Clinical features of relapse after multidrug therapy for leprosy in China

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Key lessons
In China:
• All MB relapse cases had new skin lesions
• All MB relapse cases had positive skin smears again, after previously becoming negative
• PB relapses were only diagnosed after a gap of 4 years from completion of MDT
• All PB relapses had new skin lesions and were confirmed histologically

Summary
Background: Although the World Health Organization (WHO) has defined relapse in leprosy, it is often difficult to confirm a relapse, especially in paucibacillary (PB) patients.
Objective: To study features of relapse cases in order to determine the information needed to allow better management of relapses in the leprosy control programme.
Design: A retrospective survey by questionnaire was carried out at national level at the end of 2012.
Results: There were 40 relapsed patients on register. The clinical form of leprosy was TT5, BT4, BB5, BL13 and LL13. Twenty-eight patients had had a positive skin smear test at the start of MDT, with a BI ranging from 0.83 to 6.0. At the time of completing MDT, the skin smear test remained positive in seven patients. After completion of MDT, other family members of 13 patients were identified as new leprosy patients. All relapse cases showed one or more active skin lesions. There were 33 patients with a positive skin smear test at the time of relapse. A total of 23 patients had a biopsy at the time of relapse, including seven patients with a negative skin smear test. The histological features of relapsed BB-LL patients included granulomas.
containing macrophages or epithelioid cells with sparse lymphocytes and acid-fast bacilli. The histological features of seven patients with negative skin smears showed epithelioid cell granulomas with dense lymphocytes surrounding the granuloma, but without distinct edema in the dermis. The average interval from completion of MDT to the diagnosis of relapse was 168·5 ± 92·6 months with a range of 21–322 months. During the study, nine patients were tested for rifampicin resistance, but none showed any mutation.

**Conclusions:** Leprosy relapse after MDT usually occurred late and all relapse cases had new active skin lesions. Most patients relapsed with a positive skin smear after previously reaching negative BI status. Relapse with a negative skin smear test should be confirmed very cautiously.

**Introduction**

Relapse after multidrug therapy (MDT) for leprosy is always concerning to health workers in the leprosy control programme. Although the World Health Organization (WHO) has defined relapse in leprosy, it is often difficult to confirm a relapse, especially in paucibacillary patients, in whom the differentiation of relapse from reversal reaction is very difficult. What are the clinical features of leprosy relapse? Are there any predisposing factors influencing the risk of relapse after therapy? In order to study the features of relapse, we carried out a national survey in China at the end of 2012 to collect information to allow better management of relapses in the leprosy control programme.

**Material and methods**

A retrospective survey by questionnaire was carried out at national level at the end of 2012. All data from patients who had relapsed after MDT and who were registered between January 2011 and September 2012, were collected by health workers at county level. All questionnaires were sent to the National Center for Leprosy Control through each provincial centre. All clinical data, including age, sex, clinical form of leprosy, time of completing MDT, time of relapse, clinical manifestations of relapse, bacteriological indices before and after MDT and at the time of relapse, were collected for analysis.

All patients had been treated with MDT, 6 months for paucibacillary (PB) cases and 24 months for multibacillary (MB) cases. Eight patients had had DDS monotherapy before the MDT era, but had then been treated with MDT.

A relapse is defined as the recurrence of the disease at any time after the completion of a full course of treatment with WHO recommended MDT. Relapse is diagnosed by the appearance of definite new skin lesions and/or an increase in the bacteriological index of two or more units at any single site. A biopsy can give additional information by showing specific histopathological changes of leprosy and may show the presence acid-fast bacilli (AFB).

In our programme, relapse in patients with negative skin smears is indicated by the appearance of new symptoms and signs of the disease occurring 4 years or more after stopping MDT, to minimize the risk of confusing relapse with reaction. There should be a history of full disappearance of skin lesions, and biopsy showing evidence of active disease, while excluding leprosy reaction.
Some patients had a skin sample taken to test for rifampicin resistance mutations by polymerase chain reaction (PCR). The data were processed using SPSS software version 16·0 and descriptive statistics was used for analysis.

Results

A total of 52 patients were reported to have relapsed after MDT during the study period, but adequate information was available only for 40 patients. In the other 12 patients, either the diagnosis of relapse was not fully documented, or the relapse time was very close to the time of completion of MDT which suggested a leprosy reaction.

Among 40 relapsed patients, 28 were male and 12 were female. The average age at relapse was 50·5 ± 14·7 with a range of 25–76 years old. The clinical form of leprosy was TT5, BT4, BB5, BL13 and LL13. Twenty-eight (70%) patients had a positive skin smear test at the start of MDT, with a BI ranging from 0·83 to 6·0. Eleven (27·5%) patients had an initial BI ≥ 3·0.

During MDT, 10 (25%) patients had developed leprosy reactions or neuritis and were treated with prednisone at 40 mg or more per day for more than 3 months.

