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Incidence rates of acute nerve function impairment in leprosy: a prospective cohort analysis after 24 months (The Bangladesh Acute Nerve Damage Study)

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Summary In this paper, the incidence rates and cumulative incidence of nerve function impairment (NFI) and leprosy reactions over 24 months follow-up of the prospective cohort of 2664 new leprosy cases are presented. Graphs showing the cumulative incidence of NFI relative to time since registration are presented. Hazard ratios (HRs) for the development of NFI for four variables are given. The majority of patients who developed NFI after registration did so in the first year (67% of multibacillary (MB) patients, and 91% of paucibacillary (PB) patients who developed NFI). Thirty-three percent of all MB patients who developed NFI after registration did so in the second year of follow-up. No PB patients developed NFI for the first time in the last 6 months of follow-up. However, seven NFI events occurred amongst PB patients in that period, amongst those who had already had one NFI event. The incidence rate (IR) of NFI amongst MB patients was 24/100 person-years at risk (PYAR), and amongst PB patients was 1.3/100 PYAR. The HR for the development of NFI amongst MB patients compared with PB patients was 16 using univariate analysis. Amongst patients who had long-standing NFI present at registration, the IR was 27/100 PYAR compared with 1.7/100 PYAR amongst those who did not have long-standing NFI. The HR for developing acute NFI amongst those with long-standing NFI present at registration compared with those without was 14 using univariate analysis. When multivariate regression analysis is applied, the apparently significant univariate HRs for sex and age disappeared. The resultant multivariate HR for leprosy group is 8.8, and 6.1 for the presence/absence of long-standing NFI at registration. In all, 142/166 (86%) of all new NFI events were silent, underlining the need for regular nerve function testing. IRs are presented for the four 6-month periods of the 24-month follow-up. They show a clear stepwise reduction over the total period. The IRs amongst MB patients and those with long-standing NFI present at

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registration are very high at 34 and 41/100 PYAR, respectively, for the first 6 months of follow-up. Even during the final 6-month period, the IR is maintained at a moderately high level (18 and 15/100 PYAR, respectively).

Introduction

Nerve function impairment (NFI) in leprosy is the key outcome of the pathological processes involved in infection by *Mycobacterium leprae*. In order to understand more clearly the epidemiology of NFI and its incidence, risk factors and response to treatment, a prospective cohort study has been initiated at the Danish Bangladesh Leprosy Mission (DBLM), and its design, methodology and intake status have been described in an earlier paper.[1]

NFI results from a variety of pathological and immunological processes taking place in peripheral nerves. These include the presence of *M. leprae* in the nerve, trauma, oedema causing increased intraneural pressure, vascular changes and hypersensitivity granuloma.[2] 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.[3] 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',[4] 'silent neuropathy'[5] or 'quiet nerve paralysis'.[6] Van Brakel has suggested that epidemiologically silent neuropathy is not equivalent to a 'reversal reaction expressing itself in the nerves', but has multiple aetiologies.[5]

In this paper, the incidence rates (IRs) and cumulative incidence of NFI and other reactive phenomena amongst patients in the BANDS cohort are presented for different risk variables (or categories of risk factor) including leprosy group (PB/MB), sex, age and presence or absence of long-standing NFI at registration. Cox's proportional hazards regression analysis has been carried out to determine the HRs of the four variables using both univariate and multivariate methods.

Follow-up of patients included in the cohort is continuing 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 analysis presents the results at 24 months of follow-up.

Materials and methods

THE PATIENT COHORT AND FOLLOW-UP

The study group is the cohort for the Bangladesh Acute Nerve Damage Study (BANDS).[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. 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 reversal reaction caused skin patches that had been invisible at the time of registration to become visible, thus making 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] Patients have completed at least 24 months of follow-up after registration, and all analysis in this paper is based on that 24-month period.

Analysis will focus on the incidence of new nerve function impairment (NFI) during follow-up as the main outcome. The definition of NFI used is as follows:

Sensory NFI: 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 NFI: 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 are described in the earlier paper.[1] The testing methods have been validated in a separate publication.[7] 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

IRs have been calculated using the number of patients developing NFI or reactions as the numerator, and cumulative person-years at risk as the denominator, expressed as 100 person-years at risk (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 24 months from the time of registration. Patients were censored 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).

Graphs showing the cumulative incidence of NFI against time since registration amongst the cohort patients are shown. These curves show the probability of developing NFI at any given time, and are the inverse of survival curves. The log rank test has been carried out to assess the significance of differences between the curves at the mid-points in follow-up, i.e.12 months, and the *P*-value has been given on the graphs. The cumulative incidence at 24 months is also given numerically in the tables.

Cox's proportional hazards regression analysis (using a backward stepwise method) has been carried out to determine the hazards ratio for the four variables.[8] Univariate analysis shows the HR for each variable considered separately, and multivariate analysis has been used to build a model fitted to the data in order to determine the prognostic strength of each variable for the development of NFI. The univariate HR is more accurate than a simple relative risk calculated using a 2×2 table, since it makes allowance for censoring of patients from the calculation once they develop an event. However, the HR may be interpreted in the same way as relative risk.

