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Clinical variables associated with leprosy reactions and persistence of physical impairment

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ABSTRACT

Introduction: Leprosy is a chronic disease that affects skin and peripheral nerves. Disease complications include reactional episodes and physical impairment. One World Health Organization (WHO) goal of leprosy programs is to decrease the number of grade 2 impairment diagnoses by 2015. This study aims to evaluate clinical factors associated with the occurrence of leprosy reactions and physical impairment in leprosy patients. **Methods:** We conducted a retrospective study of data from medical records of patients followed in two important centers for the treatment of leprosy in Aracaju, Sergipe, Brazil, from 2005 to 2011. We used the chi-square test to analyze associations between the following categorical variables: gender, age, operational classification, clinical forms, leprosy reactions, corticosteroid treatment, and physical impairment at the diagnosis and after cure. Clinical variables associated with *multibacillary leprosy and/or reactional episodes* and the *presence of any grade of physical impairment after cure* were evaluated using the logistic regression model. **Results:** We found that men were more affected by multibacillary forms, reactional episodes, and grade 2 physical impairment at diagnosis. Leprosy reactions were detected in a total of 40% of patients and all were treated with corticosteroids. However, physical impairment was observed in 29.8% of the patients analyzed at the end of the treatment and our multivariate analysis associated a low dose and short period of corticosteroid treatment with persistence of physical impairments. **Conclusions:** Physical impairment should receive an increased attention before and after treatment, and adequate treatment should be emphasized.

Keywords: Leprosy. Leprosy reactions. Physical impairment. Corticosteroid treatment.

INTRODUCTION

Leprosy is a chronic disease caused by infection with *Mycobacterium leprae*. The bacillus affects the skin and Schwann cells of the peripheral nerves, resulting in cutaneous lesions and neuropathy. Loss of sensory, motor, and autonomic nerve function in the eyes, hands, and feet can result in secondary complications, such as deformity, impairment, psychological disturbances, and social exclusion[1,2].

Periods of acute immunologic hypersensitivity known as reactional episodes can occur before the diagnosis and during or after treatment and cause nerve injury if not appropriately treated[3]. There are two primary types of hypersensitivity reaction: type 1 reactions, also referred to as reversal reactions (RR) (exacerbation of cellular immunity), and type 2 reactions, or erythema nodosum leprosum (exacerbation of humoral immunity)[3]. There is a clear recommendation for corticosteroid treatment of severe type 1 reactional episodes by the Brazilian Ministry of Health: 1 to 2mg/kg of body weight for at least 12 weeks. For severe type 2 reactions, the Brazilian Ministry of Health recommends the same dose of corticosteroid plus thalidomide[4].

Assessment of physical impairment in leprosy is employed as an epidemiological indicator to evaluate leprosy programs, determine early or late diagnosis, and monitor patient follow-up in health care center over the course of treatment[5]. The World Health Organization's (WHO) global strategy (2011 to 2015) aims to reduce the rate of new cases of grade 2 physical impairment[4]. Additionally, early detection of new cases of leprosy and corticosteroid treatment for severe reactional episodes may prevent future cases of irreversible nerve damage[6].

The State of Sergipe is located in northeastern Brazil and is a priority for the national leprosy control program. In the last seven years, 3,039 patients were registered in the Brazilian Information Health System of the *Sistema de Informação de Agravos de Notificação* (SINAN), and the percentage of grade 2 impairments at diagnosis increased between 2005 and 2010 (from 4.8% to 8.7%). These numbers call attention to the need to perform studies evaluating epidemiological and clinical

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factors associated with physical impairment[7]. This study aims to evaluate clinical factors associated with the occurrence of physical impairment in leprosy patients from two centers for the treatment of leprosy patients in Sergipe.

