CLINICAL SCIENCE

Leprosy reactions: coinfections as a possible risk factor

Ana Carolina F. Motta, Karla Juliana Pereira, Daniela Chaves Tarquínio, Mariana Bellini Vieira, Karina Miyake, Norma Tiraboschi Foss

University of São Paulo, Ribeirão Preto Medical School, Division of Dermatology, Departamento de Clínica Médica, Ribeirão Preto/SP, Brazil.

OBJECTIVE: This study aimed to determine the frequency of coinfections in leprosy patients and whether there is a relationship between the presence of coinfections and the development of leprosy reactional episodes.

METHOD: A cross-sectional study based on an analysis of the medical records of the patients who were treated at the Leprosy Clinics of the Ribeirão Preto Medical School, University of São Paulo, was conducted from 2000 to 2010. Information was recorded regarding the age, sex, clinical status, WHO classification, treatment, presence of reactions and coinfections. Focal and systemic infections were diagnosed based on the history, physical examination, and laboratory tests. Multinomial logistic regression was used to evaluate the associations between the leprosy reactions and the patients' gender, age, WHO classification and coinfections.

RESULTS: Two hundred twenty-five patients were studied. Most of these patients were males (155/225 = 68.8%) of an average age of 49.31 $\pm$ 15.92 years, and the most prevalent clinical manifestation was the multibacillary (MB) form (n = 146), followed by the paucibacillary (PB) form (n = 79). Erythema nodosum leprosum (ENL) was more prevalent (78/122 = 63.9%) than the reversal reaction (RR) (44/122 = 36.1%), especially in the MB patients (OR 5.07; CI 2.86-8.99; $p<0.0001$) who exhibited coinfections (OR 2.26; CI 1.56-3.27; $p<0.0001$). Eighty-eight (88/225 = 39.1%) patients exhibited coinfections. Oral coinfections were the most prevalent (40/88 = 45.5%), followed by urinary tract infections (17/88 = 19.3%), sinusopathy (6/88 = 6.8%), hepatitis C (6/88 = 6.8%), and hepatitis B (6/88 = 6.8%).

CONCLUSIONS: Coinfections may be involved in the development and maintenance of leprosy reactions.

KEYWORDS: Leprosy Reaction; *Mycobacterium leprae*; Oral Infection; Coinfection.

Motta AC, Pereira KJ, Tarquínio DC, Vieira MB, Miyake K, Foss NT. Leprosy reactions: coinfections as a possible risk factor. Clinics. 2012;67(10):1145-1148.

Received for publication on March 28, 2012; **First review completed on** April 16, 2012; **Accepted for publication on** May 24, 2012

E-mail: anacfm@usp.br

Tel.: 55 16 3633-0236

INTRODUCTION

Leprosy reactional episodes (REs) are serious complications of leprosy because these reactions are most likely the predominant cause of permanent nerve damage, leading to disability and deformities (1). There is an urgent need to understand the pathogenesis of these alterations to determine which patients may be considered to be at risk. These episodes represent an exacerbation of the inflammatory process that can occur before, during and after treatment for leprosy (2,3). There are two well-recognized types of reactions: the reversal reaction (RR) and erythema nodosum leprosum (ENL). RRs may be caused by an increase in the cell-mediated Th1 response to *Mycobacterium leprae*. ENL is a systemic inflammatory process with the clinical manifestations of an acute inflammatory reaction; this reaction is characterized by intralesional neutrophilic infiltrations and a Th2 response (3,4).

No potential conflict of interest was reported.

Because both types of reactions are accompanied by an increased release of inflammatory markers (5,6), it is possible that these episodes might be associated with infectious processes, such as systemic viral infections, urinary tract infections or oral infections. These coinfections can over-stimulate the host immune system through the release of numerous inflammatory markers, including cytokines, acute-phase proteins and chemokines (7-9).

The follow-up of leprosy patients is often interrupted by recurrent leprosy REs that interfere with the course of the disease; therefore, it is important to evaluate the role of coexistent factors in each patient that could be related to the exacerbation of the *M. leprae* infection. To this end, the present study aimed to determine the clinicopathological profiles of leprosy patients based on the occurrence of leprosy REs and to evaluate whether the presence of these reactions could be associated with coinfections.