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 person-years at risk) 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

Four variables have been selected for analysis. They are: sex, leprosy group (MB/PB), age (adult/child) and the presence or absence of long-standing NFI at registration (i.e. >6 months duration). These four 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. Classification into MB and PB for treatment purposes is usually carried out using either the WHO method of counting skin patches[9] or a similar procedure such as the Bangladesh system of counting patches and enlarged nerves,[10] in combination with skin smear results.

As already mentioned, all patients with acute NFI/reaction (≤6 months duration) needing treatment 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, 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 or are not at increased risk of developing another episode.

The reliability of long-standing NFI present or absent at registration as a predictive variable for NFI outcome was tested by carrying out a Cox's multivariate regression analysis using sex, leprosy group and age as dependent variables, to see whether there was a significant difference between the two groups with long-standing NFI present or absent.

Proportions and rates have been expressed using two-digit precision.

Results

STATUS OF THE COHORT AT 24 MONTHS, AND TREATMENT COMPLETION RATE

Table 1 shows the status of the BANDS cohort patients at 24 months from the time of registration. 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. Of these, 2127 completed PB/MDT within 9 months, a treatment completion rate of 96%. It is not possible to calculate treatment completion rates for the MB group since 36 months has not yet elapsed for all MB patients. Relapse rates have not been presented since 2 years of follow-up is not long enough to assess this in the standard way.

PROPORTION OF PATIENTS DEVELOPING ACUTE NFI FOR THE FIRST TIME DURING FOLLOW-UP, AND TOTAL NUMBER OF NFI EVENTS OCCURRING IN THE COHORT.

Figure 1 shows the number of patients who had developed NFI by the time of registration and during 24 months of follow-up, divided into 6-month periods, and broken down by leprosy group. Ten percent (7.6–14) of all MB patients had NFI present at the time of registration, and a further 25% (21–30) went on to develop NFI during the first 24 months of follow-up

Table 1. Status of BANDS cohort patients at 24 months from registration. Fourteen patients who were originally classified PB at registration were reclassified as MB during follow-up (see text)

Status at 24 months	Patients who were classified MB at registration	Patients who were classified PB at registration	Total
Continuing regular follow-up	398 90%	2061 93%	2459 92%
Lost to follow-up	33 7.4%	102 4.6%	135 5.0%
Died	11 2.5%	28 1.3%	39 1.5%
Transferred to other project	2 0.5%	29 1.3%	31 1.2%
Total	444 100%	2220 100%	2664 100%

(rounding up the hidden decimal places), which is a total prevalence of acute NFI of 36% (31–40) amongst MB cases from registration to the end of 24 months follow-up. Amongst PB cases, 2.0% (1.5–2.7) had acute NFI present at registration, and a further 2.4% (1.8–3.2) went on to develop an episode of NFI during follow-up, which is a total of 4.4% (3.6–5.4). In 35% (29–41) of all patients with acute NFI, the event took place before registration. Conversely,

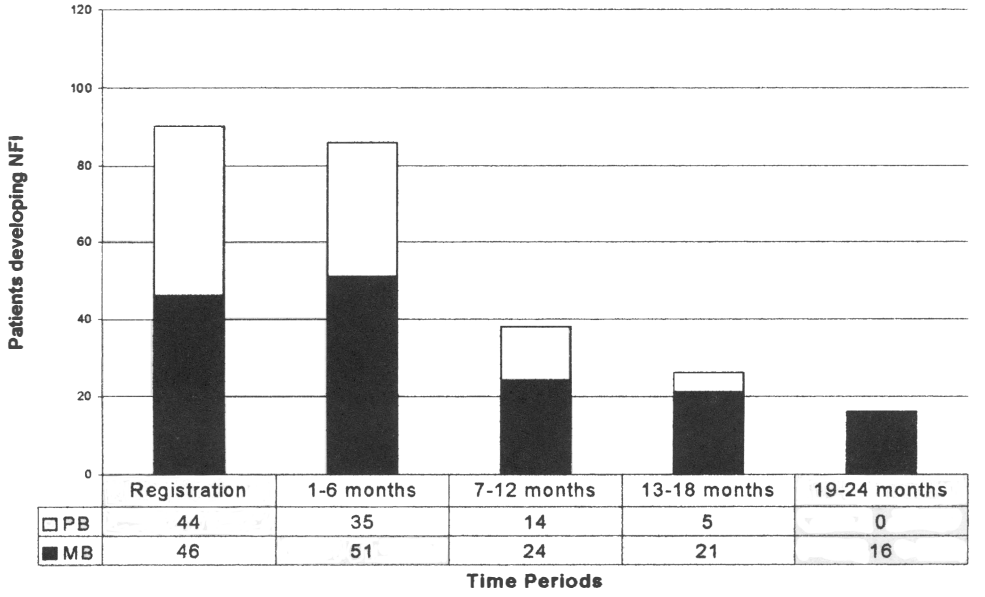

Figure 1. Bar graph and table showing number of patients developing NFI by registration time and during 24 months of follow-up (first NFI event only).