METHODS

We conducted a retrospective study of data from the medical records of patients followed in two centers for the treatment of leprosy located in the City of Aracaju, State of Sergipe, Brazil, from 2005 to 2011. From a total of 545 records of patients diagnosed with leprosy, 51 patients were excluded because they did not finish the specific treatment, were transferred during the first two months of treatment, or the records did not contain the necessary information. A total of 494 patient records were analyzed. The analyzed variables were: gender, age (≥ 15 years and < 15 years), the classification of physical impairment at diagnosis and after treatment (grade 0, 1 and 2) based on the WHO and the Brazilian Ministry of Health standard examination, operational classification: paucibacillary (PB) and multibacillary (MB), clinical forms (indeterminate leprosy, tuberculoid leprosy, borderline leprosy, lepromatous leprosy, and pure neural leprosy), reactional episodes, and treatment with corticosteroids. We defined the type 1 reaction as an episode characterized by acute inflammation in skin lesions or nerves[8,9] and the type 2 reaction as the appearance of inflamed cutaneous nodules with or without neuritis[9].

Nerve involvement in leprosy is considered to occur when there are signs of pain or nerve thickening on palpation of the nerves, when there is loss of sensitivity according to the monofilament test, or when any motor impairment is observed. However, for this analysis, we only considered the objective scale of physical impairment as defined by the WHO. This scale ranksphysical impairment in leprosy as follows: grade 0 (no anesthesia and no visible impairment to the eyes, hands, or feet), grade 1 (anesthesia but no visible deformities to the eyes, hands, or feet), and grade 2 (hand ulcers, absorption or contractures of the digits, plantar ulcers, callosities, foot drop, or claw). This assessment should be conducted at the beginning and the end of treatment or at any time during treatment if the patient has a complaint.

The severity of the disease is associated with clinical forms with high bacilli loads (MB forms)[10,11] or the occurrence of reactional episodes[12].Thus, we investigated the association of the demographic and clinical data with these two variables as well as with physical impairment.

Statistical analysis

We created a database in Statistical Package for the Social Sciences (SPSS) statistical program version 17.0.0. Categorical variables are presented as simple or frequency count sand percentages and quantitative variables as means and standard deviations. To analyze the associations between categorical variables we used thechi-square test. To assess the factors associated with MB leprosy and reactional episodes, we used a logistic regression model in which *MB leprosy and/or reactional episode* was considered the dependent variable, where as gender and physical impairment at diagnosis were the independent variables. In addition, the logistic regression model was used to evaluate the *presence of any grade of physical impairment after treatment* as the dependent variable and male gender, reactional episodes, and a *corticosteroid dose lower than 20mg for a period less than 30 days* as independent variables. We adopted $\alpha = 0.05$ as the level of significance.

RESULTS

We analyzed the medical records of 494 patients, 268 (54%) men and 226 (46%) women)of the two major centers for the treatment of leprosy patients in Sergipe from 2005 to 2011. We found similar percentages of PB forms (50.8%; 251/494, 95% CI [46.8 to 55.1]) and MB forms (49.2%; 243/494, 95% CI [44.9 to 53.2]). However, men presented a higher frequency of MB forms. Of the 268 men, 162 (60.4%) were affected by MB forms compared with 81 (35.8%) of the 226 women ($p< 0.001$). Physical impairment was evaluated and recorded in 396 (80.2%) of the 494 patients at diagnosis (200 men and 196 women). Men presented twice as much grade 2 physical impairment at diagnosis [12% (24/200)] as women [6.1% (12/196); $p = 0.04$], and reactional episodes were more frequently observed in MB forms [57.2% (139/243); $p < 0.0001$] and in men [45.1% (121/268)] than in women [33.6% (76/226); $p = 0.009$] **(Table 1)**.

Ages were registered for 488 patients and ranged from 3 to 85 years (mean ± SD, 41 ± 18.2). Eight percent of the patients (39/488) were children aged younger than 15 years. Clinical forms were registered in 424 patients. The predominant clinical form of leprosy was tuberculoid (TT) [40.1% (170/424)], followed by borderline (BB) [20.1% (85/424)], indeterminate (IL) [18.4% (78/424)], lepromatous (LL) [17.2% (73/424)], and pure neural (PN) [4.2% (18/424)].

