous/mucosal ratio in the group with complete higher education, which was equal to 9.3 (Table 1).

Regarding clinical evolution, 169 (77.5%) cases progressed to cure. Of these, 148 (87.6%) presented the cutaneous form and 21 (12.4%) presented the mucosal form, resulting in a cutaneous/mucosal ratio of 7.0 (Table 1). We observed 25 treatment abandonment cases, 20 (80%) in patients with the cutaneous form. Among the 4 cases of relapse, 75% were related to patients with the mucosal clinical form (Table 1).

Table 2 presents the analyses performed based on the medical record data collection of 185 confirmed cases of ACL between 2007 and 2018, residing at Governador Valadares. Individuals with the mucosal clinical form had a longer lesion time compared to those affected by the cutaneous form (p<0.00001, $V^2$=0.52). In addition, patients with the mucosal form had a higher chance of not progressing to cure when compared to patients with the cutaneous form (p<0.0001, $V^2$=0.32). It was also identified that mucosal leishmaniasis cases resulted in a long time for clinical cure compared to cutaneous leishmaniasis cases (p=0.03, $V^2$=0.2).

The independent samples t-test and Mann-Whitney test were used to analyze variables comparing the cutaneous and mucosal clinical forms. The results showed that carriers of the mucosal form were treated with a greater number of vials of meglumine antimoniate when compared to the number of vials used for the treatment of the cutaneous form (p<0.01).

Logistic regression was performed to analyze the relationship between clinical form and time of lesion, number of vials of meglumine antimoniate, clinical cure, and time to closure. The evaluation of the effect of the variables on clinical cure was performed by analysis of statistical significance. At first, variables were included individually, followed by the addition of the others variables mentioned. The best model obtained for predicting clinical cure involved the clinical form variable. The clinical form was responsible for explaining 21.0% of the cure. Patients with the mucosal form were 9.7 times more likely not to progress to clinical cure when compared to those affected by the cutaneous form (95% - CI= 1.0 - 3.6) (p<0.001), although this variable explained only 21% of the outcome ($R^2$ Nagerlkerke=0.21).

The linear regression model suggests significant decreasing temporal trends for the detection coefficients for both sexes separately and the following coefficients: female with the cutaneous form, and male with the mucosal form (Table 3).
### Table 1. Analysis of sociodemographic and clinical variables for American Cutaneous Leishmaniasis, Governador Valadares, Minas Gerais, Brazil, 2007 to 2020

| Variable                  | Mucosal n (%) | Cutaneous n (%) | Cutaneous/mucosal ratio | Odds ratio | IC 95%        | P value | Cases n (%) |
|---------------------------|---------------|-----------------|-------------------------|------------|---------------|---------|-------------|
| **Clinical Form**         |               |                 |                         |            |               |         |             |
|                           | Mucosal       | Cutaneous       |                         |            |               |         |             |
|                           | n (%)         | n (%)           |                         |            |               |         |             |
| **Age group**             |               |                 |                         |            |               |         |             |
| 19 years or less          | 2 (6.1)       | 31 (93.9)       | 15.5                    | 1          | -             |         | 33 (15.1)  |
| 20 - 39 years             | 7 (12.7)      | 48 (87.3)       | 6.9                     | 2.26       | 0.44 – 11.59  | 0.27    | 55 (25.2)  |
| 40 - 59 years             | 12 (17.1)     | 58 (82.9)       | 4.8                     | 3.21       | 0.67 – 15.25  | 0.1     | 70 (32.1)  |
| 60 years or more          | 15 (25.0)     | 45 (75.0)       | 3                       | 5.17       | 1.10 – 24.21  | 0.02    | 60 (27.5)  |
| **Race/color**            |               |                 |                         |            |               |         |             |
| White                     | 12 (16.7)     | 60 (83.3)       | 5                       |            |               |         | 72 (33.0)  |
| Black                     | 21 (17.1)     | 102 (82.9)      | 4.9                     |            |               |         | 123 (56.4) |
| Others                    | 0 (0.0)       | 2 (100.0)       | -                       |            |               |         | 2 (0.9)    |
| Ignored/blank             | 3 (14.3)      | 18 (85.7)       | 6                       |            |               |         | 21 (9.6)   |
| **Schooling**             |               |                 |                         |            |               |         |             |
| Higher education          | 2 (20.0)      | 8 (80.0)        | 4                       | 1          |               |         | 10 (4.6)   |
| Illiterate                | 0 (0.0)       | 2 (100.0)       | -                       | 1.33       | 0.30 – 5.77   | 0.71    | 2 (0.9)    |
| Elementary school         | 16 (15.4)     | 88 (84.6)       | 5.5                     | 0.73       | 0.14 – 3.74   | 0.49    | 104 (47.7) |
| High school               | 3 (9.7)       | 28 (90.3)       | 9.3                     | 0.43       | 0.06 – 3.02   | 0.35    | 31 (14.2)  |
| Ignored/not applicable    | 15 (21.1)     | 56 (78.9)       | 3.7                     |            |               |         | 71 (32.6)  |
| **Clinical evolution**    |               |                 |                         |            |               |         |             |
| Cure                      | 21 (12.4)     | 148 (87.6)      | 7                       | 1          |               |         | 169 (77.5) |
| Deaths by ACL             | 0 (0.0)       | 1 (100.0)       | -                       | 4.9        | 1.40 – 17.24  | 0.02    | 1 (0.5)    |
| Abandonment               | 5 (20.0)      | 20 (80.0)       | 4                       | 1.76       | 0.60 – 5.20   | 0.3     | 25 (11.5)  |
| Others                    | 5 (33.3)      | 10 (66.7)       | 2                       | 3.52       | 1.10 – 11.32  | 0.03    | 15 (6.9)   |
| Deaths by Other causes    | 5 (62.5)      | 3 (37.5)        | 0.6                     |            |               |         | 8 (3.7)    |