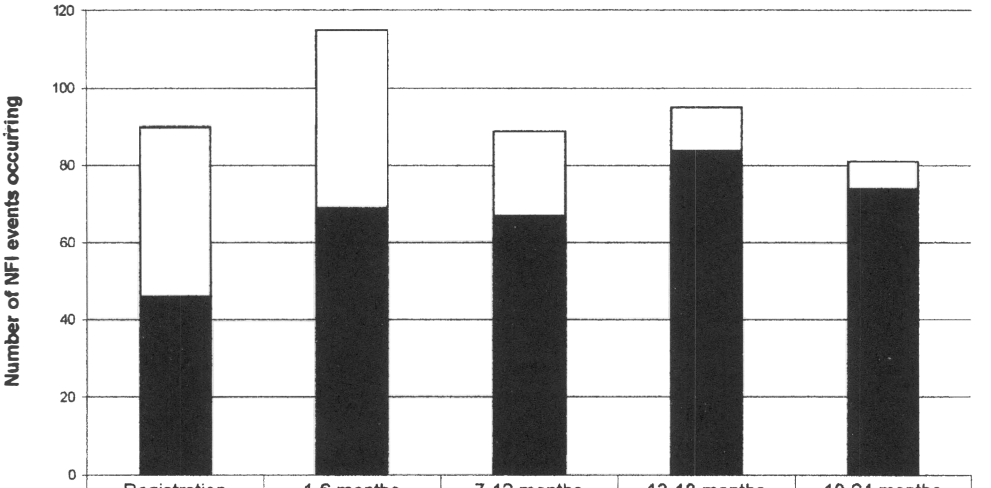

Figure 2. Bar graph and table showing total numbers of NFI events occurring in BANDS cohort by registration and during 24 months of follow-up.

68% (59–71) of all acute NFI events took place after registration. Amongst PB patients who had acute NFI, the proportion who had their NFI event before registration [45%, (35–55)] is higher than for MB patients [29% (22–37)]. The majority of patients developing NFI after registration did so in the first year [75%, (67–81)], around half of them in the first 6 months [52%, (44–60)]. No new PB patients developed NFI after 18 months of follow-up. However, new MB patients continued developing NFI after the first year, although the number reduced. In all, 9.6% (5.8–15) of all patients who developed NFI during follow-up did so in the final 6 months, all of them MB patients.

Although most MB patients who developed NFI during treatment did so in the first year after registration, a third did so in the second year [33%, (25–43)]. For the PB group, 9.3% (3.5–21) of those who developed NFI during follow-up did so in the second year, all of those in the first 6 months of that year. Of the total cohort, 8.3% (6.0–11) of the MB patients developed new NFI in the second year of treatment, compared with 0.2% (0.1–0.6) of the PB patients.

Figure 2 shows the total number of NFI events (Figure 1 shows *patient* numbers developing NFI) occurring during the 24-month follow-up period, again presented in 6-month blocks with breakdown by leprosy group. The pattern is quite different from that of Figure 1, and is due to the number of patients who developed repeated NFI events. Whilst Figure 1 shows that the number of *patients* developing NFI for the first time diminishes over 2 years, the total number of NFI events does not diminish to the same extent, the numbers being sustained by a core of patients who suffered repeated events of NFI. Indeed, the number of NFI events amongst MB patients is nearly *constant* over the 2 years. The number of events amongst PB patients is smaller, but seven events [8%, (3.6–17)] occurred in the last 6 months, during a time when no new patients developed a new NFI event.

Table 2. Incidence rates and cumulative incidence of NFI amongst BANDS cohort patients for 4 risk variables over 24 months follow-up period

Type of NFI	Category	Risk factors	Total cases	Case with events	Incidence rate (events per 100 PYAR)	Cumulative incidence at 24 months
All NFI	None	All	2510	166	3.7	0.069
	Sex	Male	1371	113	4.7	0.087
		Female	1139	53	2.5	0.049
	Group	MB	357	112	24.4	0.369
		PB	2153	54	1.3	0.026
	Age	≥15 (adult)	2049	155	4.3	0.079
		≤14 (child)	461	11	1.3	0.025
	Long-term NFI at registration	Present	264	96	26.6	0.392
		Not present	2246	70	1.7	0.033
SensoryNFI	All	None	2510	123	2.7	0.052
	Sex	Male	1371	83	3.5	0.064
		Female	1139	40	1.9	0.037
	Group	MB	357	85	18.5	0.292
		PB	2153	38	0.9	0.018
	Age	≥15 (adult)	2049	118	3.3	0.061
		≤14 (child)	461	5	0.6	0.012
	Long-term NFI at registration	Present	264	78	21.6	0.333
		Not present	2246	45	1.1	0.021
Motor NFI	All	None	2510	60	1.3	0.026
	Sex	Male	1371	41	1.7	0.032
		Female	1139	19	0.9	0.018
	Group	MB	357	43	9.4	0.162
		PB	2153	17	0.4	0.008
	Age	≥15 (adult)	2049	52	1.4	0.027
		≤14 (child)	461	8	0.9	0.018
	Long-term NFI at registration	Present	264	27	7.5	0.129
		Not present	2246	47	0.8	0.016

RELIABILITY OF LONG-STANDING NFI AS A PREDICTIVE VARIABLE

A Cox multivariate analysis showed no significant difference between the two groups of patients defined by the presence or absence of long-standing NFI at registration. *P*-values for interaction were 0.14 for sex, 0.18 for leprosy group and 0.63 for age. It was concluded that the presence/absence of long-standing NFI at registration is acceptable to use in analysis.

