Ricardo Arraes Alencar Ximenes[I]

Maria Eugênia Novinsk Gallo[II]

Maria de Fátima de Medeiros Brito[III]

Retreatment in leprosy: a case-control study

Retratamento de hanseníase: estudo de caso-controle

ABSTRACT

OBJECTIVE: To assess risk factors for retreatment of leprosy patients.

METHODS: A case-control study with patients from two reference care units in Recife, northeastern Brazil, in 2003. The case group included retreated patients (N=155) and the control group comprised those patients who were not retreated (N=155) matched by year of diagnosis and health care unit. Univariate and multivariate analyses were conducted to test the associations and odds ratios and related 95% confidence intervals were estimated.

RESULTS: The following factors were found to be significantly associated ($p<0.05$) with retreatment: occurrence of adverse immunological reactions after treatment completion (OR=2.3; 95% CI=1.18;4.83), final bacterial index ≥ 1 (OR=6.43; 95% CI=1.67;24.74), therapeutic regimen consisting of sulfone monotherapy (OR=10; 95% CI=0.01;0.78) and reports of household contacts (OR=2.2; 95% CI=0.24;0.85).

CONCLUSIONS: The study findings reinforce that the use of dapsone monotherapy should be discontinued, and highlight the need for epidemiological monitoring of specific groups of leprosy patients after treatment completion through periodical clinical and laboratory evaluation. Further studies to explore the association between final bacterial index and retreatment are strongly recommended.

KEY WORDS: Leprosy, epidemiology. Leprosy, therapy. Leprostatic agents, administration & dosage. Treatment outcome. Recurrence, prevention & control. Case-control studies.

[I] Departamento de Medicina Tropical. Centro de Ciências da Saúde. Universidade Federal de Pernambuco (UFPE). Recife, PE, Brasil

[II] Laboratório de Hanseníase. Instituto Oswaldo Cruz. Fundação Oswaldo Cruz. Rio de Janeiro, RJ, Brasil

[III] Hospital das Clínicas. UFPE. Recife, PE, Brasil

Correspondence:
Maria de Fátima de Medeiros Brito
Pós-graduação em Medicina Tropical
Bloco A – Hospital das Clínicas – UFPE
Av. Prof. Morais Rego, s/nº
Cidade Universitária
50670-420 Recife, PE, Brasil
E-mail: fatimabrito@elogica.com.br

RESUMO

OBJETIVO: Analisar os fatores de risco para retratamento da hanseníase.

MÉTODOS: Estudo de caso-controle com pacientes de duas unidades de referência para tratamento da hanseníase, em Recife, Pernambuco, no de 2003. O grupo de casos incluiu pacientes retratados (N=155) e foi comparado com o grupo controle (N=155), pacientes não retratados pareados por ano-diagnóstico e unidade de saúde. Para testar as associações foram realizadas análises uni e multivariadas, e calculados odds ratios com respectivos intervalos de confiança de 95%.

RESULTADOS: Os seguintes fatores apresentaram associação estatisticamente significante (p<0,05) com retratamento: reação hansênica após tratamento (OR=2,3; IC 95%:1,18;4,83); índice baciloscópico final $\geq$ 1 (OR=6,43; IC 95%:1,67;24,74); tratamento com a monoterapia sulfônica (OR=10; IC 95%: 0,01;0,78); relato de contato intradomiciliar com portadores de hanseníase (OR=2,2; IC 95%:0,24;0,85).

CONCLUSÕES: Os resultados reforçam o desuso da monoterapia sulfônica e apontam a necessidade de se monitorizar grupos específicos de pacientes após alta terapêutica, através do acompanhamento clínico e laboratorial periódico. Recomenda-se a realização de novos estudos para explorar a associação entre o índice baciloscópico final e retratamento.

DESCRITORES: Hanseníase, epidemiologia. Hanseníase, terapia. Hansenostáticos, administração e dosagem. Resultado de tratamento. Recidiva, prevenção e controle. Estudos de casos e controles.

INTRODUCTION

The major indicator of treatment effectiveness in leprosy cases is low relapse rate after its completion. Official Brazilian data from Sistema Nacional de Agravos de Notificação (Disease Reporting National System – SINAN, 2002)* show that from 1994 to 2000 nearly 4,500 patients were reintroduced into the multidrug therapy (MTD)/World Health Organization (WHO) regimens, thus once again becoming part of the active record and showing increasing prevalence. Of these, 2,221 cases were diagnosed as relapses. In 2002 only, 1,394 cases of relapse were reported.

