

# Clinical and laboratory characteristics in the retreatment of leprosy relapse

## *Características clínico-laboratoriais no retratamento por recidiva em hanseníase*

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## **Abstract**

**Objective:** To compare clinical and laboratory data of leprosy patients diagnosed in specialized services in the State of Mato Grosso, Brazil, during the initial treatment and the retreatment of relapse. **Methods:** A cross-sectional study of patients with diagnosis of leprosy relapse was conducted in specialized health services of five cities, between 2005 and 2007. Initial treatment was described as t1 and relapse treatment as t2. **Data Source:** *Sistema de Informação de Agravos de Notificação* (Sinan – Reportable Diseases Information System), medical records, laboratory tests, and files of individual reports and of physical disability assessments. The chi-square test ( $\chi^2$ ) was applied at a significance level of 5%. **Results:** The clinical dimorphic form prevailed in t2 when compared with t1 (39.6% versus 11.3%;  $p = 0.003$ ); 20.8% of relapse cases showed a bacilloscopy index  $\geq 4+$  in relation to those in t1 ( $p = 0.034$ ); an increase in the number of (17%) cases of relapse with physical disability at level 0 was found, compared to patients evaluated during the diagnosis (58.5% versus 41.5%); an increase (7.5%) in the recurrence of disabilities at level 2 was observed, when compared to t1 (9.4% versus 9%); and there was a higher prevalence of cases not evaluated for disability between t1 (45.3%) and t2 (22.6%) ( $p = 0.040$ ). **Conclusion:** Cases of relapse characterized the aggravation of the disease, indicated by the increase in the bacilloscopy index and level of physical disability. Attention should be paid to the diagnostic confirmation of relapse using bacilloscopy tests, especially in multibacillary cases, and systematic neurological assessment of all leprosy patients.

**Keywords:** Leprosy. Relapse. Epidemiology. Cross-Sectional Studies. Prevention and Control. Disease Reporting.

## Resumo

**Objetivo:** Comparar as características clínico-laboratoriais dos doentes de hanseníase durante o tratamento inicial e no retratamento por recidiva diagnosticada em unidades de saúde de referência no Estado de Mato Grosso. **Método:** Estudo transversal de casos diagnosticados de recidiva em hanseníase em unidades de referência de 2005 a 2007 em cinco municípios do Estado. O tratamento inicial foi considerado t1 e a recidiva t2. Fontes de dados: Sistema de Informação de Agravos de Notificação, prontuários, exames laboratoriais, ficha de notificação individual e de avaliação de incapacidade física. Utilizou-se para a comparação e cálculo de proporções o teste do Qui-quadrado ( $\chi^2$ ) ao nível de significância de 5%. **Resultados:** Verificou-se predomínio da forma clínica dimorfa em t2 quando comparada a t1 (39,6% *versus* 11,3%;  $p = 0,003$ ); 20,8%, dos casos em recidivas apresentaram índice baciloscópio  $\geq 4+$  se comparados aqueles em t1 ( $p = 0,034$ ); aumento (17%) dos casos de recidiva com grau zero de incapacidade quando comparados aos pacientes avaliados no momento do diagnóstico (58,5% *versus* 41,5%); aumento (7,5%) de recidivas com incapacidades grau 2 quando comparadas a t1 (9,4% *versus* 1,9%); predomínio de casos não avaliados quanto a incapacidade física entre t1 (45,3%) e t2 (22,6%); ( $p = 0,040$ ). **Conclusão:** Os casos de recidiva caracterizam o agravamento da doença indicadas pelo aumento do índice baciloscópio e do grau de incapacidade física. Recomenda-se maior atenção à confirmação diagnóstica de recidiva por meio de exames baciloscópicos, em especial nos multibacilares, e da avaliação neurológica sistemática de todos os pacientes de hanseníase.

**Palavras-chaves:** Hanseníase. Recidiva. Epidemiologia. Estudos transversais. Prevenção e Controle. Notificação de Agravos.

## Introduction

Currently, there are 228,474 cases of leprosy worldwide. Brazil contributes to 92.4% of all cases recorded in the Americas and it ranks second in absolute number of cases, only surpassed by India<sup>1</sup>.

