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Are the clinical features of leprosy and American tegumentary leishmaniasis worse in patients with both diseases?

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ABSTRACT

This cross-sectional population-based study compared clinical features of leprosy and American tegumentary leishmaniasis (ATL) in patients diagnosed with both diseases (n=414) and in those diagnosed with only leprosy (n=27,790) or only ATL (n=24,357) in Mato Grosso State, which is a hyperendemic area for both diseases in Midwest Brazil. All new cases of leprosy and ATL reported in the area from 2008 to 2017 were included. Patients diagnosed with both diseases were identified by a probabilistic linkage procedure applied to leprosy and ATL databases of the national reporting system. The distribution of the frequency of clinical features between groups was compared by the chi-square test, followed by a multivariate logistic regression. Patients diagnosed with both leprosy and ATL presented higher odds of having nerve damage (OR: 1.34; 95% CI: 1.09–1.66) and leprosy reactions (OR: 1.35; 95% CI: 1.04–1.76) compared to patients diagnosed only with leprosy. Mucocutaneous leishmaniasis (OR: 2.29; 95% CI: 1.74–3.00) was more frequent among patients with both diagnoses when compared to patients who only had ATL. In conclusion, patients diagnosed with both leprosy and ATL present more severe clinical features of such diseases. Our data can be useful for designing health policies aimed at timely and integrated management of leprosy and ATL in co-endemic areas.

KEYWORDS: Coinfection. Comorbidity. Cutaneous leishmaniasis. Leprosy. Mucocutaneous leishmaniasis.

INTRODUCTION

Leprosy and American tegumentary leishmaniasis (ATL) are both neglected tropical diseases with similar biological, clinical, and immunological features[1,2]. Leprosy is mainly caused by the *Mycobacterium leprae* bacillus, whereas ATL is caused by varied species of protozoa of the genus *Leishmania*. Both are obligate intracellular pathogens that cause cutaneous manifestations and can result in irreversible physical disabilities and deformities if left undiagnosed and untreated[1]. The pattern of T cell-mediated immune response plays a key role in the clinical course of both, leprosy and ATL. The predominance of Th1 cells ensures a more intense and specific cellular immune response, which provides a pole of resistance to the infection. In contrast, the predominance of Th2 cells stimulates the humoral immunity, which is related to greater susceptibility and morbidity[3]. Although some case reports have suggested that leprosy/ATL coinfected patients develop a specific immune response to each pathogen[4], the occurrence of both diseases in the same individual may impact the clinical features of leprosy and ATL[5].

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Some authors[6] have shown that the occurrence of leprosy and ATL in the same patient is a rare event. However, in a retrospective cohort, our research group has recently reviewed and identified a relevant number of patients who were diagnosed with both diseases over a 10-year period in a hyperendemic area for leprosy and ATL in Brazil. The time elapsed between the diagnosis of both diseases was associated with sociodemographic characteristics, namely male gender, age group between 40-55 years and low level of education[7]. However, the clinical aspects of leprosy and ATL in patients affected by both diseases were not comprehensively reviewed. A better understanding of these characteristics can contribute to adequate clinical management of patients affected by both diseases. In addition, it can support the design of integrated surveillance and control measures aimed at early diagnosis and treatment[2,4]. Therefore, the present study aimed to compare the clinical characteristics of leprosy and ATL between patients diagnosed with both diseases and those diagnosed only with leprosy or ATL.

MATERIALS AND METHODS

Design and study area

This is a cross-sectional, population-based study that compared the clinical characteristics of leprosy and ATL between three distinct groups of patients. The L + ATL group was composed of patients diagnosed with both, leprosy and ATL; the L group was composed of patients diagnosed only with leprosy, and the ATL group was composed of patients diagnosed only with ATL. All cases were registered from 2008 to 2017 in Mato Grosso State, Midwest Brazil.

The Amazon rainforest, Cerrado (a savanna-like vegetation) and Pantanal (wetland) make up a total area of 903,207 km^2 of Mato Grosso State. The population is estimated at 3,567,234 inhabitants, who are distributed among 141 municipalities[8]. Despite the implementation of measures by the Brazilian Ministry of Health aimed at the surveillance and control of leprosy and ATL, the State remains a historically hyperendemic region for both diseases. Annually, Mato Grosso reports an average of 2,820 and 2,477 new cases of leprosy and ATL, respectively[9].