Reactional episodes were detected in 40% (197/494; 95%CI [35.6 to 44.1]) of the patients and were more frequently observed in MB forms [57.2% (139/243); $p < 0.0001$]. The RR, or the type 1 reaction, was the most common [75.1% (148/197)] and more frequent during treatment for leprosy.

Figure 1 shows the frequency of recorded physical impairment examinations in the 494 patients included in this study before and after treatment and the frequency of any grade of physical impairment found in the examined patients. At diagnosis, 80.2% (396/494) of the patients were evaluated for physical impairment, and 36% (143/396) exhibited grade 1 [27% (107/396)] or grade 2 [9% (36/396)] physical impairments. After treatment, the assessment of physical impairment was recorded in only 37.4% (185/494) of patients, and 29.8% (55/185) of these patients exhibited physical impairments.

Based on the frequency of grade 1 and 2 of physical impairment found after treatment (30%) and considering that an examination to evaluate the grade of physical impairment was not recorded after treatment for a majority of patients [62.5% (309/494)], physical impairment might have been detected in 93 additional patients had they been examined.

TABLE 1 - Clinical characteristics according to gender of leprosy patients attended from 2005 to 2011 in Sergipe, Brazil.

Variable*	Male % (n/total)	Female % (n/total)	p
Operational classification			
paucibacillary form	39.6 (106/268)	64.2 (145/226)	
multibacillary form	60.4 (162/268)	35.8 (81/226)	< 0.001
Leprosy reactions	45.1 (121/268)	33.6 (76/226)	0.009
Physical impairment at diagnosis			
grade 0 (no impairment)	61.0 (122/200)	66.8 (131/196)	
grade 1	27.0 (54/200)	27.0 (53/196)	
grade 2	12.0 (24/200)	6.1 (12/196)	0.040

*Chi-square test.

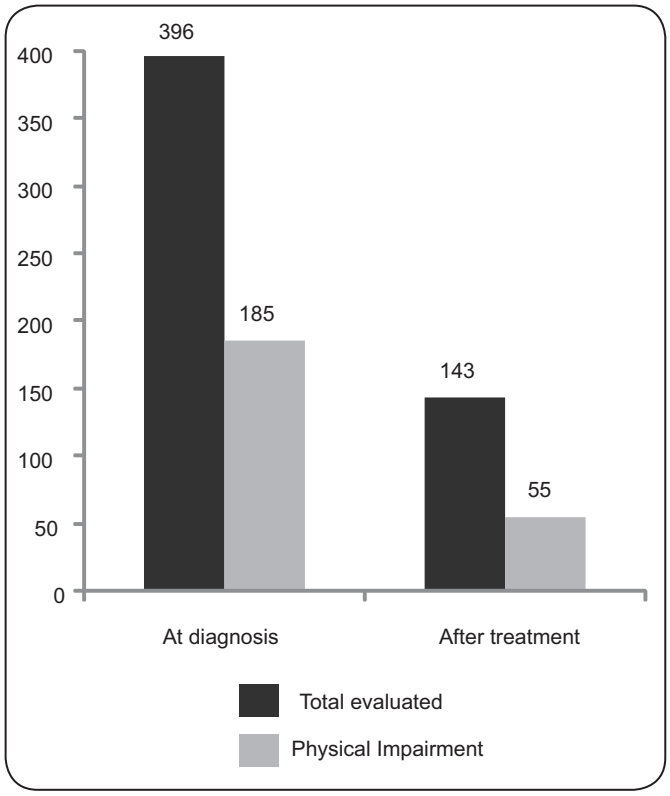

FIGURE 1 - Number of leprosy patients with recorded neurological examinations and any grade of physical impairment detected at diagnosis and at the end of treatment attended in the two major leprosy centers in Sergipe, Brazil, from 2005 to 2011.