INCIDENCE RATES AND CUMULATIVE INCIDENCE OF NERVE FUNCTION IMPAIRMENT, TYPE 1 REACTION AND SILENT NFI DURING FOLLOW-UP

Table 2 shows the IRs expressed per 100 person-years at risk (PYAR) of NFI, and the cumulative incidence at 24 months. Results are shown for all episodes of NFI (including 'silent' NFI, and NFI occurring as part of a type 1 or type 2 reaction), and for sensory and motor NFI separately. The definition of NFI used strictly follows the definitions given in the

Table 3. Incidence rates and cumulative incidence of type 1 reaction amongst BANDS cohort patients for four risk variables over 24-month follow-up period

Category	Risk factors	Total cases	Cases with events	Incidence rate (events per 100 PYAR)	Cumulative incidence at 24 months
All	None	2510	62	1.4	0.026
Sex	Male	1371	41	1.7	0.032
	Female	1139	21	1.0	0.020
Group	MB	357	49	10.7	0.169
	PB	2153	13	0.3	0.006
Age	≥15 (adult)	2049	54	1.5	0.028
	≤14 (child)	461	9	1.1	0.021
Long-term	Present	264	11	3.1	0.051
NFI	Not present	2246	51	1.2	0.024

earlier paper.[1] For all NFI events, the IR amongst MB cases of 24/100 person-years at risk (PYAR) compares with 1.3/100 amongst PB cases. For the risk factor of presence of long-standing NFI at registration, the IR is even higher at 27/100 PYAR compared with 1.7/100 PYAR amongst those without NFI at registration. The IR amongst males (4.7/100 PYAR) is approximately double that amongst females (2.5), and that amongst adults (4.3) over three times that amongst children (1.3). The cumulative incidences parallel the IRs.

Overall, the incidence rate of sensory NFI (SNFI) is double that of motor NFI (MNFI) (IR = 2.7/100 PYAR cf. 1.3/100 PYAR) in the cohort. The IR of SNFI amongst patients with long-standing NFI is proportionately higher compared with that for MNFI , the rate being triple rather than double (22/100 PYAR for SNFI, cf. 7.5/100 PYAR for MNFI).

Table 3 shows the same statistics for type 1 reaction. type 1 reaction as defined for Table 3 means patients with a skin reaction with or without NFI. The overall IR for type 1 reactions is nearly a third of the rate for NFI, 1.4/100 PYAR compared with 3.7/100 PYAR. There is an interesting contrast in IRs between the type 1 reaction patients and the NFI patients. There is a 15-fold difference between the IRs for development of NFI amongst the patients in the presence/absence of NFI at registration category (27 versus 1.70); but only a 2-fold difference in the same category for the development of type 1 reaction (3.1 versus 1.2).

Table 4 shows IRs and cumulative incidences for patients with silent NFI (silent neuropathy). The pattern for silent NFI is very similar to that for NFI in general, which is not surprising since the majority of NFI cases were in fact silent (142/166, 86%). The IR for silent NFI is 3.2/100 PYAR.

TYPE 2 REACTIONS

Only eight patients developed a type 2 reaction during follow-up, an IR of 1.6 events per 100 PYAR amongst the MB leprosy group.

GRAPHS SHOWING CUMULATIVE INCIDENCE OF DEVELOPING NFI

Figures 3, 4, 5 and 6 show the cumulative incidence of NFI over the 24 months of follow-up. The four graphs show curves for the respective variables of sex, leprosy group, age, and

Table 4. Incidence rates and cumulative incidence of silent NFI amongst BANDS cohort patients for 4 risk variables over a 24-month follow-up period

Category	Risk factors	Total cases	Cases with events	Incidence rate (events per 100 PYAR)	Cumulative incidence at 24 months
All	None	2510	142	3.2	0.060
Sex	Male	1371	95	4.0	0.074
	Female	1139	47	2.3	0.043
Group	MB	357	93	20.3	0.322
	PB	2153	49	1.2	0.023
Age	≥15 (adult)	2049	135	3.7	0.070
	≤14 (child)	461	7	0.8	0.016
Long-term NFI	Present	264	86	23.9	0.363
	Not present	2246	56	1.4	0.026

presence or absence of long-standing NFI at registration (i.e. >6 months duration). All four curves show significant differences between the four pairs of risk factors, which are most marked for leprosy group and the presence/absence of long-standing NFI at registration. The log rank test shows the difference between survival probabilities at 12 months to be statistically significant with a P-value of <0.001 for all four curves (χ^2 with 1 df for male/female = 14; for MB/PB = 265; for adult/child = 14; for long-standing NFI present/absent at registration = 326).

