

INFECTIOUS DISEASES

Incidence of acute nerve function impairment and reactions in leprosy: a prospective cohort analysis after 5 years of follow-up

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Background Nerve function impairment (NFI) is the key outcome of the pathological processes of infection with *Mycobacterium leprae*, which can continue after completion of multidrug therapy (MDT) and lead to disability after leprosy patients are released from treatment. The objective of this study was to assess the need for and duration of surveillance of NFI.

Methods Prospective cohort study of 2664 new leprosy patients in Bangladesh, with an observation period of 36 months in paucibacillary (PB) patients, and 60 months in multibacillary (MB) patients. Incidence rates (IR) were calculated with the number of patients developing NFI, type 1 and type 2 reactions, and silent neuritis for the first time after registration as the numerator, and cumulative person-years at risk (PYAR) as the denominator. Survival curves to the first event of NFI were also calculated.

Results The IR of first event of NFI amongst MB patients was 16.1 per 100 PYAR, with 121/357 (34%) developing NFI during the observation period. Of the 121 with a first event of NFI, 77 (64%) had this within a year after registration, 35 (29%) in the second year, and the remaining 9 (7%) after 2 years. The IR of first event of NFI amongst PB patients was 0.9 per 100 PYAR, with 54/2153 (2.5%) developing NFI during the observation period. Of the 54 with a first event of NFI, 48 (89%) had this within a year after registration, 3 (5.5%) in the second year, and the remaining 3 (5.5%) cases after 2 years. The percentage of PB patients with no NFI at registration surviving without developing NFI during the observation period was 99% and for PB patients with NFI at registration 92%. In MB patients without NFI at registration, the percentage surviving with no NFI during the observation period was 84% and for MB patients with NFI at registration only 36%.

Conclusion New episodes of NFI and reactions after registration are common, in particular in MB patients with long-standing NFI at registration. The study highlights the importance of continuing surveillance for NFI of this risk group after registration for 2 years. Active surveillance beyond 2 years is not indicated.

Keywords Leprosy epidemiology, peripheral nerve disease

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In order to understand more clearly the epidemiology of nerve function impairment (NFI) and its incidence, risk factors, and response to treatment, a prospective cohort study has been initiated at the Danish Bangladesh Leprosy Mission (DBLM). The design, methodology, and intake status have been described in an earlier paper.¹ The incidence rates of acute NFI after a follow-up period of 24 months in this cohort of 2664 newly

diagnosed leprosy patients was described previously.² Follow-up of patients included in the cohort continued for up to 3 years from the time of registration in the case of paucibacillary (PB) patients, and for up to 5 years for multibacillary (MB) patients. This paper presents the results at 5 years (60 months) of follow-up.

NFI results from a variety of pathological and immunological processes taking place in peripheral nerves. These include the presence of *Mycobacterium leprae* in the nerve, trauma, oedema causing increased intraneural pressure, vascular changes, and hypersensitivity granuloma.³ Reactive states, including type 1 and type 2 reactions, are widely accepted as common causes of NFI and of these, type 1 or reversal reaction is regarded as the leading cause.⁴ However, nerves are often functionally impaired without developing obvious symptoms such as skin reactions or nerve pain, and this condition is variously called 'silent neuritis',⁵ 'silent neuropathy',⁶ or 'quiet nerve paralysis'.⁷

The majority of patients developing NFI events do so in the first year after registration.^{2,8-12} Although the proportion of patients experiencing their first NFI event diminishes with time, evaluation of the Bangladesh Acute Nerve Damage Study (BANDS) cohort at 24 months showed that amongst MB patients there was a moderate number who had their first episode after 18 months of multidrug therapy (MDT).² This highlighted the importance of continuing vigilance after registration for at least 2 years, especially in the case of MB patients. It is known that NFI and reactions continue after 2 years.¹¹⁻¹⁴ Because of the need to prevent further disability in leprosy patients after completion of MDT, it is important to know how often NFI and leprosy reactions may be expected beyond 2 years after registration, and which patients are at particular risk.

In this paper, the incidence rates (IR) and cumulative incidence of NFI and other reactive phenomena amongst patients in the BANDS cohort are presented for the following risk variables: leprosy group (PB/MB) and presence or absence of NFI at registration. Survival curves to the first event of NFI during the 60-month observation period have been calculated and are also presented in the paper.

