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Delay in presentation, an indicator for nerve function status at registration and for treatment outcome—the experience of the Bangladesh Acute Nerve Damage Study cohort

P. G. NICHOLLS*, R. P. CROFT**,
J. H. RICHARDUS***, S. G. WITHINGTON+ &
W. C. S. SMITH*
**Department of Public Health, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen, AB25 2ZD, UK*
***56A St Peters Road, Reading, RG6 1PH, UK*
****Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands*
+The Leprosy Mission Bangladesh, House 17a, Road 3, Banani DOHS, Dhaka, Bangladesh

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Summary The objective of our research was to relate delay in presentation in the Bangladesh Acute Nerve Damage Study cohort to intake status and to treatment outcome. The Bangladesh Acute Nerve Damage Study (BANDS) is a prospective cohort study of 2664 consecutive newly registered patients at clinics run by the Danish-Bangladesh Mission Leprosy (DBLM) project in Nilphamari, northern Bangladesh. The 1-year intake began in April 1995. Three-year follow-up for PB cases and 5 years for MB cases was completed in 2001. Delay in presentation in the BANDS cohort is associated with increased signs of nerve function impairment at registration. Individuals presenting with no nerve impairment and maintaining nerve function to the end of follow-up had the shortest mean delays. Individuals presenting with impairment that did not improve during follow-up had the longest mean delays. Discussion focuses on the value of setting a threshold value defining early presentation. Since the WHO Grade 2 disability rate effectively sanctions lengthy delays where there is no impairment, an indicator relating directly to delay is preferred as an indicator for good practice in leprosy control.

Introduction

Delay in presentation has been identified as an important factor contributing to grade 2 (visible) disability as defined by WHO.[1] In Ethiopia, Meima *et al*.[2] found an overall grade 2

Correspondence to: P. Nicholls (e-mail: public_health@abdn.ac.uk

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disability rate of 23%. Disability increased with delay, so for individuals delaying 3–4 years the rate was 67% and for individuals delaying more than 4 years the rate was 81%. Schreuder reported similar findings in Thailand.[3] In Zimbabwe, longer delays were linked to men, to older age groups and to MB disease.[4]

While it is apparent that delay in presentation is closely related to disability, the acute signs arising from reactions are often the triggers to presentation. Hastings[5] describes the reactional episodes responsible for virtually all the signs of the disease that arise acutely, often forcing those affected to seek medical attention for the first time. It follows that some individuals experiencing the signs of reaction present earlier than they might otherwise have done.

The grade 2 disability rate has been identified as a convenient indicator of progress in leprosy control 1. ILEP statistics for 2000–2001[6] show a global WHO grade 2 disability rate of 4%, a substantial reduction compared to earlier years. However, 34 countries continue to report rates of 10% or more. In total, there are 102 projects with more than 100 new case registrations in the year where the rate exceeds 10%. In 26 of these it exceeds 20%. Such evidence suggests inadequacies in efforts to achieve early detection, a principle central to efforts to eliminate leprosy.[7] The situation is not limited to countries where leprosy continues as a public health problem. In countries that have already reached the elimination target reduced awareness of the disease and failure to treat those presenting threatens to reverse the progress already made.[8]

In earlier publications, we described the patients enrolled in the Bangladesh Acute Nerve Damage Study (BANDS), the incidence and risk factors for new nerve function impairment (NFI) during follow-up and the treatment outcomes.[9–13] The present research is concerned with outcomes related to delay in presentation, recorded as duration of symptoms at registration. Our focus is on overall delay and its implications for the patient at the time of presentation through to the time of final assessment and discharge from follow-up.