Relapse rates may be overestimated. Several authors have pointed out the occurrence of adverse immunological reactions after completion of therapeutic treatment.[1,5,9,10] These events are quite frequent in the first years after treatment, but they need to be differentiated from relapses, requiring clinical and laboratory resources.

It is difficult to apply the criteria proposed for diagnosing relapse or differentiating it from a leprosy reaction, especially in primary care settings. This is due to the lack of information and standardization in medical records of patients treated in different health units and Brazilian regions, as well as non-performance or lack of reliability of slit-skin smear and histological examinations.

The objective of the present study was to investigate risk factors for leprosy retreatment since there is little reference to these factors in the literature.

METHODS

The study was carried out at two reference care units for the treatment of leprosy in the city of Recife, northeastern Brazil, in 2003. Patients were diagnosed and treated in accordance with the Brazilian Ministry of Health guidelines.

This investigation was designed as a retrospective case-control study with 310 patients. A total of 155 patients undergoing leprosy retreatment after considered cured were included in the case group. The same number of patients who received specific treatment during the same period (with a margin of ± two years) in the same care units and who were considered cured and

had not undergone leprosy retreatment were included in the control group. Controls were matched to cases on the basis of year of leprosy diagnosis and care unit attended to minimize or eliminate the confounding effect of these two factors. Patients who were retreated after treatment abandonment and those retreated due to incorrect allocation of the therapeutic regimen were excluded from the study. The decision to provide retreatment was made by experienced leprosy clinicians working under routine conditions, after careful clinical and slit-skin smear examinations and, in few cases, skin biopsies.

Data were obtained from a secondary database and validated with the medical records from the reference units. The following risk factors potentially associated with retreatment were studied: therapeutic regimen; classification (based on clinical criteria and slit-skin smear examination); initial and final bacterial index; presence of reactions after treatment; type of reaction; therapeutic regimen for the reaction; and reports of household contacts with leprosy.

The sample size was estimated based on the desired values for the probabilities of type I (α) and type II (β) error, respectively, 0.05 and 0.20, and assuming a frequency of exposure (post-treatment reaction) of 50% and an odds ratio (OR) of 2.0 (based on a pilot study as no previously published reports were found in the literature). Based on these parameters, the sample size estimated was 148 individuals for each group.

The associations between the dependent variable and each of the independent variables were investigated using calculations of matched OR, 95% confidence intervals and p-values (p<0.05). Multivariate analysis was carried out with conditional logistic regression. The model was initially saturated with all variables that, in a preceding univariate model, had a p-value <0.10 for its association with the outcome, and the statistical significance of dropping each variable out was tested. Data analysis was conducted using Epi Info version 6.04, SPSS-PC version 8.0, and the Stata 8 packages.

The study was approved by the Ethics Committee of the Universidade de Pernambuco (CISAM/UPE – Protocol No. 046/2002).

RESULTS

The time elapsed from the beginning of leprosy treatment was similar in both groups due to the matching, ≤ 1 year for 68.5% of the patients, > 1 and ≤ 2 years for 16.5% and ≥ 3 for 15.0%.

Univariate analysis showed no statistically significant associations between retreatment and sex, age group, operational classification and initial bacterial index. Reports of household contacts with leprosy and final

bacterial index were associated with retreatment. Patients who had reactions after treatment were about twice as likely to require retreatment as those who did not have any reactions after treatment completion. Type of reaction and the therapeutic regimen used for treating reactions were not associated with retreatment. Patients who received dapsone monotherapy were ten times more likely to undergo retreatment (Table 1).

Using a step-down procedure, the conditional multiple logistic regression analysis indicated that the following variables were independently associated with the outcome (retreatment): reaction after treatment, final bacterial index, reports of household contacts and therapeutic regimen remained in the final model (Table 2). The adjusted odds ratios (OR) were very similar to those obtained in the univariate analysis, thereby suggesting that confounding effects of each variable on other variables were small or nonexistent.

DISCUSSION

The present study indicates that the multiple factors for leprosy retreatment are presence of a reaction after treatment completion, reports of household leprosy contacts, dapsone monotherapy and a final bacterial index ≥ 1.

A broad approach was taken to identify risk factors for retreatment among patients with history of previous leprosy treatment. This approach differs from that of most previous studies that focused either on relapse or leprosy reactions. This knowledge may contribute to the development of potential preventive measures for avoiding unnecessary retreatment. In addition to further studies, this knowledge may help achieving reduced retreatment rates and benefit patients at an individual level, and contributes towards better organizing health care provision.

These patients were presumably relapsed patients following the criteria proposed by the Brazilian Ministry of Health. Nonetheless, there may have been a proportion of false positives, i.e., patients with immunological reactions who were diagnosed as relapse cases. Furthermore, even if immunological reactions are ruled out, active disease may have been due to bacterial persistence or to reinfection caused by the irreversible immunological deficiency specific to *Mycobacterium leprae*.