Materials and Methods

The patient cohort and follow-up

The study group is the BANDS cohort.¹ The 2664 patients recruited over a 12-month period comprise 1481 males (56%) and 1183 females (44%). In all, 2220 (83%) of the patients were PB, and 444 (17%) were MB. All patients have been treated according to WHO guidelines for MDT current at the time of the study as follows: PB cases: Rifampicin 600 mg supervised dose, DDS 100 mg daily, total 6 months' treatment; MB cases: Rifampicin 600 mg and Clofazimine 300 mg supervised dose, DDS 100 mg daily and Clofazimine 50 mg daily, total 24 monthly doses. This dose regimen is used for all normal-sized adults; lower doses for small adults and children are given according to the Bangladesh national treatment guidelines. Amongst the PB group, 14 patients were reclassified as MB during the course of follow-up, and they were started on MB/MDT. In these patients, a type 1 reaction (reversal reaction) caused skin patches that had been invisible at the time of registration to become visible. This made reclassification of these patients into the MB group necessary, since classification was based on a count of patches

combined with the number of palpable enlarged nerves and skin smear results (>10 skin patches and enlarged nerves and/or skin smear positive = MB). However, since these cases were correctly diagnosed as PB according to the diagnostic tools available at the time of registration, they have been considered as PB for the purposes of analysis. In other words, the initial classification of PB or MB was 'fixed' for subsequent analysis.

Details of follow-up procedures have been described.¹ PB patients have completed at least 36 months, and MB patients at least 60 months of follow-up after registration. Duration of follow-up was based on available information at the time of occurrence of NFI after completion of MDT, which is more common in MB as compared with PB leprosy. All analysis in this paper is based on these follow-up periods.

Analysis will focus on the incidence of the first episode of NFI during follow-up as the main outcome. The definition of NFI used is as follows:

Sensory nerve function impairment

Reduction by ≥ 2 points in the sensory distribution of any one nerve, as tested by ballpoint pen using the standard test sites described.¹ The following nerves were tested for sensory function: ulnar, median, and posterior tibial.

Motor nerve function impairment

Reduction by ≥ 2 in the MRC grade of the movement tested of any one nerve as described earlier. The following nerves were tested for motor function: facial, ulnar, median, radial, and lateral popliteal.

Full details of testing and other outcome definitions such as type 1 reaction (reversal reaction), type 2 reaction (erythema nodosum leprosum [ENL]), and silent neuritis are described in the earlier paper.¹ The testing methods have been validated in a separate publication.¹⁵ In this paper, a patient is said to have developed an 'NFI event' (positive outcome) if he or she has had either sensory or motor NFI, or both, unless stated otherwise.

Statistical methods

IR have been calculated using the number of patients developing a first event of NFI or reactions as the numerator, and cumulative person-years at risk (PYAR) as the denominator, expressed as 100 PYAR.

Patients who were lost to follow-up, died, or who were transferred out of the project were included in the denominator for as long as follow-up was possible, up to the final assessment around 36 months in PB, and around 60 months in MB patients. Patients were discontinued from the denominator as soon as they developed an event of the type for which the IR was being calculated (i.e. NFI or reaction).

Survival curves were calculated of the percentage of patients surviving without a first event of NFI or reaction against time since registration. The log rank test was carried out to assess the significance of differences between the curves at end-point, and the *P*-value has been given in the text. The cumulative incidence at final assessment is given.

Number of at-risk cases used in calculations

The number of at-risk cases (which appears in the denominator of the incidence calculation, to determine the number of PYAR) is the total number of patients in the BANDS cohort (2664), less the number of patients who had an episode of NFI or reaction

that needed prednisolone treatment at registration (119), less the number of other patients who received prednisolone treatment at the time of registration for any other reason (e.g. those who did not strictly fulfil the standard treatment criteria, but who still received prednisolone) (35), leaving the total number of patients entering the denominator at the beginning of the study as 2510.

Risk factors considered for analysis

Two variables have been selected for analysis. They are: leprosy group (MB/PB) and the presence or absence of long-standing NFI at registration (i.e. >6 months duration). These two have been selected because they are fundamental to the assessment of a leprosy patient at registration, and can be carried out without difficulty in any control programme. For other basic variables such as age and sex it has been shown previously that they are not strong predictors for the occurrence of NFI during treatment and follow-up.¹⁶ Classification into MB and PB for treatment purposes is usually carried out using either the WHO method of counting skin patches¹⁷ or a similar procedure such as the Bangladesh system of counting patches and enlarged nerves,¹⁸ in combination with skin smear results.