Data source, population, and study variables

Data were extracted from leprosy and ATL databases of the Brazilian Notifiable Diseases Information System (SINAN – Sistema de Informacao de Agravos de Notificacao), which is coordinated by the Epidemiological Surveillance Sector of Mato Grosso State's Health Department. We included all new cases of leprosy and ATL reported and confirmed by clinical-epidemiological and/or laboratory criteria from 2008 to 2017. Relapses, duplicate entries, non-autochthonous patients, misdiagnosed cases, records with inconsistencies, transfers, reinsertion into the system for a new round of treatment after a previous treatment abandonment and/or failure were excluded[7].

A total of 28,204 and 24,771 cases of leprosy and ATL, respectively, met these criteria. As previously described[7], a probabilistic linkage procedure between leprosy and ATL databases was performed by means of the Link Plus 3.0 beta software (Centers for Disease Control and Prevention, Atlanta, GA, USA) in order to identify patients diagnosed with both diseases. In summary, the probabilistic linkage employed blocking variables (patient's name, gender and date of birth) and matching variables (patient's name, gender, date of birth, mother's name and municipality of residence). To detect potential matches, we considered a minimum linkage value of seven. All potential matches were manually inspected to ensure true matches, resulting in 414 patients being diagnosed with both leprosy and ATL. Thus, the study population was allocated into three observational groups, as follows: the L + ATL group (n = 414), the L group (n = 27,790), and the ATL group (n = 24,357).

We selected demographic variables (gender and age) present in both leprosy and ATL databases and specific clinical variables for each disease. For leprosy, the following clinical variables were collected and categorized: operational classification (paucibacillary/multibacillary), clinical form according to the Madrid classification (indeterminate/tuberculoid/borderline/lepromatous), nerve damage (no/yes), degree of physical disability at diagnosis (grade 0/grade 1/grade 2), leprosy reactions (no/yes), bacilloscopy (negative/positive), first multidrug therapy regimen (paucibacillary/multibacillary) and case detection mode (active/passive). All variables were collected at diagnosis, except for leprosy reactions. The occurrence of reactive episodes was monitored monthly throughout the treatment period through the leprosy follow-up bulletin. For ATL, the following specific variables were collected: clinical form (cutaneous/mucocutaneous), cutaneous leishmaniasis scar (no/yes), HIV/ATL coinfection (no/yes), confirmation criteria (laboratory/clinical-epidemiological), direct parasitological examination (negative/positive), intradermal leishmanin (Montenegro) skin test (negative/positive), histopathology (not compatible/compatible/positive for amastigotes), and

initial treatment (pentavalent antimonial/other). An additional missing category was considered for all variables with missing or unreported data.

Statistical analysis

Our main hypothesis was that patients diagnosed with both diseases (L + ATL group) differ in terms of the severity of their clinical features, compared to patients diagnosed with only one disease (L group and ATL group). Thus, we defined the diagnosis of leprosy and ATL in the same individual as the main outcome. The distribution of proportions of clinical variables in patients from group L + ATL was compared with that among patients from group L and group ATL using the univariate chi-square test followed by the calculation of crude odds ratios (OR) with 95% confidence intervals (CI). A significance level of 5% was considered.

The crude OR results were adjusted using logistic regression models considering the clinical characteristics of leprosy (model I – L + ATL group and L group) and ATL (model II – L + ATL group and ATL group). For multivariate modeling, we included all variables with a p-value < 0.20 in the univariate analysis and with data completeness greater than 70%. According to the Brazilian Ministry of Health, the percentage of completeness can be used to classify data quality using SINAN data, as excellent (≥ 90%), regular (between 70% and 89%) or poor (< 70%)[10]. Moreover, similarly to the study conducted by Lima and Duarte[11], the missing category was considered for modeling. In particular, the variables "clinical form" and "first multidrug therapy regimen" were not considered for model I due to collinearity with the variable "operational classification". Both models were developed using the stepwise forward approach with variable maintenance of $p < 0.05$ or those variables considered relevant to the outcome. The effect of adding predictors and their interactions was evaluated using the Akaike's information criterion. The Hosmer- Lemeshow's test was used to verify the goodness of fit of the final models. All analyses were performed by the STATA/SE 12.0 software (StataCorp LP, College Station, TX, USA).