Between 2004 and 2010, there were 2,596 cases of leprosy recurrence on a global level. In Brazil, in 2009 alone, there were 1,483 cases of recurrence, totaling 3.9% of the increase in cases during this period<sup>2</sup>.

According to parameters of 2011 the state of Mato Grosso, in the Center-West region of Brazil, is a hyper-endemic area with 2,569 new cases and a general detection coefficient of 84.6/100,000 inhabitants, with significant differences among distinct areas of this state<sup>3,4,5</sup>.

Since the 1980s, the World Health Organization (WHO) has recommended the use of polychemotherapy (PCT) and this measure has led to the treatment and cure of more than 14 million patients with leprosy<sup>6</sup>.

Although the recommended treatment is effective, there has been evidence of possible resistance to the existing chemotherapeutic drugs. This has been proved experimentally by Pettit and Rees (1964), using the inoculation technique with *Mycobacterium leprae* standardized by Shepard (1960). The result associated with the irregular use of the previously mentioned therapeutic scheme leads to low adherence to treatment and the possibility of occurrence of leprosy recurrence and, consequently, the permanence of the source of infection in the community<sup>7-10</sup>.

The fact that *M. leprae* is not cultivated in vitro makes it difficult to define the parameters for laboratory confirmation of the initial diagnosis, treatment efficacy monitoring and leprosy recurrence<sup>11-13</sup>.

There is no consensus on the criteria established for the diagnostic confirmation of recurrence. The following variations are included: reappearance of new lesions and/or nerve injuries with clinical and histopathological signs consistent with active forms (*borderline-borderline*/BB, *borderline-lepromatous*/BL and *lepromatous*/LL),

according to Ridley-Jopling's classification (1966)<sup>14,15</sup>; new skin lesions; increase in the bacilloscopy index (BI) >2+ in one or more areas; and viability of *M. leprae* through inoculation in mice paw<sup>16</sup>; reactivation after six months of regular treatment with multi-drug therapy; anesthetic lesions and/or exacerbation of previous lesions; bacteriological evidence with or without clinical activity; nerve lesions with or without neuritis in cases of paucibacillary leprosy; and diagnostic confirmation with biopsy<sup>17</sup>; reactivation and presence of new anesthetic lesions confirmed with bacilloscopy exam and skin biopsy<sup>18</sup>.

Studies aimed at the technical-scientific support and infrastructure available for professionals to accurately diagnose recurrence in health services are essential. The present study aimed to compare the clinical and laboratory characteristics of individuals with leprosy during the initial treatment and during new treatment of recurrence diagnosed in referral health clinics of the state of Mato Grosso.

## Materials and Methods

A cross-sectional epidemiological study was conducted to analyze cases of leprosy recurrence diagnosed in referral health clinics of five cities of the state of Mato Grosso (Cáceres, Cuiabá, Diamantino, Rondonópolis and Várzea Grande) between 2005 and 2007. There are 1,032,523 inhabitants in these five cities, 36.2% of the total state population estimated to be 2,854,462 inhabitants at the time of this study<sup>19</sup>.

The criteria for the diagnosis of recurrence used in specialized health clinics are defined in the protocols adopted by the Brazilian Ministry of Health<sup>11</sup>: patients who were discharged as cured subsequently had new lesions and/or the exacerbation of previous lesions, new neurological lesions with an unsatisfactory response after treatment with corticosteroids and/or thalidomide, and results of bacilloscopy/histopathological tests compatible with active forms.

The comparative analysis of the

investigated groups included the cases diagnosed as recurrence, which were described as time 2 (t2) and recorded in the databases of the *Sistema de Informação de Agravos de Notificação* (Sinan/MT – State of Mato Grosso Information System for Notifiable Diseases) between January 1<sup>st</sup> 2005 and December 31<sup>st</sup> 2007, in the cities selected for this study. Of all 82 cases of recurrence reported in this period, 53 (64.6%) were considered to be occurrences of leprosy recurrence with the validation of the information found in the medical records available in the specialized treatment units. The exclusion of 29 individuals was due to transfers to other states and diagnostic errors. The initial treatment group or time 1 (t1) included the records of leprosy cases that had been discharged as cured before the recurrence under study occurred. The sources of data were as follows: Sinan/leprosy/MT, medical records, laboratory tests, individual report files and physical disability assessment. Laboratory tests of bacilloscopy and histopathology were performed in the state and municipal *Laboratório Central de Saúde Pública* (Central Laboratory of Public Health) and in the *Instituto Lauro de Souza Lima de Bauru - São Paulo* (ILSL), respectively. The study variables were the following clinical/laboratory characteristics: clinical form, number, type and location of leprosy lesion, nerve thickness, reactive state, adverse effects, bacilloscopy and histopathology, and level of physical disability as assessed during diagnosis.