Of the 494 patients included in this study, 40% (197/494, 95%CI [35.6 to 44.1]) experienced reactional episodes, and all 197 received corticosteroid treatment. However, 162/197 (82.2%) patients received a dose below 20mg of prednisone for less than 30 days. After corticosteroid treatment of these 162 patients, only 54 underwent neurological assessment at the beginning and at the end of the treatment. Of these patients, the grade of physical impairment of 52% (28/54) remained the same or increased. For instance, of these 54 patients, 26 patients had grade 0 physical impairment before treatment. Of these 26 patients, 18 continued to exhibit no signs of nerve injury after treatment, however, 7 patients progressed to grade 1 and 1 patient to grade 2 physical impairment. Of 23 patients presenting with grade 1 physical impairment before treatment, 14 remained at grade 1, one patient progressed to grade 2, and only eight patients improved to grade 0 after treatment. Of 5 patients diagnosed with grade 2 physical impairment before treatment, four patients remained with grade 2, whereas one patient improved to grade 1 after treatment.

To assess the factors associated with *MB leprosy and/or reactional episode*, we used a logistic regression model in which *MB leprosy and/or reactional episode* was a dependent variable and gender and grade 1 and 2 of physical impairment at diagnosis were independent variables. **Table 2** shows an independent association between *MB leprosy and/or reactional episode* and factors such as male gender (OR 2.42, 95%CI [1.49 to 3.95]; p<0.001) and grade 2 (OR 6.32, 95%CI [1.98 to 20.15]; p=0.002) or grade 1 (OR 2.72, 95%CI [1.50 to 4.92]; p=0.001) physical impairment at diagnosis. When the *presence of any grade of physical impairment after cure* was evaluated as a dependent variable with male gender, age, reactional episodes, and a *corticosteroid dose lower than 20mg for a period less than 30 days* as independent variables, we observed an independent association of the *presence of any grade of physical impairment after cure* with this treatment regimen (OR 4.94, 95%CI [2.49 to 9.82]; p<0.001). No associations with male gender, age, and leprosy reactions were detected.

DISCUSSION

The morbidity associated with leprosy is related to multiple skin lesions observed in MB forms[11], leprosy reactions[12], and physical impairment[13], which are the disease's

TABLE 2 - Logistic regression analysis of factors associated with *multibacillary/leprosy reaction* and *physical impairment after treatment* in leprosy patients attended from 2005 to 2011 in Sergipe, Brazil.

Dependent variables	Independent variables	OR	95% CI	p
Multibacillary/leprosy reaction				
	Gender			
	male	2.42	1.49-3.45	<0.0001
	female	1		
	Physical impairment at diagnosis			
	grade 2	6.32	1.98-20.15	<0.002
	grade 1	2.72	1.50-4.92	<0.001
	grade 0	1		
Physical impairment after treatment*				
	Corticosteroid treatment dose			
	< 20mg for < 30 days	4.94	2.49-9.82	<0.001
	higher doses	1		

Model: Logistic regression after adjustment of the model (Forward Stepwise); *Variables that were not associated independently with physical impairment after treatment: gender (p=0.44), age (p=0.17), and reactional episode (p=0.24). OR: odds ratio; CI: confidence interval.

primary complications. It is important to identify the clinical characteristics that can predict these deleterious outcomes. In this study, we found independent associations of male gender with MB forms, leprosy reactions, and physical impairment. A higher prevalence of leprosy in men is reported by others[2,13,14] as well as associations between male gender and MB forms of leprosy[7], leprosy reactions[15], and physical impairment[7]. This frequency of complication among men might be related to socio-cultural issues, such as higher exposure as a result of more intense social or work activities, less pursuit of health care, and the fear of losing one's employment because of the stigma of leprosy[2].

Interestingly, in leishmaniasis, which is another disease caused by an intracellular organism, epidemiological data and experimental animal studies also suggest higher susceptibility in males[16]. A study using an experimental model of infection by *Paracoccidioides braziliensis* demonstrated the influence of sex hormones on the immune response, revealing that testosterone promotes an increased production of interleukin-10 (IL-10), and less protection against this infection[17]. There is no study on this issue in the context of leprosy.

The global strategy for the control of leprosy from 2011 to 2015 aims to reduce the rate of new cases with grade 2 physical impairment worldwide by more than 35% by the end of 2015, compared with the baseline at the end of 2010[4]. The number of thickened nerves is significantly associated with increased risk for physical impairments[2,18]. Furthermore, physical impairment at diagnosis has been associated with a worse prognosis for deformities[19,20].