Ethics statement

Ethical approval was obtained from the Ethical Committee for Human Research of the Federal University of Rondonopolis (CAAE Nº 01735018.6.0000.8088). The participants' consent was not obtained as the study used secondary data only. The Ethical Committee confirmed the appropriateness of this approach.

RESULTS

Among the patients diagnosed with both leprosy and ATL during the study period (L + ATL group), most were male (83.09%). The mean (standard deviation – SD) age was 43.88 (14.93) years. As for the individuals included in group L and group ATL, 54.20% and 80.63% were males with a mean (SD) age of 43.28 (17.10) and 36.10 (17.37) years, respectively.

Given the clinical characteristics of leprosy, most patients diagnosed with both diseases were classified as multibacillary (76.09%) and borderline (55.80%) clinical forms. Regarding the occurrence of nerve damage, first multidrug therapy regimen and case detection mode, most cases presented affected nerves (59.90%), adherence to the multibacillary treatment scheme (75.37%), and were passively detected (77.78%). In addition, 36.23% of the individuals had some physical disability at diagnosis, and 17.63% presented leprosy reactions. As for bacilloscopy, only 24.40% of the results were positive, however, there was a high percentage of missing data (39.13%) (Table 1).

Regarding ATL, individuals from the group L + ATL predominantly presented cutaneous leishmaniasis (84.06%). Among those with mucocutaneous leishmaniasis (15.94%), most did not have a cutaneous scar (51.51%). Considering HIV/ATL coinfection, only 0.24% of the individuals were positive, but this variable presented poor completeness (38.41%). Most ATL cases were confirmed by laboratory evidence (89.13%). Direct parasitological examination and the Montenegro skin test were positive in 74.40% and 20.53% of the cases, respectively. In histopathology, the incidence of amastigotes and findings compatible with ATL were recorded in 10.63% and 2.66% of the cases, respectively. Most patients (93.96%) were treated with pentavalent antimonial (Table 2).

Individuals diagnosed with both diseases differed significantly from those diagnosed only with leprosy considering the following variables: gender ($p < 0.001$), clinical form ($p = 0.006$), nerve damage ($p = 0.012$), degree of physical disability ($p = 0.016$), leprosy reactions ($p = 0.002$) and bacilloscopy ($p < 0.001$) (Table 1). In the multivariate analysis, it was identified that the odds of patients diagnosed with both leprosy and ATL having nerve damage (OR: 1.34; 95% CI: 1.09–1.66) and leprosy reactions (OR: 1.35; 95% CI: 1.04–1.76) increased when compared to the odds of patients diagnosed only with leprosy. The final model was adjusted for the effect of gender, age group, and operational classification (Table 3).

Patients from the L + ATL group differed significantly from those diagnosed only with ATL regarding age ($p < 0.001$), clinical form ($p < 0.001$) and direct

Table 1 - Comparison between patients diagnosed with leprosy and American tegumentary leishmaniasis (L + ATL group) and patients diagnosed only with leprosy (L group), according to gender, age group, and clinical characteristics of leprosy, Mato Grosso State, Brazil, 2008–2017.