At the time of completing MDT, seven patients still had a positive skin smear test with a BI ranging from 0·25 to 3·2. Twenty-six patients had negative smears, and the skin smear was not done in seven patients. During the years after completion of MDT, however, the skin smear of all seven positive patients became negative. After completion of MDT, other family members of 13 patients were identified as new leprosy patients.

All patients showed one or more active skin lesions such as erythema, nodules, plaques or skin infiltration at the time of relapse. Thirty-three (82·5%) had a positive skin smear test at diagnosis of relapse. The average BI was 1·95 ± 1·86 with a range of 0·2–4·8. A total of 23 patients had a biopsy at diagnosis of relapse, including all seven patients with a negative skin smear test. The histological features of relapsed BB-LL patients included granulomas containing macrophages or epithelioid cells with sparse lymphocytes and acid-fast bacilli. The histological features of seven patients with negative skin smears showed epithelioid cell granulomas with dense lymphocytes surrounding the granuloma, but without distinct edema in the dermis; these seven patients also had a long time interval between completion of MDT and relapse.

The average interval from completion of MDT to the diagnosis of relapse was 168·5 ± 92·6 months with a range of 21–322 months. The average interval from the first symptoms of relapse to the formal diagnosis of relapse was 21·7 ± 14.0 months with a range of 6–74 months.

Two patients, who had been treated as PB cases for MDT, were MB at relapse. During the study, nine patients with a positive skin smear were tested for rifampicin resistance, but none showed any mutation.

Discussion

MDT recommend by WHO since 1982 is still very effective for the treatment of leprosy. Till now, after treatment with either 24 or 12 months of MDT, the reported relapse rate in MB cases has been very low, and relapses that do occur tend to be late. Fajardo et al. report that
relapses after MDT occurred later than 5 years after the initiation of therapy,\(^8\) while Dogra et al.\(^9\) reported that out of 730 leprosy patients treated with one year of the WHO-MB regimen, 13 patients relapsed later than 3 years after release from MDT. In our study of 40 patients, the average interval from completion of MDT to relapse was 168.5 ± 92.6 months with a range of 21–322 months. The late appearance of relapse after treatment with MDT is an important diagnostic feature.

True relapses present with the occurrence of new active skin lesions in patients who have completed an adequate course of MDT.\(^10\) In addition, a positive skin smear positive for AFB at relapse in a previously skin smear negative case is a very important indicator for true relapse.\(^11\) In our study, 33 patients had a positive skin smear at the time of relapse, in addition to new active skin lesions. There was full documentation to confirm these relapses. However, sometimes it is very difficult to distinguish relapse from reversal reaction when the skin smear is negative,\(^12\) and relapse can even occur concomitantly with leprosy reaction. WHO also does not clearly define relapse for paucibacillary patients.\(^1\) But in the field, health workers can encounter relapse in patients with negative skin smears. In our programme, we defined PB relapse as the reappearance of symptoms and signs of the disease occurring 4 years or more after completing MDT, with a history of complete disappearance of old skin lesions before the appearance of new skin lesions. The biopsy should show evidence of active disease and exclude leprosy reaction. In our study, there were seven patients who relapsed with a negative skin smear, but based on the clinical analysis and histological examination, all had enough evidence to be confirmed as relapse cases.

Some researchers report that the risk of relapse is linked to a high bacterial load before MDT\(^5\) and that the number of skin lesions and involvement of nerves were additional risk factors for relapse,\(^7\) but in our study we have not observed a close relationship among patients with high BI before relapse. Of 40 relapsed patients, only 28 patients had an initial positive skin smear, with a range of 0.83–6.0. Eleven patients had an initial BI ≥ 3.0 which only accounted for 27.5% of all relapsed patients. Both PB and MB patients can relapse. However, there were two patients who had a change in type of relapse, previously PB cases relapsing as MB cases. This may be related to misclassification of the first episode and inadequate treatment.

Reinfection is a possible cause of relapse in leprosy. In our study, family members of 13 relapsed patients who had already completed MDT, developed leprosy. This suggests that the source of infection may have continued to exist near the patient which resulted in a relapse, so reinfection cannot be excluded as the cause of these relapses.

Relapse due to ‘persisters’ also cannot be excluded. It is reported that 16% of BL-LLs patients showed viable leprosy bacilli (demonstrated by growth in the mouse foot-pad) after 12 months’ MDT.\(^13\) These viable leprosy bacilli may be persisters with a very low metabolic rate. The very low relapse rate (usually less than 1%) after completion of MDT shows that the presence of such viable bacilli does not correlate with a high risk of relapse.

There was little possibility that relapse resulted from rifampicin resistance; nine (22.5%) patients had samples tested for rifampicin resistance, with none showing any drug mutation. All 40 relapse cases have now been retreated with one year WHO MB-MDT and have responded well.

In conclusion, leprosy relapse after MDT usually occurred late and all patients relapsed with definite, new, active skin lesions. Most patients relapsed with a positive skin smear after previously reaching BI negativity. Relapse with a negative skin smear should be confirmed very cautiously.
References

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