The proportion of patients evaluated using a neurological examination and diagnosed with physical impairment facilitates an indirect assessment of the effectiveness of programs to prevent impairment[18].The Brazilian Ministry of Health has established that the physical impairment evaluation should be performed in at least 90% of the leprosy patients at diagnosis and 75% after treatment. In the present study, we demonstrate that leprosy reactions and physical impairment are frequent in this population. However, a number of patients in these medical centers are not tested for impairment at diagnosis and a larger number of patients are not assessed at the end of treatment. These results may reflect problems with professional training for the prevention of leprosy-related physical impairment. It is essential to develop strategies that emphasize the importance of the neurological examination to prevent physical impairments[19].

Leprosy reactions are associated with the development of physical impairments. Early identification combined with the proper treatment of leprosy reactions can be an effective strategy to prevent physical impairment in leprosy[13,14]. Prednisone is the drug of choice not only for the treatment of leprosy reactions and silent neuritis events[21] but also to reduce swelling and prevent further physical impairment[18].

The Brazilian Ministry of Health guidelines suggest the administration of 1 to 2mg/kg of prednisone daily for at least 90 days to treat severe reactions[19]. However, in this study, patients were treated with smaller doses of steroids over a shorter period. This approach may be insufficient to reverse nerve damage, resulting in a high frequency of physical impairment after treatment. In fact, in the present study, we demonstrated an independent association between the persistence of physical impairment after treatment and treatment with corticosteroids in a dose lower than 20mg for a period less than 30 days.

Although there is a clear recommendation by the Brazilian Ministry of Health to treat leprosy reactions with corticosteroids,

controversy remains regarding the dose and duration of corticosteroid treatment that is necessary to prevent physical impairment. A multicenter study in Bangladesh and Nepal demonstrated a decrease in primary outcome events of leprosy-related reactions and associated impairment of nerve function by prophylactic oral corticosteroids for 4 months in MB patients. However, this significant effect was not sustained after one year[22]. A clinical trial using oral corticosteroids for neuropathy demonstrated that during the first month higher doses of steroids produced better results. However, earlier treatment with lower doses was also effective[23]. The administration of the correct dose of prednisone improved the clinical and electrophysiological condition of PN patients, contributing to the prevention of further neurological damage[24].