As already mentioned, all patients with acute NFI/reaction (≤ 6 months duration) needing treatment with prednisolone at registration have been excluded from analysis, since it is difficult to be certain of whether a subsequent 'NFI event' truly represents a new episode or a continuation of the first. In addition, for this group of patients outcome will have been modulated by having received prednisolone therapy, and therefore a comparison with patients who did not receive prednisolone is not possible. However, it was felt important to consider whether patients who had long-standing NFI at registration (>6 months duration) are at increased risk of developing another episode.

Results

Status of the cohort at 5 years

Table 1 shows the status of the BANDS cohort patients at 3 years (PB) and 5 years (MB) from the time of registration. A total of 2076 PB patients (93%) remained under observation for the complete follow-up period of 36 months and 363 MB patients (82%) for the complete follow-up period of 60 months. Patients were considered to be lost to follow-up if their date of expected contact with DBLM staff was more than 3 months overdue despite active attempts at tracing. Out of 2220 PB patients, 14 were reclassified as MB during treatment, leaving 2206.

Incidence rates and cumulative incidence of all nerve function impairment, type 1 and 2 reactions, and silent nerve function impairment during follow-up

Table 2 shows the IR expressed per 100 PYAR of NFI, and the cumulative incidence at final assessment. Results are shown for all episodes of NFI, and for type 1 reaction, type 2 reaction, and silent neuritis separately. A breakdown is also given for any new event of NFI in patients with and without NFI at registration. The definition of NFI used strictly follows the definitions given in the earlier paper.¹ For all NFI events, the IR amongst MB cases of 16.1/100 PYAR compares with 0.85/100 amongst PB cases. For the risk factor of presence of long-standing NFI at registration, the IR is even higher at 46.2/100 PYAR compared with 7.4/100 PYAR amongst those without NFI at registration in MB patients, and 4.42/100 versus 0.61/100 in PB patients. The cumulative incidences parallel the IR.

The same statistics for type 1 and 2 reactions, and silent neuritis are also shown in Table 2. Type 1 reaction as defined for Table 2 means patients with a skin reaction with or without NFI. The overall IR for type 1 reactions in MB patients is half of the rate for NFI, 8.0/100 PYAR compared with 16.1/100 PYAR. In PB patients this difference in IR is 0.30/100 PYAR compared with 0.85/100 PYAR. Only eight patients developed a type 2 reaction during follow-up. The overall IR for type 2 reactions in MB patients is 1.1/100 PYAR compared with 16.1/100 PYAR for all NFI and 8.0/100 PYAR for type 1 reaction.

The IR and cumulative incidences for patients with silent NFI (silent neuropathy) are very similar to those for NFI in general, which is not surprising since the majority of NFI cases were in fact silent (151/175, 86%). The IR for silent NFI is 13.4/100 PYAR amongst MB patients, and 0.79/100 PYAR amongst PB patients.

Incidence rates of nerve function impairment during 6- and 12-month blocks of follow-up

Figures 1, 2, and 3 show the IR for development of the first event of NFI during follow-up. The first year is divided into two periods of 6 months, while the following years are divided into periods of 12 months. The numerator is the number of events occurring during these periods. The denominator is the number of days at risk for patients continuing in follow-up with no new outcome events. These IR have been calculated for the diagnostic groups PB/MB and include the first event of NFI (Figure 1), the first event of type 1 reaction (Figure 2), and the first event of type 2 reaction (Figure 3). For all there is a stepwise reduction in IR for successive 6-month and 12-month periods.

Table 1 Status of BANDS cohort patients at 3 years (36 months) for paucibacillary (PB) patients, and at 5 years (60 months) for multibacillary (MB) patients from registration, according to diagnostic group (MB or PB) and outcome of follow-up. N = 2664