METHODS

Subjects

The present investigation was a cross-sectional study of leprosy patients' medical records, conducted at the University Hospital of the Ribeirão Preto Medical School from 2000 to 2010. All of the patients who were treated at

the Leprosy Clinics and whose diagnoses were based on the Ridley and Jopling classification criteria (1966) (10) were included in the study. The following clinical data were considered: age at diagnosis, gender, clinical form of leprosy, World Health Organization (WHO) classification, REs, multidrug therapy (MDT) and coinfections confirmed by clinical and laboratory examinations. Subjects were excluded if they had not concluded treatment or if they were pregnant or breastfeeding. The study was approved by the Ethics Committee of the University Hospital, Ribeirão Preto Medical School, University of São Paulo, Brazil.

Study design

The clinical forms of leprosy were characterized as indeterminate (I), tuberculoid (TT), borderline tuberculoid (BT), borderline (BB), borderline lepromatous (BL), and lepromatous leprosy (LL); the leprosy reactions were characterized as RRs or ENL. The frequencies of the clinical forms and REs were correlated with the frequency of coinfections. The diagnosis of leprosy REs was based on the presence of erythema and/or the infiltration of the previous lesions; new erythematous or hypochromic lesions; nerve thickening; edema of the hands, feet or face and/or diffuse cutaneous hyperesthesia (for RRs); and the presence of erythematous nodules, with or without systemic symptoms such as fever, asthenia, nerve thickening and pain, myalgia and lymphadenitis (for ENL).

Statistical analysis

The odds ratio obtained by multinomial logistic regression was used to evaluate the associations between the leprosy reactions and the gender, age, WHO classification and coinfections. The statistical significance of these associations was evaluated by the chi-square (χ^2) test. The level of significance was set at 5% in all of the analyses, which were performed using the Statistical Analysis System - SAS® 9.0 software (San Diego, Cary, NC, USA).

RESULTS

Subjects

The results of the 225 leprosy cases, which were screened for leprosy reactions and coinfections, are presented in Tables 1 and 2. Of the 225 patients, 155 (68.8%) were male, and 70 (31.1%) were female. The mean age of the patients was 49.31 ± 15.92 years (range: 4-89). Regarding the clinical forms, 5.7% (13/225) of the patients exhibited I leprosy, 9.3% (21/225) exhibited TT, 20% (45/225) exhibited BT, 10.6% (24/225) exhibited BB, 20.4% (46/225) exhibited BL, and 33.7% (76/225) exhibited LL. Regarding the operational forms, 35.1% (79/225) were PB patients, and 64.9% (146/225) were MB patients (Table 1).

Reactional episodes

One-hundred twenty-two (122/225 = 54.2%) patients exhibited REs, 78 (78/122 = 63.9%) presented with ENL, and 44 (44/122 = 36.1%) exhibited RRs. One-hundred three (103/225 = 45.8%) patients did not exhibit any REs (Table 2). ENL was more prevalent in the MB patients (74/78 = 94.9%) (OR 5.07; CI 2.86-8.99; $p<0.0001$) and in those patients who exhibited coinfections (47/88 = 53.4%) (OR 2.26; CI 1.56-3.27; $p<0.0001$). The analysis of the RE evolution based on the MDT revealed that most of the patients with REs (69/122 = 51.6%) presented these reactions during their MDTs (Table 1).

Table 1 - The number (n) and row percentages (%) of the demographic and clinical data from the leprosy patients managed at the Leprosy Clinics of the Ribeirão Preto Clinical Hospital at the Medical School of São Paulo University, calendar period 2000-2010.

Variables	Patients	
	n	%
Gender		
Male	155	68.9
Female	70	31.1
Age (years)		
≤30	27	12.0
31-45	62	27.5
46-60	79	35.1
>60	57	25.3
WHO classification		
PB	79	35.1
MB	146	64.9
Leprosy evolution		
<6 months	71	31.5
6–12 months	65	28.8
>12 months	89	39.5
Leprosy treatment - MDT		
6 months	35	15.5
12 months	115	51.1
>12 months	65	28.8
Reactional episodes		
Erythema nodosum	78	34.6
Reverse reaction	44	19.6
No reaction	103	45.7
Reactional episodes evolution*		
Before MDT	49	40.1
During MDT	63	51.6
After MDT	49	40.1
Coinfections		
Yes	88	39.1
No	137	60.9

MDT: multidrug therapy; *Thirty-nine patients presented more than one reactional episode: 1 before and after MDT, 1 before and during MDT, 35 during and after MDT, and 2 before, during and after MDT.