*Note: IC95% - Confidence interval 95%
†Source: Notified Diseases Information System (Sinan) and Reference Center for Endemic Diseases and Special Programs Dr. Alexandre Castelo Branco (CREDEN-PES) – Municipal Health Department of Governador Valadares, Minas Gerais, Brazil.
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Table 2. Inferential statistics between the variable clinical form and duration of injury, clinical cure and outcome of cases for American cutaneous leishmaniasis, Governador Valadares, Minas Gerais, Brazil, 2007 to 2018.

| Variable          | Clinical Form | Cases n | Cramér’s V | P value |
|-------------------|---------------|---------|------------|---------|
|                   | Cutaneous n (%) | Mucosal n (%) |             |         |
| Lesion time       |               |         |            |         |
| Up to 2 months    | 55 (94.8)     | 3 (5.2) | 58         |         |
| Between 2 and 6 months | 14 (93.3)   | 1 (6.6) | 15         | 0.52    |
| More than 6 months | 14 (50.0)    | 14 (50.0) | 28         | <0.001  |
| Clinical cure     |               |         |            |         |
| Yes               | 83 (87.4)     | 12 (12.6) | 95         |         |
| No                | 5 (41.7)      | 7 (58.3) | 12         | 0.38    |
| Closure           |               |         |            |         |
| Up to 6 months    | 106 (83.5)    | 21 (16.5) | 127        |         |
| Between 6 and 10 months | 30 (66.7)  | 15 (33.3) | 45         | 0.03    |
| More than 11 months | 12 (92.3)   | 1 (7.7) | 13         | 0.03    |

*Source*: Notified Diseases Information System (Sinan) and Reference Center for Endemic Diseases and Special Programs Dr. Alexandre Castelo Branco (CREDEN-PES) – Municipal Health Department of Governador Valadares, Minas Gerais, Brazil.

Table 3. Time trend of detection coefficients for American cutaneous leishmaniasis, Governador Valadares, Minas Gerais, Brazil, 2007 to 2020.

| Detection coefficient (per 100 thousands inhabitants) | Linear trend | P value |
|------------------------------------------------------|--------------|---------|
|                                                      | β            | R²      |         |
| To Governor Valadares                                | -0.76        | 0.46    | <0.01   |
| To females                                           | -0.79        | 0.61    | <0.01   |
| To males                                             | -0.72        | 0.31    | <0.05   |
| To females with cutaneous form                        | -0.71        | 0.56    | <0.01   |
| To males with mucous form                             | -0.21        | 0.43    | <0.05   |

*Source*: Notified Diseases Information System (Sinan) and Reference Center for Endemic Diseases and Special Programs Dr. Alexandre Castelo Branco (CREDEN-PES) – Municipal Health Department of Governador Valadares, Minas Gerais, Brazil.
DISCUSSION

Data from the present study suggest that between 2007 and 2020, the detection rate showed a decreasing temporal trend, which contrasts with the findings of the study carried out between 2001 and 2006, which showed an increase of 18.5 times (from 6 to 111) the number of reported cases. Another study carried out at Alagoas also showed a downward trend, raising hypotheses of multifactorial occurrence, comprising socioeconomic, environmental, and ecological aspects. In addition, the disease has a seasonal variation, either by climatic factors or by population dynamics of vectors and hosts, promoting annual incidence fluctuations.