INCIDENCE RATES OF NFI DURING 6-MONTH BLOCKS OF FOLLOW-UP

Table 5 shows the IRs for development of the first event of NFI, expressed for the four 6-month periods comprising the 24 months of follow-up. The number of events occurring

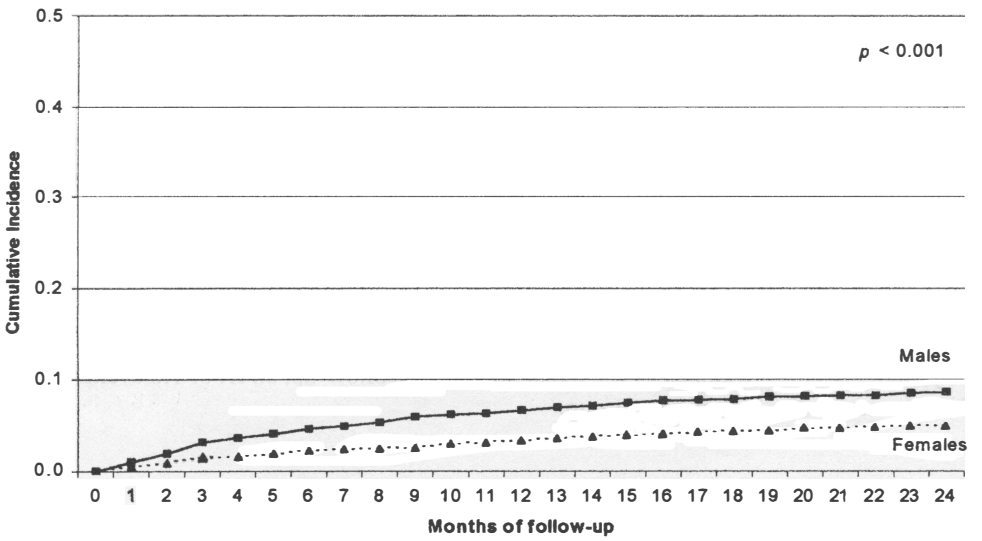

Figure 3. Cumulative incidence of NFI amongst 1371 males and 1139 females during 24 months of follow-up.

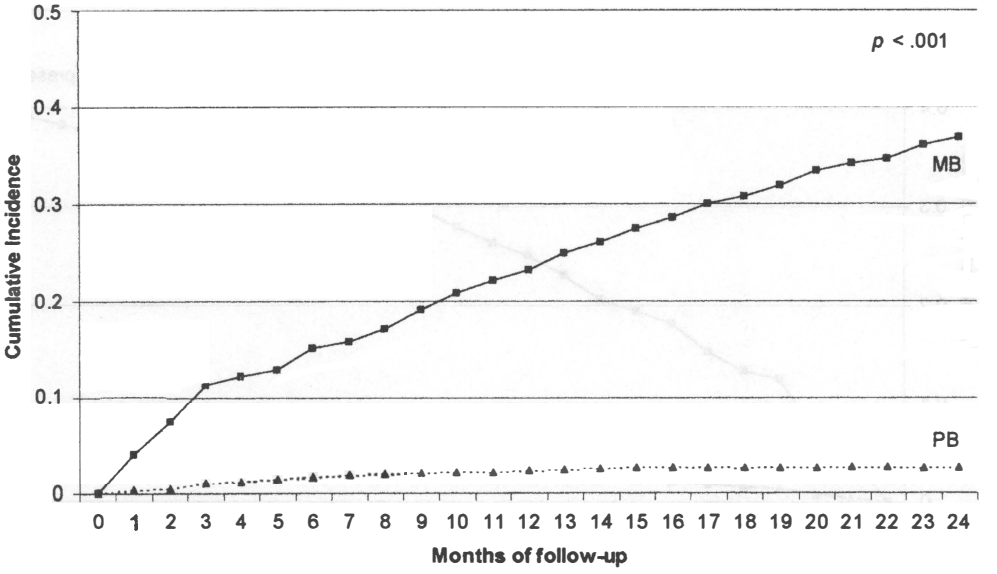

Figure 4. Cumulative incidence of NFI amongst 357 MB and 2153 PB patients during 24 months of follow-up.

during these 6-month periods have been summed to produce the numerator, and the number of days at risk during that period only used for the denominator. These IRs have been calculated for the four different risk variables of sex, leprosy group, age, and presence or absence of long-standing NFI at registration. For each variable there is a stepwise reduction in IR for successive 6-month periods. The IR amongst MB patients during the first 6 months

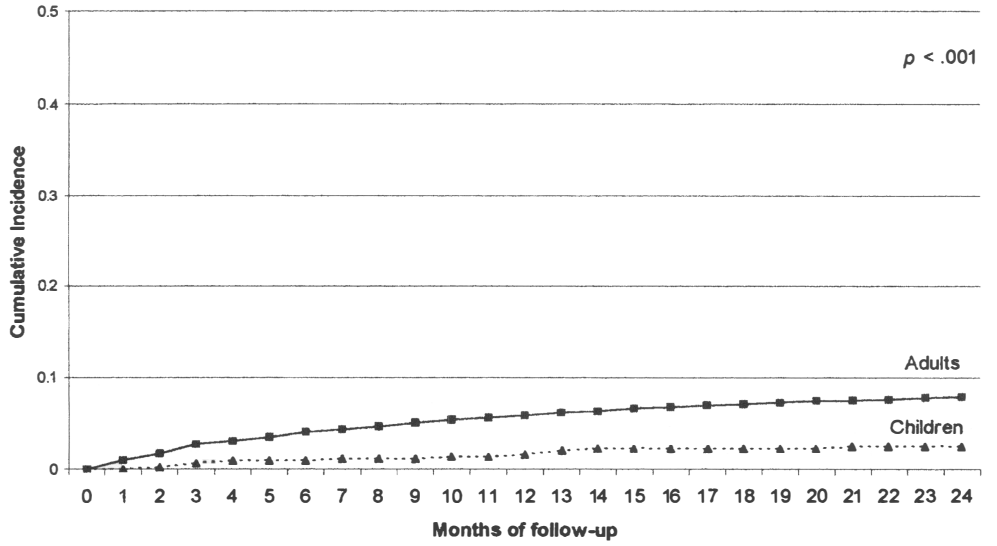

Figure 5. Cumulative incidence of NFI amongst 2049 adults and 461 children during 24 months of follow-up.