Coinfections

Eighty-eight patients (88/225 = 39.1%) exhibited coinfections, whereas 137 (137/225 = 60.9%) were free of coinfections (Table 2). The most prevalent coinfections were chronic oral infections (40/88 = 45.5%), followed by urinary tract infections (UTIs) (17/88 = 19.3%), sinusopathy (6/88 = 6.8%), hepatitis C (6/88 = 6.8%), hepatitis B (6/88 = 6.8%), and intestinal parasitosis (5/88 = 5.7%). The other infections (8/88 = 9.1%) included pneumonia, oropharyngeal infections, syphilis, leishmaniasis, tuberculosis, and staphylococcus infections.

DISCUSSION

The determination of which patients may be considered to be at risk of developing leprosy REs has important implications for reducing the morbidity of these inflammatory reactions (11-15). The analysis of our results revealed that 122 (54.2%) patients presented with REs (Table 1), and most of the cases (98/122 = 80.3%) were associated with MB patients rather than PB patients (24/122 = 19.7%). Although these data are consistent with those from other studies

Table 2 - A comparison of the number (n) and percentages (%) of reactional episodes (RE) by gender, age and the presence of infections among the leprosy patients managed at the Leprosy Clinics of the Ribeirão Preto Clinical Hospital in the Medical School of São Paulo University, calendar period 2000-2010.

Variables	Reversal reaction (n = 44)	Erythema nodosum (n = 78)	None reaction (n = 103)	*p*-value*
Gender				
Male	28 (63.6)	56 (71.8)	71 (68.9)	0.64
Female	16 (36.4)	22 (28.2)	32 (31.1)	
Age (years)				
≤30	7 (15.9)	7 (9)	13 (12.6)	0.20
31-45	9 (20.4)	28 (36)	25 (24.2)	
46-60	12 (27.3)	26 (33.3)	41 (39.8)	
>60	16 (36.4)	17 (21.7)	24 (23.4)	
WHO classification				
PB	20 (45.4)	4 (5.2)	55 (53.4)	<0.0001
MB	24 (54.5)	74 (94.8)	48 (46.6)	
Coinfections				
Yes	15 (34.1)	47 (60.3)	26 (25.2)	<0.0001
No	29 (65.9)	31 (39.7)	77 (74.8)	

*chi-square test.

(12-14), the results are not typical of a non-endemic region, such as the area of this present investigation. However, these findings can be explained by the fact that the present study was conducted at a referral center that treats patients with more severe complications, such as leprosy reactions.

Of the two main types of leprosy reactions, ENL is the most common, with a prevalence of approximately 50% among leprosy patients (12,14). Most people with ENL have acute multiple episodes of ENL or chronic ENL over several years. ENL is recurrent, especially in MB patients. These episodes involve a type 2 immune-mediated reaction that is characterized by a peripheral inflammatory reaction (6), and the disease may manifest as fever, arthralgias, myalgias, an orexia, and sparse, tender, and erythematous nodules on the extensor surfaces of the extremities. Conjunctivitis, neuritis, synovitis, nephritis, hepatosplenomegaly, orchitis, and lymphadenopathy may also occur (16). Our results demonstrated that 63.9% (78/122) of the patients with RE had ENL (Tables 2 and 3). In addition, a high prevalence of ENL was associated with the MB patients; ENL occurred in 74 (74/78 = 94.9%) MB patients as opposed to 4 (4/78 = 5.1%) PB patients. Subjects exhibiting REs were treated with steroids or immunosuppressive drugs and corticosteroids, and those patients who presented with multiple recurrent episodes were excluded from the study.

The analysis of the RE evolution with respect to MDT revealed that most of the patients with REs (69/122 = 51.6%) exhibited these reactions during their MDTs (Table 1). The MDT consists of dapsone, rifampicin and clofazimine; based on the bacteriostatic effect of dapsone on *M. leprae*, this therapy would be expected to promote moderate bacillary destruction and, consequently, a decreased inflammatory reaction. However, MDT drugs have different mechanisms of action, and the bactericidal drug rifampicin (600 mg/month) promotes massive bacillary destruction and the release of many antigenic fractions that cause an inflammatory reaction. This reaction, in most cases, is not controlled by clofazimine (300 mg/month) or by a daily dose of dapsone (100 mg) and clofazimine (50 mg). These facts could explain the high proportion of reactions during MDT in the present study.

The results of the multinomial analysis, after adjusting for the gender and age group, revealed that the operational classification and the presence of coinfections were

Table 3 - Multinomial logistic regression model of the risk factors for reactional episodes (reference = no reaction) by the gender, age, WHO classification, and presence of coinfections in the leprosy patients managed at the Leprosy Clinics of the Ribeirão Preto Clinical Hospital in the Medical School of São Paulo University, calendar period 2000-2010. Odds ratio (OR), 95% confidence interval (95% CI) and *p*-value.

