

Retreatment of leprosy relapse* *O retratamento por recidiva em hanseníase**

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Abstract: BACKGROUND - Studies concerning re-treated leprosy patients are justified by the difficulty in differential diagnosis between a reactional state following the end of a specific treatment for leprosy and its relapse, owing to limitations in clinical and laboratorial criteria to distinguish them.

OBJECTIVES - To verify diagnostic procedures (clinical and laboratorial) that subsidized relapse treatment and occurrence of reactional episodes, in particular those that occurred after treatment completion.

METHODS - A hundred fifty-five leprosy patients retreated for relapse in two leprosy reference units in the municipality of Recife/PE, Brazil, in a retrospective case series study.

RESULTS - Clinical criterion was the most used to decide for re-treatment of relapse, and new described lesions were mainly of macular and infiltrative type. Reactional episodes after discharge occurred in 34% of these patients, and 33.9% related the presence of contacts with hanseniasis. Only 14.9% of the 155 studied patients had histological examinations performed, and 18.1% did not have bacilloscopy carried out before re-initiating specific therapy.

CONCLUSION - This study has shown that post-treatment reactional episodes and presence of contacts with leprosy occurred in about 30% of patients who were re-treated for relapse and that further controlled studies are necessary for a better understanding of these factors.

Keywords: Hypersensitive/complications; Leprosy; Recurrence; Retreatment

Resumo: FUNDAMENTOS – Estudos sobre os pacientes hansenianos retratados justificam-se pela dificuldade do diagnóstico diferencial entre quadro reacional após alta do tratamento específico de hanseníase e recidiva, devido às limitações de critérios clínicos e laboratoriais para diferenciá-los.

OBJETIVOS – Verificar os procedimentos diagnósticos clínicos e laboratoriais que subsidiaram o retratamento por recidiva e a ocorrência de episódios reacionais, em especial os que ocorreram após o término do tratamento.

MÉTODOS – Mediante o estudo retrospectivo de série de casos foram estudados 155 pacientes hansenianos retratados por recidiva em duas unidades de referência em hanseníase, no município de Recife/PE, Brasil.

RESULTADOS – O critério clínico foi o mais utilizado para a decisão de retratamento por recidiva, e as lesões novas descritas foram principalmente do tipo mácula e infiltração. Os episódios reacionais após alta ocorreram em 34% desses pacientes, e 33,9% relatavam a presença de comunicantes com hanseníase. Dos 155 pacientes estudados apenas 14,9% realizaram exame histológico e 18,1% não realizaram a baciloscopia antes de reiniciar a terapia específica.

CONCLUSÃO – Este estudo evidenciou que os episódios reacionais após o tratamento e a presença de comunicantes com hanseníase ocorreram em torno de 30% nos pacientes retratados por recidiva e que se fazem necessários outros estudos controlados para o melhor entendimento desses fatores. **Palavras-chave:** Hipersensibilidade/complicações; Hanseníase; Recidiva; Retratamento

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INTRODUCTION

Diagnostic criteria for leprosy relapse are not well defined yet, as they vary according to location or author. Operationally, the National Coordination of Sanitary Dermatology (CNDS/MS) takes into account, for the definition of leprosy relapse, based on the World Health Organization in its own definition,¹ the occurrence of signs of clinical activity of the disease, after discharge by cure. Currently, according to the Ministry of Health,² diagnosis of relapse after MDT/WHO lies on the utilization of both suspicion and confirmation criteria.

For paucibacillary patients (PB), suspicion and confirmation criteria are strictly clinical and applied to cases in which, after discharge by cure, there is appearance of new dermatoneurological lesions or exacerbation of old lesions, neural pain or in those who present new sensitive alterations after discharge by cure, not having responded to treatment with steroids. For multibacillary patients (MB), criteria are clinical for suspicion and laboratorial for confirmation. Suspected are patients who present with skin or neurological signs and who have not responded to treatment with thalidomide and/or steroids in the recommended dosing and time. For confirmation, clinical criterion of absence of response to anti-reactional drugs and laboratorial criteria of bacilloscopic and histopathologic exams should be used. If the bacilloscopic exam reveals integer bacilli or an increase of two logs at any site, when compared to the exam at discharge, relapse is confirmed. In the histopathological examination, confirmation is made with the presence of multibacillary pattern.²

Brazilian official data show that between 1994 and 2000 4,492 patients were reintroduced in MDT/WHO schedules, returning to active recording (with no impact on prevalence) and, of these, a total of 2,221 cases were diagnosed as relapses. In 2002, 1,394 relapse cases were notified.³

After studying 310 patients with leprosy, Brito⁴ observed that those who presented reactional episodes after discharge had a three-fold increase in the probability of being treated for relapse, when compared to control group.