The non-inclusion of ill patients diagnosed as recurrence in all state health clinics is justified by the fact that 80% of these diagnoses are made in primary health clinics, which do not have appropriate technical resources. Consequently, the inclusion of such cases could create selection bias and thus affect the study<sup>5</sup>.

The SPSS 15 software program was used to manage and analyze data. Double data entry was used to check data consistency. The chi-square test ( $\chi^2$ ) and a significance level of 5% were used to compare proportions.

The present research project was assessed and approved by the Research Ethics Committee of the *Hospital Universitário Júlio Muller* (CEP/HUJM – Júlio Muller University Hospital – process 321 of April 2007).

## Results

Of the 53 cases of recurrence reported in the state of Mato Grosso between 2005 and 2007, the majority were males (66.0%, n=35) with a mean age of 46.3 years ( $\pm 16.8$ ; minimum age of 18 and maximum age of 82 years). The mean time interval between the initial treatment and the occurrence of leprosy recurrence was seven years and six months (Table 1).

Table 2 shows the results of the comparative analysis of the proportion of leprosy cases between initial treatment (t1) and recurrence (t2), according to clinical form, bacilloscopy, histopathology and level of physical disability. The group of cases in this study revealed a higher proportion of cases of recurrence with the dimorphic clinical form (39.6%), whereas these represented 11.3% of all cases in t1. In contrast, 9.4% and 13.2% of individuals in t2 were categorized in the undetermined and tuberculoid clinical forms, respectively, and of these, 13.2% and 20.8% were in the same categories in t1 [ $\chi^2 = 16.06$  (p= 0.003)]. With regard to the characteristic of the bacilloscopy tests, 54.7% of individuals had this test performed when they were cases of recurrence,

whereas 66% did so in the initial treatment; 20.8% (n=11) of cases of recurrence showed a BI  $\geq 4+$  when compared to those in the initial treatment [ $\chi^2 = 8.69$  (p = 0.034)]. Of all individuals who had a histopathological test performed, 49% (n=26) did so to have a diagnostic confirmation of recurrence [ $\chi^2 = 14.64$  (p = 0.001)]. Among the cases assessed for physical disability, there was an increase of 17% in the number of cases of recurrence with physical disability at level 0, when compared to patients assessed at the moment of diagnosis (58.5% versus 41.5%). In addition, there was an increase of 7.5% of physical disability at level 2 between t1 and t2 (9.4% versus 1.9%). There was an increase in the proportion of cases not assessed for physical disability between t1 (45.3%) and t2 (22.6%) [ $\chi^2 = 8.29$  (p = 0.040)].

There were no statistically significant differences between proportions of treatments according to the following variables: number, type and location of leprosy lesions, nerve thickness, presence and type of reactive state and adverse effect (Table 3).

## Discussion

The identification of cases of leprosy recurrence with the analysis of clinical and laboratory characteristics is key in the adoption of more effective measures to diagnose and monitor such cases in specialized health clinics.

The comparison made in this study enabled researchers to observe that the

**Table 1** - Distribution of cases of leprosy relapse regarding time interval between initial treatment (t1) and relapse (t2), Mato Grosso, 2005-2007.

**Tabela 1** - Distribuição dos casos de recidiva em hanseníase, segundo intervalo de tempo entre o tratamento inicial (t1) e recidiva (t2); Mato Grosso, 2005-2007.

Time interval (in years) t1 and t2 (n=46)*	Recurrence	
	n	%
Up to 3	13	28.3
3 to 5	07	15.2
5 to 10	08	17.4
10 and higher	18	39.1

\*Sem informação = 7; Média = 7 anos e 6 meses; Mediana = 3 anos; DP = 5,71

\*No information = 7; Mean = 7 years and 6 months; Median = 3 years; SD = 5.71

**Table 2** - Comparison of proportion of cases between initial treatment (t1) and relapse (t2) for leprosy, according to clinical and laboratory features, Mato Grosso, 2005-2007.