Variable	L + ATL group (n=414)		L group (n=27,790)		Crude OR	95% CI	*p* - value
	n	%	n	%			
Gender							< 0.001*
Female	70	16.91	12,727	45.80	1	–	
Male	344	83.09	15,063	54.20	4.15	3.21–5.37	
Age group (years)[a]							0.068
0 – 31	86	20.77	6,965	25.06	1	–	
32 – 43	119	28.74	6,933	24.95	1.39	1.05–1.84	
44 – 55	114	27.54	6,938	24.97	1.33	1.00–1.76	
> 55	95	22.95	6,954	25.02	1.11	0.82–1.48	
Operational classification							0.067
Paucibacillary	99	23.91	7,776	27.98	1	–	
Multibacillary	315	76.09	20,014	72.02	1.24	0.98–1.55	
Clinical form – Madrid classification							0.006*
Indeterminate	62	14.97	4,438	15.97	1	–	
Tuberculoid	37	8.94	3,791	13.64	0.70	0.46–1.05	
Borderline	231	55.80	15,366	55.29	1.08	0.81–1.43	
Lepromatous	53	12.80	2,750	9.90	1.38	0.95–2.00	
Missing data	31	7.49	1,445	5.20	1.54	0.99–2.37	
Nerve damage							0.012*
No	122	29.47	9,515	34.24	1	–	
Yes	248	59.90	14,622	52.61	1.32	1.06–1.64	
Missing data	44	10.63	3,653	13.15	0.94	0.66–1.33	
Degree of physical disability at diagnosis							0.016*
Grade zero	210	50.73	16,046	57.74	1	–	
Grade 1	124	29.95	7,003	25.20	1.35	1.08–1.69	
Grade 2	26	6.28	1,234	4.44	1.61	1.07–2.43	
Missing data	54	13.04	3,507	12.62	1.18	0.87–1.59	
Leprosy reactions							0.002*
No	274	66.19	20,545	73.93	1	–	
Yes	73	17.63	3,701	13.32	1.48	1.14–1.92	
Missing data	67	16.18	3,544	12.75	1.42	1.08–1.86	
Bacilloscopy							< 0.001*
Negative	151	36.47	9,778	35.18	1	–	
Positive	101	24.40	4,307	15.50	1.52	1.18–1.96	
Missing data	162	39.13	13,705	49.32	0.76	0.61–0.96	
First multidrug therapy regimen							0.152
Multibacillary	312	75.37	19,759	71.10	1	–	
Paucibacillary	99	23.91	7,728	27.81	0.81	0.65–1.02	
Missing data	3	0.72	303	1.09	0.63	0.20–1.97	
Case detection mode							0.310
Active[b]	78	18.84	5,799	20.87	1	–	
Passive[c]	322	77.78	21,313	76.69	1.12	0.88–1.44	
Missing data	14	3.38	678	2.44	1.53	0.86–2.73	

L = leprosy; ATL = American tegumentary leishmaniasis; OR = odds ratio; 95% CI = confidence interval at 95%; % = relative frequency; [a]categorized according to the quartile distribution; [b]collective examination or contact examination; [c] referral or free demand; *significant when *p*–value < 0.05.

Table 2 - Comparison between patients diagnosed with leprosy and American tegumentary leishmaniasis (ATL) (L + ATL group) and patients diagnosed only with ATL (ATL group), according to gender, age group, and clinical characteristics of ATL, Mato Grosso State, Brazil, 2008–2017.

Variable	L + ATL group (n = 414)		ATL group (n = 24,357)		Crude OR	95% CI	*p*-value
	n	%	n	%			
Gender							0.208
Female	70	16.91	4,718	19.37	1	–	
Male	344	83.09	19,639	80.63	1.18	0.91–1.53	
Age group (years)[a]							< 0.001*
0 – 23	36	8.70	6,157	25.28	1	–	
24 – 34	85	20.53	6,108	25.08	2.38	1.61–3.52	
35 – 48	123	29.71	6,070	24.92	3.46	2.39–5.03	
> 48	170	41.06	6,022	24.72	4.83	3.36–6.93	
Clinical form							< 0.001*
Cutaneous	348	84.06	22,848	93.80	1	–	
Mucocutaneous	66	15.94	1,509	6.20	2.87	2.20–3.75	
Cutaneous scar[b]							0.766
No	34	51.51	813	53.88	1	–	
Yes	29	43.94	650	43.07	1.07	0.64–1.77	
Missing data	3	4.55	46	3.05	1.56	0.46–5.27	
HIV/ATL coinfection							0.237
No	254	61.35	14,085	57.83	1	–	
Yes	1	0.24	158	0.65	0.35	0.05–2.52	
Missing data	159	38.41	10,114	41.52	0.87	0.71–1.06	
Confirmation criteria							0.922
Laboratory	369	89.13	21,746	89.28	1	–	
Clinical–epidemiological	45	10.87	2,611	10.72	1.01	0.74–1.39	
Direct parasitological examination							0.042*
Negative	31	7.49	1,554	6.38	1	–	
Positive	308	74.40	19,334	79.38	0.80	0.55–1.16	
Missing data	75	18.11	3,469	14.24	1.08	0.71–1.65	
Montenegro skin test							0.086
Negative	17	4.11	1,025	4.21	1	–	
Positive	85	20.53	4,009	16.46	1.28	0.75–2.16	
Missing data	312	75.36	19,323	79.33	0.97	0.59–1.59	
Histopathology							0.606
Not compatible	10	2.41	730	3.00	1	–	
Compatible	11	2.66	576	2.36	1.06	0.53–2.12	
Positive for amastigotes	44	10.63	3,018	12.39	1.39	0.59–3.30	
Missing data	349	84.30	20,033	82.25	1.27	0.67–2.39	
First therapy							0.665
Pentavalent antimonial	389	93.96	23,051	94.64	1	–	
Other[c]	17	4.11	807	3.31	1.25	0.76–2.04	
Missing data	8	1.93	499	2.05	0.95	0.47–1.92	