Occurrence of reactional manifestations, after therapeutic discharge, is described by many authors.⁵⁻⁷ Being quite frequent in the first years following therapeutic discharge, these manifestations demand a differential diagnosis with relapses, thus demanding both clinical and laboratorial resources.

Brazil is a country with important cultural, geographical and economical differences, which have a repercussion in health services, influencing their problem-solving power. Lack of both information and standardization of patients' prontuaries, together with

the unreliability of bacilloscopic and histopathological exams, can make it very difficult to employ the suggested criteria for diagnosing or discerning a relapse from a reactional picture, this being one of the motives leading to re-introduction of MDT schedules.

This study approaches clinical, epidemiological and laboratorial aspects for the diagnosis of relapse, and at the same time sought to highlight its relation to post-discharge reactional episodes, by means of a description of patients who were re-introduced in MDT schedules and their characteristics.

METHODS

This study was carried out in two reference units for leprosy treatment in the city of Recife, PE, Northeast of Brazil, which provide care to patients who are suspected to have leprosy and seek them, either by spontaneous demand or when they are referred from other units from both private and public services, and where they are diagnosed and treated according to the norms prescribed by the Ministry of Health (MH).²

By means of a case series, 155 patients who were retreated for leprosy relapse were investigated. Inclusion criterion was the fact that leprous patients had been submitted to retreatment after having been discharged because of cure. All patients who were retreated after having been considered cases of treatment drop-out or because of incorrect treatment schedule were excluded.

The variable considered in the study was relapse of leprosy cases. Data were initially obtained from a secondary database (Sinam) and validated with information from the respective patients' prontuaries of the reference units, by means of a form elaborated specifically for this research, in which characteristics of clinical and laboratorial procedures during initial treatment and that subsidized diagnosis of relapse were raised. For data analysis, the softwares EPI Info, version 6.04 and Microsoft Excel 97 were used.

RESULTS

Of the studied patients, the majority (80.6%) were between 15 and 65 years old and were females (52.3%). The majority had negative bacilloscopies in the initial treatment and only 16.8% had initial bacilloscopic index (IBI) > 3. It is noteworthy that 33.9% (40/118) of the patients reported presence of contacts with leprosy and 34% displayed a reactional episode after discharge. Most of them had used polichemotherapy (MDT/WHO) for initial treatment (84.4%) (Table 1).

Concerning operational classification, 65.2% of the patients (101/155) were classified as MB at

TABLE 1: Distribution of patients with leprosy according to clinical and epidemiological features in initial treatment

	n	%
Years of age		
Less than 14	23	14.9
From 15 to 65	125	80.6
65 and more	7	4.5
Gender		
Male	74	47.7
Female	81	52.3
Bacilloscopy (IBI)		
Negative	84	70.6
From 0,1 to 3	15	12.6
Higher than 3	20	16.8
Contact		
Yes	40	33.9
No	78	66.1
Theurapeutical schedule		
MDT/WHO	124	84.4
Monotherapy	23	15.6
Post-discharge hansenic reaction		
Yes	52	34
No	101	66

relapse, and, of these, only 47.7% (72/151) had this same classification at initial treatment (Table 2).

During post-discharge follow-up, 54.1% were observed to have been retreated in the first three years following discharge from specific treatment, and 44 (28.4%), had over six years since discharge from treatment (Table 3). Clinical criterion was the most used (56.5%) for decision of retreatment of relapse, and new lesions were mainly of the macular (49.4%) and infiltrative (40.3%) types. Only 14.1% were submitted to biopsy and histopathological examination, and 18.1% did not have bacilloscopy performed before reinitiation of specific therapy. A reactional picture occurred during the retreatment of 52% (78/150) of the patients. Noteworthy is the fact that 20% of the patients abandoned retreatment, and 16.1% were discharged in the course of a reactional episode.