**Tabela 2** - Comparação da proporção de casos entre tratamento inicial (t1) e recidiva (t2) em hanseníase, segundo características clínico-laboratoriais; Mato Grosso, 2005-2007.

Variables	Leprosy cases				$\chi^2$ (p value)
	t1		t2		
	n	%	n	%	
<b>Clinical form</b>					
Undetermined	07	13.2	05	9.4	16.06 (0.003)
Tuberculoid	11	20.8	07	13.2	
Dimorphic	06	11.3	21	39.6	
Virchowian	14	26.4	16	30.2	
NA/ignored*	15	28.3	04	7.5	
<b>Bacilloscopy</b>					
Yes	35	66.0	29	54.7	12.13(0.002)
No	07	13.2	21	39.6	
NA/ignored*	11	20.8	03	5.7	
<b>BI**</b>					
Negative	25	47.2	12	22.6	8.69 (0.034)
0.25 to 3.99	06	11.3	06	11.3	
≥ 4 +	04	7.5	11	20.8	
NA/ignored*	18	34.0	24	45.3	
<b>Histopathology</b>					
Yes	13	24.5	26	49.1	14.64 (0.001)
No	27	50.9	26	49.1	
Ignored	13	24.5	01	1.9	
<b>LPD ***</b>					
Level 0	22	41.5	31	58.5	8.29 (0.040)
Level 1	06	11.3	05	9.4	
Level 2	01	1.9	05	9.4	
NA/ignored*	24	45.3	12	22.6	

\* NR/Ignorado = não realizado/ignorado / \* NR/Ignorado = not done/unknown

\*\* IB = índice baciloscópio / \*\* IB = bacilloscopy index

\*\*\* GIF = Grau de incapacidade física no diagnóstico / \*\*\* GIF = Level of physical incapacity at diagnosis

dimorphic clinical form was more frequent in cases of recurrence, although tuberculoid and undetermined clinical forms were more frequent during the initial treatment. Cases of recurrence were manifested as more advanced or severe clinical forms of the disease, when compared to those in the initial treatment. The majority of cases of recurrence were diagnosed with histopathological tests. A higher proportion of cases of recurrence with physical disability at level 0 was found, although data also show recurrence with physical disability at level 2 and patients without neurological assessment.

The higher proportion of males at an

economically productive age was similar to other studies<sup>5,12,16,20,21</sup>. The risk of development of leprosy is two times higher in men than women<sup>22</sup>. This characteristic is probably associated with the cultural values of self-care and environmental factors involved in the function performed by an individual<sup>23</sup>.

Diagnoses of recurrence observed in the early and late periods, when compared to the time interval between the initial treatment and occurrence of leprosy recurrence, are in agreement with findings from other studies<sup>15,24-27</sup>. Certain factors may influence the time interval until recurrence, such as

**Table 3** - Comparison of proportion of cases between initial treatment (t1) and relapse (t2) for leprosy, according to clinical characteristics. Mato Grosso, 2005-2007.

**Tabela 3** - Comparação da proporção de casos entre tratamento inicial (t1) e recidiva (t2) em hanseníase, segundo características clínicas; Mato Grosso, 2005-2007.

Variables	Leprosy cases				$\chi^2$ (p value)
	t1		t2		
	n	%	n	%	
<b>Number of lesions</b>					
Up to 5	29	54.7	31	58.5	0.56 (0.454)
More than 5	15	28.3	22	41.5	
NA/ignored*	09	17.0	-	-	
<b>Type of lesion</b>					
Macular	09	17.0	10	18.9	1.64 (0.801)
Papular	10	18.9	13	24.5	
Infiltrated	03	5.7	02	3.8	
Nodule	06	11.3	03	5.7	
NA/ignored*	25	47.2	25	47.2	
<b>Location of lesion</b>					
Face	04	7.5	03	5.7	1.39 (0.846)
Trunk	03	5.7	02	3.8	
Limbs	11	20.8	10	18.9	
More than one location	03	5.7	06	11.3	
NA/ignored*	32	60.4	32	60.4	
<b>Nerve thickening</b>					
Yes	11	20.8	27	50.9	1.89 (0.170)
No	20	37.7	26	49.1	
NA/ignored*	22	41.5	-	-	
<b>Reactive state</b>					
Yes	18	34.0	22	41.5	0.45(0.502)
No	19	35.8	31	58.5	
NA/ignored*	16	30.2	-	-	
<b>Type of reaction</b>					
Type 1	06	11.3	09	17.0	0.54 (0.462)
Type 2	08	15.1	07	13.2	
Isolated neuritis	01	1.9	-	-	
NA/ignored*	38	71.7	37	69.8	
<b>Adverse effects</b>					
Yes	07	13.2	13	24.5	0.18 ( 0.670)
No	27	50.9	40	75.5	
Ignored*	19	35.8	-	-	