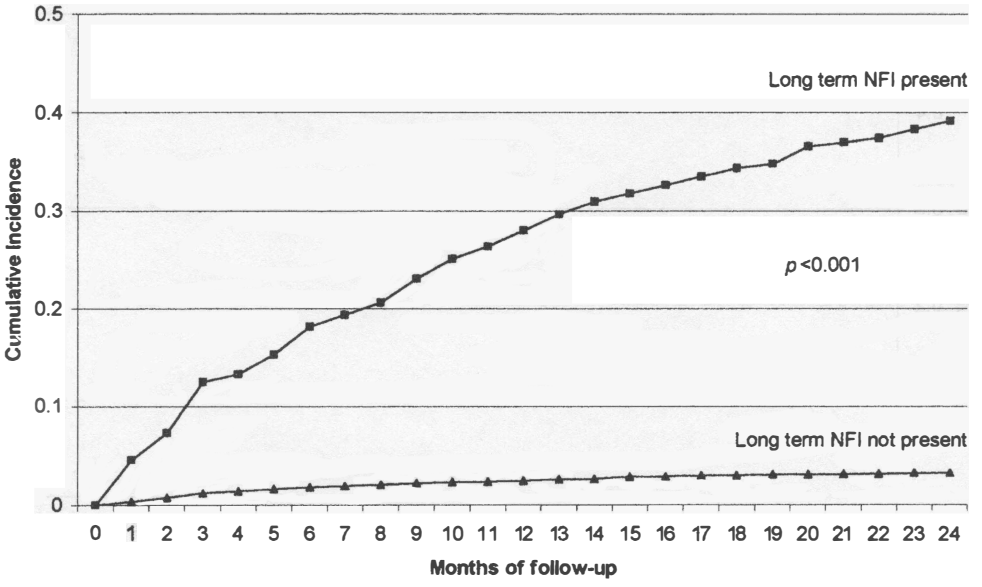

Figure 6. Cumulative incidence of NFI amongst 264 patients with long-standing NFI present at registration and 2246 patients without.

after registration is very high at 34/100 PYAR, and this has only halved to 18/100 by the last 6 months of follow-up. However, for the PB group the low IR of 3.3/100 PYAR has reduced to zero by the last 6 months of follow-up. Amongst patients with and without long-standing NFI at registration, a similar but even more marked pattern exists. Here, the IR amongst patients

Table 5. Incidence rates for NFI by 6-month period amongst BANDS cohort patients, for four risk variables over 24-month follow-up period

			Cases with events				Incidence rate (events per 100 PYAR)			
			Months of follow-up				Months of follow-up			
Category	Risk factor	Total cases	1–6	7–12	13–18	19–24	1–6	7–12	13–18	19–24
All	None	2510	86	38	26	16	7.2	3.3	2.4	1.5
Sex	Male	1371	62	26	15	10	9.5	4.3	2.6	1.8
	Female	1139	24	12	11	6	4.36	2.26	2.16	1.20
Group	MB	357	51	24	21	16	33.8	20.00	20.9	18.3
	PB	2153	35	14	5	0	3.3	1.4	0.5	0.0
Age	≥15 (adult)	2049	82	35	23	15	8.4	3.8	2.6	1.8
	≤14 (child)	461	4	3	3	1	1.78	1.4	1.4	0.5
Long-term NFI	Present	264	46	24	15	11	40.61	25.44	18.8	15.1
	Not present	2246	40	14	11	5	3.68	1.34	1.1	0.5

Table 6. Univariate and multivariate regression coefficients and hazard ratios for NFI outcome amongst BANDS cohort patients calculated for four risk variables

	Univariate analysis			Multivariate regression model		
Variable	Regression coefficient	Hazard ratio	(95% CI)	Regression coefficient	Hazard ratio	(95% CI)
Sex	0.066	1.8	(1.3–2.5)	0.012	1.3	(0.9–1.8)
Group	0.331	16.5	(11.9–22.8)	0.237	8.8	(6.2–12.5)
Age	0.070	3.3	(1.8–6.1)	0.016	1.7	(0.9–3.1)
Long-term NFI at registration	0.333	14.5	(10.6–19.4)	0.206	6.1	(4.4–8.6)

with long-standing NFI present is 41/100 PYAR, reducing by a factor of nearly 3–15/100 PYAR in the last 6 months of follow-up. Amongst patients with no long-standing NFI present at registration, the IR in the first 6 months is 3.7/100 PYAR, reducing by a factor of over 7–0.5/100 PYAR by the end of follow-up. The IR in the first 6 months amongst males is higher (9.5/100 PYAR) than for females (4.4/100 PYAR) but by the end of follow-up there is virtually no difference. Adults had a higher IR than children (8.4 versus 1.8/100 PYAR) in the first 6 months, reducing to 1.8 and 0.5, respectively, by the end of follow-up. However, numbers of children involved were small.