L = leprosy; ATL = American tegumentary leishmaniasis; OR = odds ratio; 95% CI = confidence interval at 95%; % = relative frequency; [a]categorized according to the quartile distribution; [b]evaluated only for patients with mucocutaneous leishmaniasis (n = 1,575); [c]amphotericin B or pentamidine; *significant when *p*–value < 0.05.

Table 3 - Adjusted multivariate logistic regression models corresponding to clinical characteristics of leprosy (model I – L + ATL group *vs.* L group) and American tegumentary leishmaniasis (model II – L + ATL group *vs.* ATL group), Mato Grosso State, Brazil, 2008–2017.

Variable	Adjusted OR	95% CI	*p*–value
Model I – L + ATL group *vs.* L group			
Gender			
Female	1	–	
Male	4.13	3.19–5.35	< 0.001*
Age group (years)			
0 – 31	1	–	
32 – 43	1.27	1.02–1.57	0.031*
Operational classification			
Paucibacillary	1	–	
Multibacillary	0.93	0.72–1.19	0.547
Nerve damage			
No	1	–	
Yes	1.34	1.09–1.66	0.006*
Leprosy reactions			
No	1	–	
Yes	1.35	1.04–1.76	0.026*
Missing data	1.38	1.05–1.81	0.020
Model II – L + ATL group *vs.* ATL group			
Age group (years)			
0 – 23	1	–	
24 – 34	2.34	1.58–3.47	< 0.001*
35 – 48	3.31	2.27–4.80	< 0.001*
> 48	4.34	3.01–6.25	< 0.001*
Clinical form			
Cutaneous	1	–	
Mucocutaneous	2.29	1.74–3.00	< 0.001*

L = leprosy; ATL = American tegumentary leishmaniasis; OR = odds ratio; 95% CI = confidence interval at 95%; *significant when *p*–value < 0.05.

parasitological examination ($p = 0.042$) (Table 2). In the adjusted analysis, it was observed that the odds of patients diagnosed with leprosy and ATL developing mucocutaneous leishmaniasis were 2.29 (95% CI: 1.74–3.00) times the odds of patients diagnosed only with ATL developing this clinical form. The final model was adjusted for the effect of the age group (Table 3).

DISCUSSION

This is the first systematic and population-based study addressing the clinical characteristics of leprosy and ATL among patients diagnosed with both diseases. We reviewed cases of patients diagnosed over 10 years in a Brazilian hyperendemic area[9]. Our main hypothesis was confirmed, as patients diagnosed with both diseases had significantly more severe clinical forms of leprosy (leprosy reactions and nerve damage) and ATL (mucocutaneous leishmaniasis) than those with only one disease. These findings oppose the review of 12 case reports/case series performed by Martínez *et al.*[4], who found no evidence of clinical interaction between leprosy and leishmaniasis.