\* NR/Ignorado = não realizado/ignorado / \* NR/Ignorado = not done/unknown

clinical form, therapeutic scheme, reactions, irregular treatment and bacillary load<sup>15,28-30</sup>.

The higher proportion of diagnoses of recurrence categorized in the dimorphic clinical form suggests a relationship with an individual's immune response to *M. lepra* and the severity of the disease. A study on

the interactions between pathogens and the immune system in patients with infectious diseases has contributed to the investigation of the basic regulatory mechanisms of the human immune response<sup>13,31</sup>. In the case of leprosy, there is a variety of symptoms that are manifested as distinct clinical forms and its main characteristic is the type of immune

response between host and pathogen<sup>31</sup>. For this reason, an individual's resistance to *M. leprae* is specific and suggests a genetic component<sup>32,33</sup>. It is estimated that the majority of individuals have natural resistance to *M. leprae* (80 to 95%). The remaining individuals would be in a borderline state of anergy (5%) and could develop the severe forms of this disease. In this case, the small number of prime-infected individuals develop the disease due to endogenous reactivation or due to their receiving a new bacillary load (exogenous reactivation)<sup>13,31</sup>.

It should be emphasized that higher percentages were found in the tuberculoid and undetermined clinical forms in the initial treatment. The clinical forms and, consequently, the operational classification of the first treatment could have been erroneously adopted, which may have led to recurrence<sup>12,29,30</sup>. Thus, if a multibacillary patient is initially categorized as paucibacillary and is treated with PCT/6 instead of PCT/12 as a result, the probability of occurrence of leprosy recurrence is increased. Serological tests could function as an alternative tool to classify paucibacillary and multibacillary leprosy in the first treatment and to confirm suspected cases of recurrence<sup>34,35</sup>.

Histopathological tests are diagnostic criteria of recurrence in the majority of studies, similarly to the present study<sup>15,17,18,24,28</sup>. Although this procedure is important as diagnostic support for the confirmation of recurrence, bacilloscopy tests are also essential, especially in previous multibacillary cases<sup>11</sup>. Bacillary persistence indicates a factor of development of recurrence and resulting detection of drug resistance<sup>9,21,26,28</sup>.

Due to the lack of a test considered to be

the gold standard to diagnose this disease<sup>36</sup>, referral treatment units need to have other resources to accurately diagnose recurrence, such as serological tests, morphological indices and inoculation tests in mice feet. The latter tests, although difficult to be performed, enable the viability of *M. leprae* to be observed, tests with chemotherapeutic drugs to be monitored, levels of resistance to drugs to be verified, and cases of recurrence to be confirmed<sup>9,10,34,35</sup>.

Despite the higher proportion of recurrence with physical disability at level 0 at the moment of diagnosis showing an improvement in this indicator, the higher frequency of patients with physical disability at level 2 reveals an aggravation of the disease and its consequences. However, the data found emphasizes the higher prevalence of cases ignored/not evaluated for neurological assessment. These data suggest the inefficiency of the health service with regard to systematic dermato-neurological test monitoring. The reappearance of neural impairment is a diagnostic suspicion of the occurrence of leprosy recurrence<sup>11,12,17</sup>. Studies indicate that the number of nerves affected in the beginning of the treatment, combined with other factors, determines the chances of occurrence of physical disabilities<sup>37</sup>.

In conclusion, cases of recurrence characterize the aggravation of the disease, indicated by the increase in the bacilloscopy index and level of physical disability. It is recommended that more attention should be given to the diagnostic confirmation of recurrence, using bacilloscopy tests, especially in multibacillary cases, and systematic neurological assessment of all leprosy patients.

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