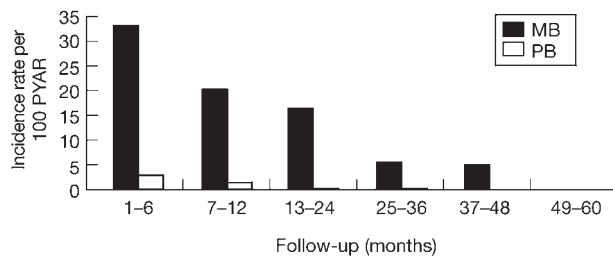
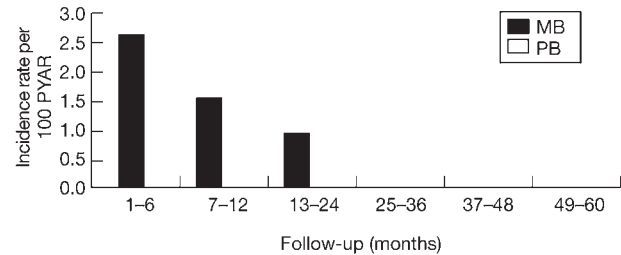
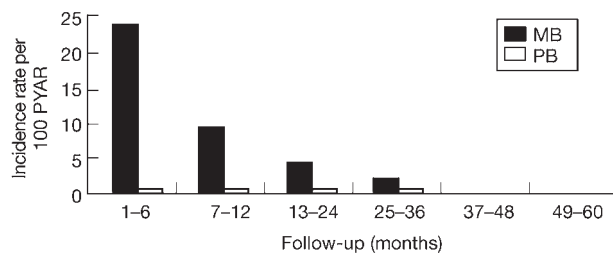
Status at 60 months	Patients who were classified MB at registration		Patients who were classified PB at registration		Total	
	N	%	N	%	N	%
In follow-up	363	82%	2076	93%	2439	92%
Lost to follow-up	44	10%	89	4%	133	5%
Died	27	6%	35	2%	62	2%
Transferred to other project	10	2%	20	1%	30	1%
Total	444	100%	2220	100%	2664	100%

Table 2 Incidence rates and cumulative incidence (%) of first event of nerve function impairment (NFI) and other reactional events amongst BANDS cohort patients, by diagnostic group—multibacillary (MB) or paucibacillary (PB)

Leprosy group	Type of reactional event	Total no. of cases	Cases with event	Incidence rate (events per 100 PYAR ^a)	Cumulative incidence at final assessment (%)
MB	All NFI	357	121	16.1	34%
	Type 1	357	60	8.0	17%
	Type 2	357	8	1.1	2%
	Silent neuritis	357	101	13.4	28%
	NFI at registration	114	78	46.2 ^b	68%
	No NFI at registration	243	43	7.4 ^b	18%
PB	All NFI	2153	54	0.85	2.5%
	Type 1	2153	19	0.30	0.9%
	Type 2	2153	n.a.	n.a.	n.a.
	Silent neuritis	2153	50	0.79	2.3%
	NFI at registration	149	18	4.42 ^b	12%
	No NFI at registration	2004	36	0.61 ^b	1.8%

^a Person-years at risk.

^b Difference between groups with and without NFI at registration is statistically significant ($P < 0.001$).

**Figure 1** Incidence rate per 100 person-years at risk (PYAR) for first events of nerve function impairment (NFI) by 6-month periods (first year) and 12-month period after the first year, according to leprosy group**Figure 3** Incidence rate per 100 person-years at risk (PYAR) for first events of type 2 reaction by 6-month periods (first year) and 12-month periods after the first year, according to leprosy group (multibacillary [MB] patients only)**Figure 2** Incidence rate per 100 person-years at risk (PYAR) for first events of type 1 reaction by 6-month periods (first year) and 12-month periods after the first year, according to leprosy group

The IR of first event of NFI (Figure 1) amongst MB patients during the first 6 months after registration is very high at 33.3/100 PYAR, representing 51 events. This figure has halved to 16.5/100 PYAR (35 events) in the second year of follow-up. In the third and fourth year the IR stabilizes around 5.5/100 PYAR (8 and 1 event respectively). No new events were observed in the final year. For the PB group, the IR for the first event of NFI is much lower, starting with 3.0/100 PYAR

(32 events) in the first 6 months and 1.5/100 PYAR (16 events) in the second 6 months. A limited number of events are observed during the second, third, and fourth year of follow-up (3, 2, and 1 event respectively), reducing the IR to around 0.5/100 PYAR. In addition, for the PB group, no new events were observed in the final year. Of all events in the MB group, 64% were observed in the first year, 29% in the second year, and the remaining 7% in the successive years.

Regarding the first event of type 1 reaction (Figure 2), the majority of cases are seen in the MB group. The IR is 23.5/100 PYAR (36 events) in the first 6 months, and decreases rapidly to 9.3/100 PYAR (12 events) in the second 6-month period, 4.2/100 PYAR (9 events) in the second year, and 2.1/100 PYAR (3 events) in the third year. No new type 1 reactions were seen during the fourth and fifth years in this group. A small but constant number of type 1 reactions were observed over all 5 years in the PB group, with a total of 19 events. Two of these cases reported after the 36-month follow-up period (not shown in Figure 2). Five of the 19 cases were redesignated as MB after initial diagnosis of PB. Of all events in the MB group, 80% were observed in the first year, 15% in the second year, and the remaining 5% in the successive years.