Table 6 shows the results of the Cox proportional hazards regression analysis. The HRs under univariate analysis shows the risk of developing NFI for four variables considered separately. All four variables all have significant prognostic strength with HRs of 1.8 for male sex, 3.3 for adult age, 14 for presence of long-standing NFI at registration and 16 for MB leprosy group. However, when the four variables are entered into a multivariate analysis, the model created does not show quite the same picture. The variables of leprosy group and presence/absence of long-standing NFI at registration still have significant HRs of 8.8 (95% CI 6.2-12) and 6.1 (4.4-8.6) respectively, but the HRs for sex and leprosy group are not significant at the 5% level (limits for the 95% CI fall below 1). This shows that it is the risk factors of leprosy group and presence/absence of long-standing NFI at registration that are the key determinants of future NFI risk.

Discussion

PROPORTIONS OF PATIENTS DEVELOPING EPISODES OF NFI

The published prevalence of reversal reactions and NFI occurring at first examination and during MDT has been comprehensively reviewed.[11,12] Amongst MB patients in field-based studies, they range from 9.6% in Indonesia[13] to 41% in Ethiopia,[14] placing the results of this study, 36% with acute NFI, near the top end of the range. However, there are considerable problems with comparison of results since the definition of 'reversal reaction' varies from one study to another. In addition, definitions of PB and MB classifications are not consistent. Amongst PB patients in this study, the proportion of 4.4% developing NFI either before or after registration compares with the results from other studies, ranging from 3.7 to 14%. Amongst both MB and PB cases, the majority of new NFI occurred *after* registration. Schreuder found that the majority, 82% of PB cases developing reversal reaction, did so before registration.

The majority of patients in the study developing NFI events did so in the first year (75%), and this is a common finding.[11–13,15] Although the proportion of patients experiencing their first NFI event diminishes with time, amongst MB patients there is a moderate number who have their first episode after 18 months of MDT (10.1% of all those who develop NFI, 3.6% of all MB patients). This highlights the importance of *continuing vigilance* after registration for at least 2 years, especially in the case of MB patients, and probably thereafter as well since it is known that NFI and reactions continue after 2 years.[11] These results are important, since treatment regimens are becoming shorter. The WHO is now recommending 12-month treatment for MB cases, and a 6-month course for PB cases with two to five skin patches.[16] Active surveillance may cease after treatment has been completed for both MB and PB cases in many LCPs, making it very important both to educate patients adequately about the symptoms of NFI and reaction, and to make it easy for such patients to refer themselves back to leprosy clinics. Fortunately, there is evidence that such an approach is effective for most patients who develop late reactions.[17]

INCIDENCE RATES OF NFI AND REACTIONS, AND HAZARD RATIOS

A broad pattern emerges, indicating that the IRs of NFI, type 1 skin 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. In addition, incidences are higher amongst males than females and adults than children, although the differences are much less marked. However, there are problems with nerve function testing in children, so results must be interpreted with caution. Other studies show a similar picture amongst MB and PB patients, although the rates given are lower than those in the present study: 1/100 PYAR amongst PB cases and 12/100 amongst MB cases in Nepal;[12] 1/100 and 6/100 respectively in an earlier, retrospective study at DBLM in Bangladesh;[18] and 1.9/100 PYAR during the first 6 months of PB/MDT, 14/100 PYAR during 24 months of MB/MDT in Thailand.[11] These compare with rates of 1.3 and 24/100 PYAR respectively in the present study. Again, comparisons must be made with caution, since there is a lack of agreement between authors about definitions of reactive events.

In Nepal, van Brakel found that the risk of developing NFI was 5 times greater amongst patients with 'extensive disease' (three or more body areas involved, roughly equivalent to our MB classification) than amongst patients with more limited disease;[19] this is similar to the finding of a significant HR of 8.8 in the multivariate analysis. Van Brakel highlighted the importance of the presence of extensive disease, identified by a body area count, as an indicator of the risk of reversal reaction. The present study strongly supports this evidence. However, Roche and others only found an odds ratio of 1.3 for 'neural type 1 reaction' in a retrospective study, also carried out in Nepal.[20]

In this study, the IR amongst patients with long-term NFI present at registration is even higher than that amongst MB cases (27 versus 24/100 PYAR amongst MB patients), and this has emerged as another strong risk factor for the development of NFI after registration, with a HR of 14 in the univariate and 6.1 in the multivariate analysis. Roche found that a disability index of >0 carried an odds ratio of 2.6 for 'neural type 1 reaction';[20] however, Schreuder found that a WHO disability grade of 1 or 2 was not a significant risk factor for the development of a reversal reaction during treatment, although it was a significant risk-factor for reversal reaction present at the time of registration.[11] In Ethiopia, de Rijk and others found that PB patients with WHO disability grade 1 or 2 had significantly more NFI/reactive events

than those without disability, but that was not true for MB patients.[14] It is true that MB leprosy group and the presence of long-standing NFI at registration overlap to a certain extent, NFI being more common amongst MB patients. However, there are a large number of MB patients who do not have impairment at registration.