Some studies have shown a significantly higher occurrence of leprosy reactions[12-15] and nerve impairment[16] in leprosy patients with other local or systemic infections. According to Motta *et al.*[14], it is likely that infections caused by other pathogens modulate the host's immune response by increasing the expression of inflammatory markers. These molecules can trigger reactive episodes in the course of leprosy. Additionally, such markers could contribute to a greater occurrence of nerve damage, which in turn is the main consequence of a predominantly Th1 immune response with the formation of granulomas in nerve structures[17,18]. A Th2 immune response may also trigger nerve damage via deposition of immune complexes and activation of complement, particularly in type 2

leprosy reaction[18,19]. Alterations in sensory, autonomic and motor functions of peripheral nerves can result in deformities and disabilities[17-20]. Notably, we identified a higher proportion of patients with physical disabilities in the univariate analysis.

In the present study, mucocutaneous leishmaniasis was more frequent among patients diagnosed with both leprosy and ATL compared to the cohort with only ATL. The development of an exacerbated INF-γ-mediated Th1 response plays a crucial role in the formation of potentially disfiguring and destructive lesions in the nasal and oropharyngeal cavities[21]. Azeredo-Coutinho *et al*.[5] previously reported an exacerbation of mucocutaneous leishmaniasis after the clinical cure of lepromatous leprosy in Brazil. This was most likely due to the IL10-mediated down-regulation effect that *M. leprae* antigens have on the IFN-γ response induced by *Leishmania* antigens. On the other hand, by analyzing a series of cases, Vernal *et al*.[6] concluded that the occurrence of leprosy and ATL in the same individual presents independent immunological mechanisms.

Despite the aforementioned divergences, the involvement of the same individuals with more severe clinical manifestations of leprosy and ATL warrants consideration in terms of the need for integrated management, as recommended by Mitjá *et al*.[2] for skin-related neglected tropical diseases. Thus, both during and after the multidrug therapy in leprosy patients previously or concomitantly diagnosed with ATL, we recommend (i) regular and more careful monitoring of leprosy reactions, (ii) increased frequency of neurological evaluations and disability tests, and (iii) surveillance for possible cases of ATL. On the other hand, patients diagnosed with ATL should be timely investigated for leprosy to prevent the development of severe conditions due to this disease, which apparently are enhanced in cases of co-diagnosis. For that, it is essential to strengthen diagnostic networks, the role of health services in the active detection of new cases and continued training of health professionals, especially those from primary health care facilities[2,7,22].

This study has some limitations. Firstly, the use of secondary data is susceptible to underreporting or missing information. In an attempt to minimize this bias, the variables were selected for statistical modeling based on the completeness of the data, and the missing information was considered during modeling. Secondly, we were unable to identify the truly coinfected patients due to the study design. However, given the long incubation period of leprosy[1], it is likely that most patients from the L + ATL group were actually coinfected. Thirdly, we did not consider the spectral poles of leprosy and ATL, the genetic susceptibility/resistance profiles, the status of HIV/leprosy coinfection, or the effect of the socioeconomic context during the analyses. For future investigations aimed at the occurrence of leprosy and ATL in the same patients, it is recommended to perform stratified analyses based on the polar forms of both diseases. Prospective follow-ups should be encouraged for more detailed assessments of the clinical impact of leprosy/ATL coinfection and its association with socioeconomic aspects, immunological profile and genetic background.

CONCLUSION

In conclusion, the diagnosis of leprosy and ATL in the same individual appears to contribute to a worse clinical presentation of both diseases, characterized by nerve damage, leprosy reactions and mucocutaneous leishmaniasis. Given the endemicity of both diseases in Brazil and other countries, our findings are relevant for the design and implementation of integrated control programs focused on timely detection and treatment, as well as monitoring of leprosy and ATL patients. Furthermore, our data may be useful in the design of predictive algorithms for the development of leprosy or ATL given a previous diagnosis of one of these diseases. Taken together and appropriately considered, these approaches can reduce the stigmatizing complications caused by both diseases.

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AUTHORS' CONTRIBUTIONS

AGC, JGGL, and EI conceived the study; AGC, JGGL, and EI designed the study protocol; AGC conducted the data collection; AGC and JGGL analyzed the data; AGC drafted the manuscript; JGGL, PS, and EI critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. AGC and EI are guarantors of the paper.

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