Finally, in Figure 3, the IR for first event of type 2 reaction is shown. These nine events were observed only in the first 24 months. The IR decreased rapidly from 2.6/100 PYAR (4 events) to 1.6/100 PYAR (2 events) in the second 6-month period, and 0.9/100 PYAR (2 events) in the second year. Of all type 2 reactions, 75% were observed in the first year and the remaining 25% in the second year.

Survival curves to first event of nerve function impairment

Figure 4 shows four survival curves to the first event of NFI during follow-up. For all patients together, the proportion surviving without NFI is 94% (Figure 4a). For PB patients this figure is 98%, which is in sharp contrast to MB patients, of whom only 67% survive without NFI (Figure 4b). Of all patients without NFI at registration, 97% survive without developing NFI during the observation period, while this figure is 68% of all patients with NFI at registration (Figure 4c). Finally, Figure 4d shows survival according to diagnostic group (PB/MB), with and without NFI at registration. The proportion of PB patients with no NFI at registration surviving without developing NFI during the observation period is 99%. The figure for those PB patients with NFI at registration is 92%. In MB patients with no NFI at registration, the percentage surviving without NFI during the observation period is 84%. Of MB patients with NFI at registration, only 36% survived without developing new NFI during follow-up. In Figures 4b, 4c, and 4d the difference between the curves at end-point are statistically significant (P -value log rank test < 0.05).

Discussion

The occurrence of NFI and reactions in leprosy at first examination and during MDT has been comprehensively reviewed.^{2,8,9,19} In addition to these studies, this paper presents information based on an observation period of 5 years, well beyond the duration of MDT. Data are based on a large prospective cohort of 2664 consecutive new patients in a single leprosy control project. Nearly 92% of these remained in the study for the complete follow-up period of 36 months for PB, and 60 months for MB patients.

The incidence of NFI, type 1, and type 2 reactions is described in two ways. Firstly, incidence rates per 100 PYAR for the first event of these outcomes are shown over the total observation period and according to separate time periods. Secondly, survival curves are calculated showing the probability of developing the first event of NFI during the observation period. The patients were stratified according to leprosy classification and presence of long-standing NFI at registration. These variables have been shown to be strong predictors for the occurrence of NFI during treatment and follow-up.¹⁶ Of all patients who were entered into the BANDS cohort, 175 (6.6%) developed new NFI after registration. The majority of these patients (125 or 71.5%) did so in the first year, with nearly half (83 or 47.4%) developing new NFI in the first 6 months after registration. In the second year the number with new NFI was 38 (21.7%); in the third year 10 (5.7%); in the fourth year 2 (1.1%); and in the final year nil. The pattern is similar for type 1 and type 2 reactions. Although the proportion of patients experiencing their first NFI event diminishes with time,