Variables	Reversal reaction *vs.* None			Erythema nodosum *vs.* None		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Gender						
Male *vs.* Female	0.81	0.55-1.20	0.29	0.80	0.53-1.20	0.29
Age (years)						
≤30†	1.0	-	-	-	-	-
31-45	0.80	0.41-1.55	0.51	1.61	0.87-2.97	0.13
46-60	0.66	0.36-1.19	0.16	0.89	0.50-1.59	0.70
>60	1.47	0.81-2.66	0.20	0.85	0.45-1.61	0.62
WHO classification						
MB *vs.* PB	1.21	0.83-1.76	0.32	5.07	2.86-8.99	<0.0001
Coinfections						
Yes *vs.* No	1.26	0.85-1.86	0.25	2.26	1.56-3.27	<0.0001

†relationship used as reference for comparison between the other variables.

significantly associated with ENL (OR 2.26; CI 1.56-3.27; $p<0.0001$) (Table 3). Bacterial loads, clinical forms, MDTs, and coinfections have been indicated as inducers or maintainers of the pathogenesis of these disorders (9,14-17). Based on the particular underlying immunological pattern of leprosy, the development and/or maintenance of these episodes might be associated with an infectious process. Therefore, leprosy patients would possess immunological characteristics that would impair the clearance of certain viruses, such as the hepatitis B virus (HBV) and hepatitis C virus (HCV) (15).

In this study, 50.8% (62/122) of the patients with REs (47 ENL and 15 RR) presented with coinfections. By contrast, most of the patients (n = 103) who did not exhibit any REs (77/103 = 74.7%) were free of coinfections (Tables 2 and 3). A relationship between systemic or focal infections and leprosy reactions has been reported (9,15,17). Studies have suggested that viral infections, such as hepatitis B and C, might be risk factors for developing leprosy reactions (15). We observed that of the patients presenting with coinfections, 13.6% (12/88) had viral hepatitis, and 5.6% (5/88) had REs. The most prevalent coinfections detected in our patients were chronic oral infections (40/88 = 45.5%), which were associated with the occurrence of ENL. During a previous study evaluating the clinical and immunological associations between oral infections and leprosy reactions, we observed that the leprosy patients with oral infections exhibited more leprosy reactions associated with higher C-reactive protein (CRP), chemokine IP-10, interleukin-1 (IL-1) and interleukin-6 (IL-6) levels than did the leprosy patients without oral infections, suggesting that oral infections can maintain the pro-inflammatory state (9,17). These findings could be explained by the coexistence of leprosy with other infections, which can modulate the inflammatory reaction by increasing the expression of inflammatory markers. Most likely, these inflammatory products could then spill over into the peripheral circulation, where they would exacerbate the insidious and chronic evolution of leprosy and consequently induce, stimulate or maintain the inflammatory reactions during the disease process (9,15-19).

A limitation of this study was the uncertainty about whether these coinfections preceded the leprosy reactions. However, because most of the patients presented with chronic, asymptomatic oral infections and were not aware of having these infections, it is likely that these coinfections preceded the leprosy reactions. Furthermore, the effects of the acute and chronic viral/bacterial/parasitic/fungal infections on the leprosy reactions were not separately evaluated. Nevertheless, we have previously reported that the presence of chronic oral infections may be involved in the development and maintenance of leprosy reactional episodes (9,17). The frequency of ENL in this sample of leprosy patients was higher in the MB patients than in the PB patients, especially those patients who exhibited coinfections; these findings suggest that MB patients who present with coinfections might be at a higher risk for leprosy reactions. Therefore, it is necessary to confirm this observation by screening leprosy patients for chronic systemic and local infections because treatment of these coinfections might improve the care of leprosy patients and help prevent the disabilities caused by leprosy reactions.

ACKNOWLEDGMENTS

The study was funded by the Foundation of Support to Teaching, Research and Assistance of the HCFMRP-USP (FAEPA).

AUTHOR CONTRIBUTIONS

Motta AC and Foss NT conceived and designed the study, analyzed the data, and wrote the paper. Motta AC, Pereira KJ, Tarquínio DC, Vieira MB, and Miyake K conducted the study.