Relapse among paucibacillary patients nearly always requires differential diagnosis with delayed reversal reaction[1,7,11] and there is no gold standard for comparison, since *M. leprae* cannot be isolated in these cases.[8] Among multibacillary patients, reversal reactions are also frequently misdiagnosed as relapses but diagnostic confirmation is possible by means of slit-skin smear

Table 1. Univariate analysis of risk factors associated with leprosy retreatment. Recife, northeastern Brazil, 2003. N=310

Risk factor category	Retreatment		Matched OR	95% CI	p-value
	Yes	No			
Age					0.0537
<14 years	23	28	1		
14–60 years	121	104	1.47	0.79;2.75	
>60 years	13	24	0.64	0.27;1.51	
Sex					0.4610
Male	74	80	1		
Female	81	75	1.2	0.73;1.94	
Operational classification					0.7220
Paucibacillary	79	76	1		
Multibacillary	72	79	0.91	0.57;1.46	
Initial bacterial index					0.0985
0.0	84	95	1		
0.1 to 3.0	15	21	0.71	0.34;1.49	
>3	20	11	2.07	0.94;4.52	
Therapy regimen					0.0009
Multidrug therapy	124	139	1		
Monotherapy	23	15	10	1.28;78.11	
Reaction after treatment					0.0157
No	52	22	1		
Yes	101	132	2.3	1.18;4.83	
Type of reaction					0.2749
No reaction	80	91	1		
Type 1	16	16	1.37	0.71;2.66	
Type 2	32	23	2.82	1.06;7.47	
Type 1 and 2	15	06	0.78	0.33;1.81	
Unknown	10	18	1.01	0.41;2.49	
Management of reaction					0.5303
Corticoid + thalidomide	17	18	1		
Corticoid	48	38	1.40	0.64;3.09	
Thalidomide	07	06	1.26	0.34;4.62	
Final bacterial index					0.0241
Negative	26	37	1		
<1	06	06	1.33	0.35;4.97	
≥1	14	03	6.43	1.67;24.74	
Not performed					
Reports of household contact with leprosy					0.0130
No	78	104	1		
Yes	40	28	2.2	1.17;4.03	

* Numbers vary because of missing information for certain variables.

examination, bacillus detection, histology, and inoculation in mouse footpads. These resources, however, may not be available under routine conditions.

Although the diagnosis of adverse immunological reactions was made by experienced leprosy clinicians, misdiagnosis may nevertheless have occurred. In addition, patients treated for leprosy with new skin lesions (including immunological reactions) are more likely to attend health units, and greater frequency of attendance may increase the likelihood that a subject will receive retreatment.

Patients who had reactions after treatment were about twice as likely to require retreatment as those who did not have any reactions after treatment completion. Brito et al[2] (2005) described the case series of the 155 patients who were being retreated for relapse. These authors

Table 2. Logistic regression model of risk factors associated with leprosy retreatment. Recife, northeastern Brazil, 2003.

Variable	Matched adjusted OR	95% CI
Reaction after treatment		
No	1.0	–
Yes	2.42	1.08;5.38
Final bacterial index		
Negative	1.0	–
<1	1.3	0.355;4.979
≥1	4.9	1.19;20.51
Reports of household contacts		
No	1.0	–
Yes	2.17	0.23;0.93
Drug regimen		
Multidrug therapy	1.0	–
Monotherapy	10.0	1.43;94.6

showed that 65% were classified as multibacillary and the most common manifestations were macular eruption and infiltration. It was highly remarkable that the most common lesions in multibacillary patients with relapse were nodules and papules. According to Gebre et al[5] (2000), the diagnosis of relapse in leprosy cases are somewhat difficult to establish, thus paucibacillary patients should use corticosteroids for a six-month period while multibacillary patients should use them for a one-year period, with or without specific therapeutic treatment, in an attempt to protect patients against neural damage. If lesions recede, it may be assumed that a reaction has occurred. If lesions remain, relapse needs to be further investigated.

Leprosy patients reporting household contacts were twice as likely to require retreatment. No investigation regarding whether or not households contacts had active disease was undertaken. Nevertheless, it is reasonable to assume that this finding indicates the possibility of reinfection given the irreversible immunological deficiency specific to *M. leprae* as suggested by Reddy & Cherian[8] (1991) and Gallo & Oliveira[3] (1997). No studies were found in the literature addressing the importance of contacts with regard to retreated patients. More complex studies using a cohort design may contribute towards elucidating these issues.