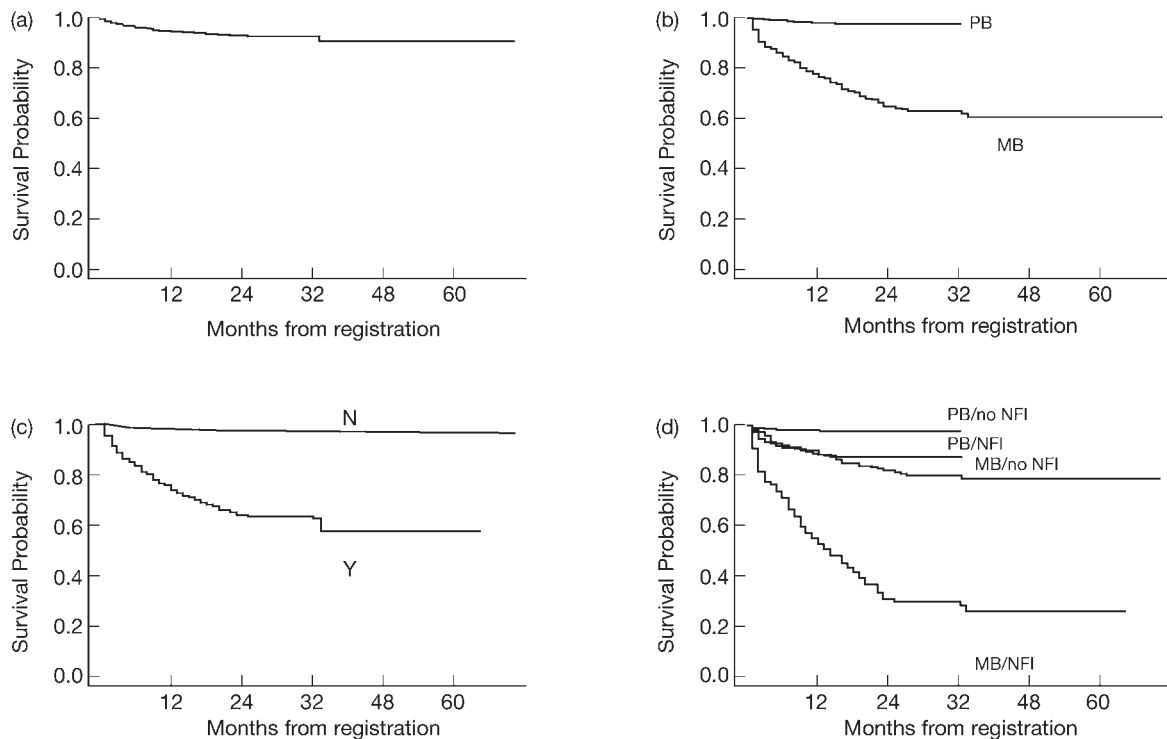


Figure 4 Survival curves to first event of nerve function impairment (NFI) during follow-up: all cases (Figure 4a); according to leprosy group (Figure 4b); history of NFI at registration (Figure 4c); and history of NFI at registration by leprosy group (Figure 4d)

amongst 357 MB patients there are 9 cases (2.5%) who have their first episode after 24 months of MDT (7.4% of all those who develop NFI).

Most patients (86%) developing an NFI event after registration experienced it 'silently', i.e. without a skin reaction or the development of nerve pain. This concurs with findings from other studies,^{9,11,12} and highlights the need for regular nerve function testing to be available for patients at clinic visits, and for patients to be aware that developing numbness in hands or feet must not be ignored. Type 1 reaction was observed in 60 MB patients (16.8%), and in 19 PB patients (0.9%). Eight patients developed type 2 reaction during treatment, out of 84 borderline lepromatous and 51 lepromatous leprosy patients in the cohort. Only one patient at registration had a type 2 reaction present, bringing the total to nine (6.7% of lepromatous patients).

The IR of NFI, type 1 reaction, and silent NFI are considerably higher amongst MB patients compared with PB patients, and amongst patients with long-standing NFI present at registration compared with those without it. These findings are discussed in detail in earlier papers reporting on the BANDS cohort.^{2,16} It has led to the formulation of a clinical prediction rule for selecting patients at risk for developing NFI after registration.²⁰ The study shows that the probability, even for high risk patients, of developing new NFI beyond 2 years after registration appears

to be very low. The AMFES study in Ethiopia had similar findings for NFI and type 1 reaction^{12,13}, but found that type 2 reactions (ENL) occurred relatively often after 2 years.¹⁴ However, the number of patients is very low. Low reported that relapse rates in patients who received MDT have, in many leprosy control programmes, led to shortening of the treatment regimen and to cessation of active surveillance after treatment, as surveillance for relapse was not cost-effective. From the point of view of detection and treatment of NFI, however, this situation is undesirable. Surveillance of high risk patients should continue for 2 years. It is also important to educate all patients adequately about the symptoms of NFI and reaction, and to make it easy for such patients to refer themselves back to leprosy clinics. It is also necessary that staff awareness of the risk of NFI after release from treatment is increased.

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KEY MESSAGES

- Of all 2664 leprosy patients included in the cohort analysis, 175 (6.6%) developed new nerve function impairment (NFI) after registration.
- Of the 175 patients who developed new NFI, 125 (71.5%) did so in the first year; 38 (21.7%) in the second year; 10 (5.7%) in the third year; 2 (1.1%) in the fourth year; and nil in the final year.
- The percentage of paucibacillary (PB) leprosy patients with no NFI at registration surviving without developing NFI during the observation period was 99%, and for PB leprosy patients with NFI at registration 92%.
- The percentage of multibacillary (MB) leprosy patients with no NFI at registration surviving without developing NFI during the observation period was 84%, and for MB leprosy patients with NFI at registration only 36%.
- New episodes of NFI and reactions after registration are common in MB patients.
- Further episodes of NFI in those with long-standing prior impairment at diagnosis is common.
- It is important to continue surveillance for 2 years after registration for NFI in MB patients with long-standing NFI at registration. Active surveillance beyond 2 years is not indicated.

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