Whilst the IR was higher amongst males compared with females, and adults compared with children, this was much less marked than with the other two risk variables. Neither van Brakel nor Roche found that male sex had a statistically significant predictive value for the development of type 1 reaction.[12,20] The multivariate analysis carried out here shows that the apparently significant predictive strength of age and sex are not significant at the 5% level in a multivariate model which includes leprosy group and presence/absence of long-standing NFI at registration as co-variables. This indicates that it is leprosy group and the presence/absence of NFI at registration which are the key risk factors for predicting future NFI amongst leprosy patients and that age and sex can safely be ignored as risk factors.

It is interesting that whilst the IR of NFI amongst patients with long-standing NFI present at registration is 15 times higher than amongst those without, it is only twice as high for type 1 reactions. It appears that the two types of reaction, one with a skin component and the other without, are independent of each other, supporting immunological evidence of antigenic heterogeneity between patients with skin and nerve disease predominating.[21] A study in Hyderabad, India found that a first symptom-to-reaction time amongst patients with neurological symptoms was twice as long as that amongst patients with skin symptoms.[22] Roche found that only 7% of cutaneous type 1 reactions occurred after 6 months of treatment, but 32% of neural type 1 reactions,[23] again supporting the view that skin and nerve reactions are relatively independent of one another.

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,[12,14] 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. The IR of silent NFI, 3.2/100 PYAR, is close to that found in Nepal (4.1).[5] It is perhaps more informative to compare the IRs of type 1 reaction with this silent NFI group, since the cases included in these two are mutually exclusive ('All NFI' patients include 24 who were included in the 'type 1 reaction' group). The differences noted in the paragraph above are even more marked when this comparison is made.

The IR for SNFI is over double that for MNFI (2.7 versus 1.3/100 PYAR, respectively). This study used the ballpoint test. Rates for SNFI could be expected to be relatively higher if more sensitive tests were performed using graded monofilaments. Van Brakel found rates considerably higher than ours (SNFI, 13/100 PYAR; MNFI, 7.5/100 PYAR[19]), but his study had a higher proportion of MB patients. In the present study, rates of SNFI and MNFI were much higher amongst the MB group (19 and 9.37/100 PYAR, respectively). It is sensory impairment which is potentially more damaging for patients, since loss of protective sensation can lead to ulceration and loss of digits unless the patient exercises great care.

The graphs showing cumulative incidence are the graphical complements to the IRs and RRs. They show clear differences in incidence between the risk factors in each category, much more marked for leprosy group and presence/absence of long-term NFI than for sex and age, although all of the differences shown are statistically significant ($P < 0.001$). These curves bring into even sharper focus the importance of considering leprosy group and presence/absence of long-term NFI at registration time in predicting the probability of developing NFI after registration.

The IRs presented for successive 6-month periods during follow-up (cf. Table 5) show some interesting trends. These statistics show as rates per 100 PYAR what was expressed as a simple proportion in Figure 1. During the first 6 months the IRs for all risk variables are at their highest, and it is during this period that patients and leprosy control staff need to be at their most vigilant, especially for MB patients and patients with a history of NFI present at registration.

It should be borne in mind that these findings are being presented at a relatively early stage and that there is one more year of follow-up for PB patients and three more for MB patients to run in the study. There is an incidence of 'late' reversal reactions or NFI occurring in the third and fourth years after RFT, although amongst PB patients this is almost zero. In Malawi only 2/17 reversal reactions occurred after the first year, since RFT amongst 498 PB patients (0.4%),[24] and there were none in Thailand.[11] At Karigiri, India, only 11 patients (1.1%) of 980 MB leprosy patients developed a reaction during 10 years of post-MDT surveillance, and most of these did so within the first 3 years.[25] In Thailand, 2/218 MB patients (1%) had a reversal reaction, and 1/218 (0.5%) an episode of silent neuropathy in the third year after registration. Given these very low incidences, it is safe to assume that the figures presented in this study for 2 years of follow-up are close to the total number that will occur.

Eight patients developed an ENL reaction during treatment, out of 84 BL and 51 LL patients in the cohort. Only one patient at registration had an ENL reaction present, bringing the total to nine (6.7% of lepromatous patients). This compares with 12% found in Thailand,[11] 17/175 (9.7%) in Nepal,[12] 11% in Zaire[26] and only 2/149 (1.3%) in Ethiopia.[14]

In conclusion, an analysis of NFI events occurring in a large prospective cohort of newly registered leprosy patients has been carried out. Whilst most NFI events occurred either before registration or during the first year after the start of MDT, amongst MB patients almost a third occurred in the second year of MDT. The IRs of NFI amongst MB patients and those with long-standing NFI present at registration are particularly high, and whilst the IR reduced over time, it was maintained at a moderately high level amongst these latter two groups of patients even at the end of follow-up. The presence of long-standing NFI at registration and MB group have emerged as important predictors for the development of NFI after registration in a regression model which included age and sex as co-variables. The subject of predicting NFI and the development of a prediction rule is an important area requiring further investigation, both for understanding the pathogenesis of nerve damage in leprosy and implementing leprosy control programmes.

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