DISCUSSION

The handling of a patient after leprosy treatment, particularly of those who exhibit reactional episodes, brings a lot of doubts concerning the presence of a disease in activity or of a reactional picture. These episodes, which are quite frequent, especially in the first year that follow discharge, demand differential diagnosis with relapses, making it necessary to

TABLE 2: Distribution of patients with leprosy according to operational classification criteria at initial and relapse diagnosis

Operational classification	n - t* ₁		n - t ₂	
	n	%	n	%
PB	79	52.3	54	34.8
MB	72	47.7	101	65.2
Total	151	100	155	100

*4 patients without information

n-t₁ - number of initial treatments

n-t₂ - number of re-treatment

use clinical and laboratorial resources. This fact has motivated the elaboration of various differential diagnostic criteria, in an attempt to guide the clinician in the adoption of roughly standardized measures for each situation. Even though criteria are to be found throughout medical literature, they are not yet well defined, varying according to location or author,⁸⁻¹⁰ with controversies among such authors. In the present study, 13.5% (21/155) of the cases were retreated as relapses in the first year of follow-up after discharge. Many of these cases probably represented reactional pictures, and this is due to difficulties for establishing diagnostic and confirmation criteria for relapses in the reference units. Las Águas¹¹ states that relapses generally do not occur before six years following discharge, and that in his personal experience this happens more often between six and 10 years. Gebre,⁹ on the other hand, states that relapses usually occur between two and three years after the end of treatment, when reactions are also more likely. Jamet et al.¹² and Marchoux,¹³ in controlled studies about relapse in multibacillary patients, concluded that they occur later, from five to seven years after the end of treatment.

One hundred and one patients (101/155) were classified as MB at retreatment, and, of these, only 72 (n=51) had such classification at initial treatment. When a PB patient relapses as an MB one, a misclassification is very likely to have occurred during initial treatment. However, patients who relapsed as PB may have been MB previously.^{14,15}

Descriptions of new cutaneous lesions were obtained in 73.6% of the cases, with a predominance of macular (43/155) and infiltrative (35/155) types. Gebre⁹ and the Marchoux Chemotherapy Study Group¹³ observed that relapse should be considered in multibacillary patients especially when the new lesions are nodular or papular. In this study, the fact that only 10.3% (9/87) of the patients had a papulenodular lesion at the moment of relapse diagnosis is attention-drawing, once the majority of the retreated were classified as MB.

TABLE 3: Distribution of patients with leprosy according to criteria for relapse re-treatment and re-treatment completion

	n	%
Re-introduction time		
Up to 1 year	21	13.5
From 1 to 2 years	32	20.6
From 2 to 3 years	31	20
From 3 to 4 years	16	10.3
From 4 to 5 years	11	7.1
5 years and more	44	28.4
Re-introduction criteria*		
Clinical	86	56.5
Histopathological examination	16	10.5
Bacilloscopic	50	32.9
Bacilloscopy in re-treatment		
Yes	127	81.9
No	28	18.1
Type of lesion**		
Macula	43	49.4
Infiltration	35	40.3
Papula	6	6.9
Nodule	3	3.4
Histopathological examination		
Yes	22	14.1
No	133	85.8
Hansenic reaction during relapse		
Yes	78	52
No	72	48
Retreatment completion criteria		
In re-treatment	16	10.3
Discharge by cure without reaction	79	51
Discharge by cure with reaction	25	16.1
Drop-out	31	20
Transference	4	2.6
Total	155	100.0

* 15 patients without information

** 23 patients without information

Of the 155 cases of leprosy retreatment, 18.1% did not have their bacilloscopies carried out to rebegin treatment, even though this is a recommendable procedure when relapse is suspected, mainly in previously multibacillary patients. The majority (57.5%) had negative bacilloscopic indices (BI), and 7.8%, BI > 3. Morphologic index (MI) was not possible to be analyzed in this work because of lack of standardization of these exams. Previous studies have shown that measurement of the MI is of difficult standardization, besides being uncertain in some conditions. MI could be useful as an indicator of relapse in MB patients,

but only when performed in a reference laboratory.^{16,17}

Of all investigated patients, only 22 had histopathological examinations performed for diagnosis of relapse. The reason for this low frequency could be unavailability of material and human resources for its realization in the studied reference units.