ACL can affect both genders and individuals of any age group. In Brazil, individuals over 10 years of age (92.5% of all cases) and males (74% in 2014) predominate. In the present study, there was a predominance of males (55%) and most cases (60%) occurred in individuals over 40 years of age. In the previous study carried out in the municipality of Governador Valadares, between 2001 and 2006, approximately 53% of the patients were male and 55% of the affected individuals were aged between 10 and 39 years. Then, both studies present a predominance of males, but the present study shows the highest percentages of cases in older age groups (over 40 years).

According to Nobres et al (2013), individuals who had fewer years of education presented more severe disease than those who had more than 12 years of schooling. In this sense, Nassif et al (2016) also obtained the results that individuals with up to 8 years of study represented approximately 61% of the patients. In fact, in the present study, most of the cases occurred in people with up to elementary school education (47.7%).

Among the cases analyzed, a longer time of disease was observed in mucosal cases. This form is the hyperergic-pauciparasitic pole, a possible evolution of the cutaneous form when there is no expected cellular immune response or adequate treatment. The history of the mucosal form evolution is preceded by a cutaneous lesion may be responsible for the longer duration of the lesion observed among the cases of the mucosal form in this study. The literature shows that in only 15% of mucosal cases previous skin lesions are not identified, which may be related to previous subclínical infections or lesions that went unnoticed. Another factor that may be related to the duration of the lesion is the greater difficulty in diagnosing mucosal leishmaniasis. Its signs and symptoms have differential diagnoses: paracoccidioidomycosis, leprosy, rhinoscleroma, yaws, tertiary syphilis, midface granuloma, and neoplasms. In addition, isolation of parasites is more difficult in the mucosal form due to their scarcity and the presence of lesions with a high degree of destruction.

The Ministry of Health recommends that the first-choice drug for treatment should be meglumine antimoniate at a dosage of 10 mg to 20 mg Sb+5/kg/day, taking into account the maximum daily dose of 1,215 mg of meglumine antimoniate (3 vials). For the cutaneous form, the suggested dose is 15 mg Sb+5/kg/day for a period of 20 days. The mucosal form recommended treatment should be performed with 20 mg Sb+5/kg/day for a period of 30 days, recommending the associated use of pentoxifylline at a dose of 400 mg, three times a day, for the same period, the latter contraindicated in children under 12 years of age. Patients over 50 years of age, with kidney, heart, and liver failure and kidney transplant recipients have liposomal amphotericin B as their first treatment choice. The recommendation of a higher dosage and period of treatment for the clinical mucosal form reaffirms the result found in this study, which found a greater number of meglumine antimoniate vials used for the treatment of the clinical mucosal form when compared to the number of vials used to treat the cutaneous form.

The analyzes performed also showed that patients with the mucosal form had a greater chance of not progressing to cure. This form is characterized by having a low response to treatment, and a higher occurrence of infectious complications and recurrence, which can occur in up to 7.5% of cases. In addition, the involvement of the nasal and oral mucosa can cause permanent deformities and the mucosal form can progress to death in up to 1% of cases. Patients with the cutaneous form have a good response to treatment and a lower recurrence rate (4.3%). This lower therapeutic response and higher occurrence of complications and recurrence, together with the recommendation of longer treatment time for the mucosal form, may also be related to the longer time required for the cure of cases in the mucosal form, observed in the present study.

The epidemiological profile found in this study was similar to that found in the literature: predominantly cutaneous form with a good prognosis. It was not possible to ascertain the impact of the COVID-19 pandemic on ACL notifications in the municipality, with a decrease of 11.8% in cases in 2020 compared to 2019.

Thus, understanding the real magnitude of the disease is a great challenge, and to minimize possible biases and inconsistencies during information processing and underreporting, primary and secondary data were used for this work. Nevertheless, the limitations of the present study were the relatively small number of cases (n=219) and the use of secondary data. In addition, medical records were not recorded for research purposes and may have some inaccuracies.

Given the significant number of patients with the mucosal clinical form and the records of dropouts and recurrences, the findings of this study highlight the importance of adapting national policies to the local reality, aiming to improve the follow-up of treatment and individuals diagnosed with ACL.
ACKNOWLEDGMENTS

To the Municipal Health Department of Governador Valadares for providing the databases of the information system on notifiable diseases and for allowing access to the medical records of patients treated at Reference Center for Endemic Diseases and Special Programs Dr. Alexandre Castelo Branco.

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Como citar este artigo / How to cite this article:
Corrêa ESA, Pazini DS, Pinho GHC, Cabral LFE, Aquino SN, Vieira APA, et al. American Cutaneous Leishmaniasis in Eastern Minas Gerais: veiled reality of a neglected disease. J Health Biol Sci. 2022; 10(1):1-7.