REFERENCES

1. Jopling WH. Classification of reaction in leprosy. Leprosy Rev. 1970;41(10):62-3.
2. Sehgal VN, Sharma V. Reactions in leprosy–a prospective study of clinical, bacteriological, immunological and histopathological parameters in thirty-five Indians. The Journal of dermatology. 1988;15(5): 412-9.
3. Rea TH, Modlin RL. Immunopathology of leprosy skin lesions. Seminars in dermatology. 1991;10(3):188-93.
4. Cuevas J, Rodríguez-Peralto JL, Carrillo R, Contreras F. Erythema nodosum leprosum: reactional leprosy. Sem Cutan Med Surg. 2007;26(2):126-30, http://dx.doi.org/10.1016/j.sder.2007.02.010.
5. Sarno EM, Grau GE, Vieira LM, Nery JA. Serum levels of tumor necrosis factor - alpha and interleukin 1 beta during leprosy reactional states. Clin Exp Immunol. 1991;84(1):103-8.
6. Foss NT, de Oliveira EB, Silva CL. Correlation between TNF production, increase of plasma C-reactive protein level and suppression of T lymphocyte response to concanavalin A during erythema nodosum leprosum. Int J Lepr Other Mycobact Dis.1993;61(2):218-26.
7. Jeffcoat MK, Geurs NC, Reddy MS, Cliver SP, Goldenberg RL, Hauth JC. Periodontal infection and preterm birth: results of a prospective study. J Am Dent Assoc. 2001;132(7):875-80.
8. Rodrigues DC, Taba MJ, Novaes AB, Souza SL, Grisi MF. Effect of non-surgical periodontal therapy on glycemic control in patients with type 2 diabetes mellitus. J Periodontol. 2003;74(9):1361-7, http://dx.doi.org/10.1902/jop.2003.74.9.1361.
9. Motta ACF, Furini RB, Simão JCL, Vieira MB, Ferreira MAN, et al. Could leprosy reactional episodes be exacerbated by oral infections? Rev Soc Bras Med Trop. 2011;44(5):633-5, http://dx.doi.org/10.1590/S0037-86822011000500022.
10. Ridley DS, Jopling WH. Classification of leprosy according to immunity: a five-group system. Int J Lepr Other Mycobact Dis 1966;34(3):255-73.
11. Lustosa AA, Nogueira LT, Pedrosa JIS, Teles JBM, Campelo V. The impact of leprosy on health-related quality of life. Rev Soc Bras Med Trop. 2011;44(5):621-6, http://dx.doi.org/10.1590/S0037-86822011000500019.
12. Kumar B, Dogra S, Kaur I. Epidemiological characteristics of leprosy reactions: 15 years experience from north India. Int J Lepr Other Mycobact Dis. 2004;72(2):125-33, http://dx.doi.org/10.1489/1544-581X(2004)072<0125:ECOLRY>2.0.CO;2.
13. Saunderson P. The epidemiology of reactions and nerve damage. Lepr Rev. 2000;Suppl:S106-10.
14. Nery JAC, Garcia CC, Wanzeller SHO, Sales AM, Gallo MEN, Vieira LMM. Características clínico-histopatológicas dos estados reacionais na Hanseníase em pacientes submetidos à poliquimioterapia (PQT). An Bras Dermatol. 1999;74:1-7.
15. Rego VPA, Machado PRL, Martins I, Trindade R, Paraná R. Type 1 reaction in leprosy: characteristics and association with hepatitis B and C viruses. Rev Soc Bras Med Trop. 2007;40(5):546-9, http://dx.doi.org/10.1590/S0037-86822007000500011.
16. Mastrangelo G, Silva Neto J, da 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(1):92-6.
17. Motta ACF, Furini RB, Simão JCL, Ferreira MAN, Komesu MC, Foss NT. The recurrence of leprosy reactional episodes could be associated with oral chronic infections and expression of serum IL-1, TNF-α, IL-6, IFN-γ and IL-10. Braz Dent J. 2010;21(2):158-64.
18. Stefani MM, Guerra JG, Sousa AL, Costa MB, Oliveira ML, Martelli CT, et al. Potential plasma markers of type 1 and type 2 leprosy reactions: a preliminary report. BMC Infect Dis. 2009;9:75, http://dx.doi.org/10.1186/1471-2334-9-75.
19. Manandhar R, Shrestha N, Butlin CR, Roche PW. High levels of inflammatory cytokines are associated with poor clinical response to steroid treatment and recurrent episodes of type 1 reactions in leprosy. Clin Exp Immunol. 2002;128(2):333-8, http://dx.doi.org/10.1046/j.1365-2249.2002.01791.x.