The study finding that patients who received dapsone monotherapy were ten times more likely to require retreatment support the fact that monotherapy regimens have limited effectiveness, as well-documented in the literature.

A slit-skin smear examination at the end of treatment was carried out only on 26.6% of the patients studied (92/310), and patients with a final bacterial index ≥ 1 were six times more likely to require retreatment. These

results, however, should be interpreted with caution due to the small number of patients studied. Sampling variability and selection bias cannot be excluded as alternative explanations. These results could also be due to misclassification, depending on the extent to which adverse immunological reactions may have been misdiagnosed as relapses. In studying relapse among multibacillary patients, Girdhar et al[6] (2000) suggested there was an increase in the bacterial index before the onset of lesions. Jamet & Baohong[7] (1995) recommended that patients with initial bacterial index ≥ 4 and final bacterial index ≥ 3 should be monitored and that examinations should be carried out in higher-quality reference laboratories.

These findings cause some concern regarding the follow-up procedures needed for these patients. The Brazilian Ministry of Health assumes that cure is achieved based on the number of doses and regularity of treatment only. The study results indicate that efforts should be made to improve the quality of laboratory tests and to make them available at the primary care level. Further investigations using a cohort design and larger sample size are needed to evaluate the association between the bacterial index, especially at the end of treatment, and retreatment.

The statistically significant association between post-treatment reactions and retreatment found in the present study are consistent with two hypotheses that should be further investigated. First, the presence of reaction after treatment completion increases the risk of relapse. Second, patients are being retreated not because they have relapses but because of reactions misdiagnosed in the clinical evaluation.

The present study on leprosy retreatment has raised questions that require additional approaches from a public health and clinical perspective. How many patients have adverse immunological reactions? How many are cases of bacterial persistence? Is the final bacterial index no longer needed at the end of treatment of multibacillary patients? How many patients are reinfected through household contacts? Further studies are needed to address these questions, particularly by using a cohort design and incorporating molecular biology techniques. Also, special monitoring procedures must be implemented after ascertaining cure of patients who are more likely to require retreatment.

In conclusion, the study findings reinforce that the use of dapsone monotherapy should be discontinued and there is need for special monitoring of specific groups of leprosy patients, i.e., those who have household contacts with leprosy, those showing reactions after the completion of treatment and those with a final bacterial index ≥ 1, through periodical clinical and laboratory evaluations.

REFERENCES

1. Becx-Bleumink M. Relapses among leprosy patients treated with multidrug therapy: experience in the leprosy control program of the All Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia; practical difficulties with diagnosing relapses; operational procedures and criteria for diagnosing relapses. *Int J Lepr Other Mycobact Dis.* 1992;60(3):421-35.

2. Brito MFM, Ximenes RAA, Gallo MEN. Retreatment of leprosy relapse. *An Bras Dermatol.* 2005; 80(3):255-60.

3. Gallo MEN, Oliveira MLW. Recidivas e Reinfecção em Hanseníase. *Medicina (Ribeirão Preto).* 1997;30(3):351-7.

4. Gallo MEN, Nery JAC, Albuquerque ECA, Signorelli M, Silva Filho VF. Multivacillar leprosy: bacilloscopic index and viability of M. leprae after 24 doses of Multidrug Therapy: World Health Organization (MDT/WHO). *An Bras Dermatol.* 2000;75(3):291-7.

5. Gebre S, Saunderson P, Byass P. Relapses after fixed duration multiple drug therapy: the AMFES cohort. *Lepr Rev.* 2000;71(3):325-31.

6. Girdhar BK, Girdhar A, Kumar A. Relapses in multibacillary leprosy patients: effect of length of therapy. *Lepr Rev.* 2000;71(2):144-53.

7. Jamet P, Ji B. Relapse after long-term follow up of multibacillary patients treated by WHO multidrug regimen. *Int J Lepr Other Mycobact Dis.* 1994;62(4):622.

8. Reddy PK, Cherian, A. Relapse in Hansen's Disease after multidrug therapy and its differential diagnosis with reversal reaction. *The Star.* 1991:8-12.

9. Scollard DM, Smith T, Bhoopat L, Theetranont C, Rangdaeng S, Morens DM. Epidemiologic characteristics of leprosy reactions. *Int J Lepr Other Mycobact Dis.* 1994;62(4):559-67.

10. Waters MFR. Distinguishing between relapse and late reversal reaction in multidrug (MDT) treated BT leprosy. *Lepr Rev.* 2001;72(3):250-3.

11. WHO Study Group. Chemotherapy of leprosy. Geneva: World Health Organization; 1994. (WHO Technical Report Series, 847).