In conclusion, our data suggest that increased attention should be paid to men by the leprosy control program because men present higher frequencies of MB forms and severe outcomes, including leprosy reactions and grade 2 physical impairment at diagnosis. Additionally, it is essential to develop strategies that emphasize the importance of performing the neurological examination and the adequate treatment of leprosy reactions to prevent physical impairment after treatment.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. Alves CJM, Barreto JA, Fogagnolo L, Contin LA, Nassif PW. Avaliação do grau de incapacidade dos pacientes com diagnóstico de hanseníase em Serviço de Dermatologia do Estado de São Paulo. Rev Soc Bras Med Trop 2010; 43:460-461.
2. Moschioni C, Antunes CMF, Grossi MAF, Lambertucci JR. Risk factors for physical disability at diagnosis of 19,283 new cases of leprosy. Rev Soc Bras Med Trop 2010; 43:19-22.
3. Souza LWF. Reações hansênicas em pacientes em alta por cura pela poliquimioterapia. Rev Soc Bras Med Trop 2010; 43:737-739.
4. World Health Organization (WHO). Weekly epidemiological record. WHO; 2011.
5. Raposo MT, Caminha AVQ, Heukelbach J, Sánchez-González MA, Medeiros JLA, Nemes MIB. Assessment of physical impairments in leprosy patients: a comparison between the world health organization (WHO) disability grade and the eye-hand-foot score. Rev Inst Med Trop 2011; 53:77-81.
6. Schuring RP, Richardus JH, Steyerberg EW, Pahan D, Faber WR. Preventing nerve function impairment in leprosy: validation and updating of a prediction rule. Plos Neglec Trop Dis 2008; 3:283-287.
7. Oliveira DT, Bezerra MM, Almeida JAP, Duthie M, Reed S, Jesus AR. Neurological disability in leprosy: incidence and gender association in Sergipe, Brazil. Geospatial Health 2012; 6:125-129.
8. Foss NT. Episódios reacionais na hanseníase. Med Rib Pret 2003; 36:453-459.
9. Kahawita IP, Walker SL, Lockwood DNJ. Leprosy type 1 reactions and erythema nodosum leprosum. An Bras Dermatol 2008; 83:75-82.
10. Ranque B, Nguyen VT, Vu HT, Nguyen TH, Nguyen NB, Pham XK, et al. Age is an important risk factor for onset and sequelae of reversal reactions in vietnamese patients with leprosy. CID 2007; 44:33-40.
11. Trindade MAB, Varella TCN, Cisneron CGC, Bottini V, Mour AKA. Delayed diagnosis of multibacillary leprosy: a report of eigth cases. Braz J Infect Dis 2009; 13:155-157.
12. Balagon MVF, Gelber RH, Abalos RM, Cellona R. Reactions following completion of 1 and 2 years multidrug terapy (MDT). Am J Trop Med Hyg 2010; 83:637-644.
13. Mastrangelo G, Silva Neto J, Silva GV, Scoizzato L, Fadda E, Dallapicola M, et al. Leprosy reactions: the effect of gender and household contacts. Mem Inst Oswaldo Cruz 2011; 106:92-96.
14. Richardus JH, Nicholls PG, Croft RP, Withington SG, Smith WCS. Incidence of acute nerve function impairment and reactions in leprosy: a prospective cohort analysis after 5 years of follow-up. Inter J Epid 2004; 33:337-343.
15. Guerra JG, Penna GO, Castro LCM, Martelli CMT, Stefani MMA. Eritema nodoso hansênico: atualização clínica e terapêutica. An Bras Dermatol 2002; 77:389-407.
16. Travi L, Osorio Y, Melby PC, Chandrasekar B, Arteaga L, Saravia NG. Gender is a major determinant of the clinical evolution and immune response in hamsters infected with *leishmania*. Infection Imunity 2002; 70:2288-2296.
17. Pinzan CF, Ruas LP, Casabona-Fortunato AS, Carvalho F, Roque-Barreira MC. Immunological basis for the gender differences in murine paracoccidioides brasiliensis infection. Plos One 2010; 5:107-57.
18. Smith WCS, Nicholls PG, Das L, Barkataki P, Suneetha S, Suneetha L, et al. Predicting neuropathy and reactions in leprosy at diagnosis and before incident events results from the INFIR Cohort Study. Plos Neglec Trop Dis 2009; 3:1-8.
19. Ministério da Saúde (MS). Portaria 3.125. Secretaria de Vigilância em Saúde 2010. Brasília: MS; 2010.
20. Slim FJ, Schie CH, Keukenkamp R, Faber WR, Nollet F. Effects of impairments on activities and participation in people affected by leprosy in the Netherlands. J Rehabil Med 2010; 42:536-543.
21. Brakel WH, Nicholls PG, Wilder-Smith EP, Das L, Barkataki P, Lockwood DNJ. Early diagnosis of neuropathy in leprosy- comparing diagnostic tests in a large prospective study (the INFIR cohort study). Plos Neglec Trop Dis 2008; 2:1-12.
22. Smith WCS, Anderson AM, Withington SG, Brakel WHV, Croft RP, Nicholls PG, et al. Steroid prophylaxis for prevention of nerve function impairment in leprosy: randomised placebo controlled trial (TRIPOD 1). BMJ 2004; 328:1-5.
23. Garbino JA, Virmond MCL, Ura S, Salgado MH, Bernard N. A randomized clinical trial of oral steroids for ulnar neuropathy in type 1 and type 2 leprosy reaction. Arq Neuropsiquiatr 2008; 66:861-867.
24. Jardim MR, Illarramendi X, Nascimento OJM, Nery JAC, Sales AM, Sampaio EP, et al. Pure neural leprosy steroids prevent neuropathy progression. Arq Neuropsiquiatr 2007; 65:969-973.