There is disagreement in the literature surrounding the correlation between clinical diagnosis and histopathological examination.^{18,19} Some authors^{6,20} find the latter little efficacious for distinguishing between reaction and relapse in PB patients, Shetty,²¹

when observing 25 paucibacillary patients with the appearing of new lesions and/or exacerbation of pre-existing ones after MDT completion, verified, by means of a histopathological exam validated with inoculation in mouse paw, that it was the bacterial viability frequency in the lesions that provided evidence for a reactional picture.

Observing 15 paucibacillary patients with the appearance of new lesions and / or exacerbation of preexisting lesions after the end of MDT by means of histological study validated by mouse paw inoculation, it was seen that the frequency of bacterial viability in lesions showing evidence of a reactional picture at the histological test superior to those which did not show it was actually a relapse, thus bringing into question the value of the histological test for a differential diagnosis between the reactional picture and a relapse.

Of the studied patients, 33.9% reported the presence of contacts who also suffered from leprosy.

It is important to reflect on the possibility of reinfection, based on irreversibility of immunological deficiency specific to *M. leprae*.^{5,22} It would be reasonable to suppose that this result signals the possibility of reinfection. Even though hard to prove scientifically, this hypothesis should not be forgotten.

It is worth remembering that for technical and operational reasons, it was not possible to identify, during data collection from the prontuaries, which was the polar form of the contact, neither if he or she had or had not received specific treatment. Clarifying of this question demands further studies.

Of the 155 patients treated for relapse, 34% had a reactional episode after treatment. The importance of differential diagnosis between these post-treatment episodes and relapse has long been known. Diagnosis of relapse in PB patients almost always requires differential diagnosis with tardive reverse reaction, which could be mistaken for relapse.²³ In paucibacillary patients, relapse could be mistaken for tardive reverse reaction and there is no gold standard for comparison, since *M. leprae* cannot be isolated in these instances.⁹ In a study carried out in India by Lobo²⁴ 40,000 PB patients who concluded treatment were observed; 0.29% of which were considered to have relapse according to clinical criteria, although many of these cases were later perceived to be tardive reverse reactions. This was confirmed in a study carried out in Ethiopia, in which over half of PB patients who had received the diagnosis of relapse were actually having a reactional picture.⁶

Among MB patients, reverse reaction is also often confounded with relapse, but diagnostic confirmation would be possible with bacilloscopic exam, by the presence of integer bacilli, histology and incu-

tion in mouse paw. A common problem in relapse diagnosing is the performance of only the bacilloscopic exam, which was also observed in this study (results not shown). Procedure guidelines in leprosy treatment programs include performance of two exams to confirm relapse diagnosis, with positivity of MI, or an increase of + 2 logs in BI.⁶

The efficacy of leprosy control actions could be assessed by proportion of ill patients that are discharged because of cure. For the studied relapse case series, it was not possible to verify closing of all cases due to a percentage of 32.9% of them with insufficient data (patients undergoing treatment, drop-out and transference).

When the current situation of follow-up of retreatment cases is analyzed, considering as a favorable result the sum of non-medicated discharges by cure of reaction and administrative discharges, and as unfavorable medicated discharges of reaction and drop-outs, it is observed that 57.4% (89/155) of the patients had a favorable closing, 26.9% (46/155), unfavorable and 12.9% (20/155) undefined (under retreatment or transference).

From what is exposed retreatment of relapse in leprosy should be re-evaluated in what concerns epidemiological (active search of contacts), clinical (installation of standardized protocols to establish a differentiation between an active reactional episode after treatment closure and relapse) features and in the performance of laboratorial exams.

CONCLUSIONS

Results found point out to the need for availability of clinical and laboratorial conditions (standardization of bacilloscopy with BI and MI, performance of biopsy in active lesions with Baar stain) for health unities that treat and follow up patients with leprosy, in order to improve differential diagnosis between relapse and post-discharge reactional episode.

Also necessary are interventions by the Leprosy Control Program (HCP), with surveillance procedures of contacts in relatives of patients suspected of relapse, as well as intervention in endemic areas. □

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