Materials and methods

The BANDS cohort is formed by the 2664 patients newly registered for multi-drug therapy (MDT) during the 12 months from April 1995 to March 1996. Patients were registered at rural and urban clinics run by the Danish Bangladesh Leprosy Mission, centred on Nilphamari in north-west Bangladesh, serving a population of around 6 million people. The follow-up period was 3 years for paucibacilliary (PB) cases and 5 years for multibacilliary (MB) cases. Nerve enlargement was assessed at registration. Full details of the research design and methods have been presented in an earlier publication,[9] including arrangements for sensory and motor testing. The resulting data were entered on computer in a FoxPro database. The present analysis has relied on purpose-written Dbase programs and EPI-INFO procedures. The identification of risk factors used logistic regression procedures within STATA. We used the non-parametric Kruskal–Wallis test to assess differences in delay between groups.

An important issue underlying the present analysis relates to the unreliability of patients' estimates of time since first symptom. At registration, clinic staff were instructed to validate the patient's reported duration of symptoms by cross-checking against significant family, local or national events or religious festivals. Staff also enquired about early symptoms that might not have been considered important by the patient. In each case, this process resulted in a best estimate of duration of symptoms at the time of registration that was recorded on

patient record cards in years and months. It may be assumed that, for shorter delays, this procedure addressed patient's tendency to report delay in 6 month or 12 month units. Longer delays will have been little changed.

Results

DELAY IN PRESENTATION, DEMOGRAPHIC AND CLINICAL VARIABLES

Table 1 provides a demographic profile of the study cohort and summarizes delay in presentation. Mean delay for the whole cohort of 2664 individuals was 27·8 months, median 12 months. We found no significant difference in delay between men and women, but we did find statistically significant differences in delay between age groups with a trend towards increasing delay with age ($P < 0{\cdot}01$). The oldest age group (65+ years) had a mean delay more than 3 times that of the youngest (≤14 years). The median delay for all age groups up to 34 years was 12 months. For age groups 45 years and above, the median was 24 months. Contact survey and referrals by doctors, health workers and others were the most effective in achieving early presentation. Field survey was the most common referral route, but did not achieve early presentation.

Among clinical variables (Table 2), we found mean delay by individuals with grade 2 disability double that for individuals with no disability. While differences between Ridley–Jopling types broadly reflect PB/MB differences the long delays within the pure neural group draw attention to the difficulty in identifying early signs of this type of leprosy. We found individuals treated for reactions at intake had reduced delays ($P < 0{\cdot}01$). For all nerves we found a consistent pattern for definite (2+ point) loss, sensory or motor, to be associated with greater mean delay. We also found a strong association between delay and computed variables reflecting the total of sensory or motor points lost over all nerves. Mean delays were

Table 1. Delayed presentation and demographic variables

	Number of cases	Mean delay	Median delay	Statistical significance
Sex				
Males	1481	28·7 months	12 months	
Females	1183	26·8 months	12 months	
Age groups				
Up to 14 years	469	13·8 months	12 months	
15–24 years	456	20·7 months	12 months	
25–34 years	601	27·9 months	12 months	
35–44 years	528	33·1 months	18 months	
45–54 years	332	37·7 months	24 months	
55–64 years	180	37·8 months	24 months	
65+ years	98	47·3 months	24 months	$P < 0{\cdot}01$
Method of detection				
Survey	1221	32·9 months	18 months	
Voluntary	1133	24·7 months	18 months	
Referred	93	19·5 months	12 months	
Contact survey	217	18·8 months	12 months	$P < 0{\cdot}01$

Table 2. Delay in presentation and clinical variables

	Number of cases	Mean delay	Median delay	Statistical significance
Diagnostic group				
MB	444	28·4 months	18 months	
PB	2220	27·7 months	12 months	$P<0·01$
Leprosy type				
Indeterminate	49	18·7 months	6 months	
TT	263	23·0 months	12 months	
BT	2087	28·3 months	12 months	
BB	18	36·3 months	12 months	
BL	84	22·4 months	12 months	
LL	51	31·4 months	18 months	
PN	112	36·3 months	12 months	$P<0·01$
Skin smear[a]				
Negative	2475	27·9 months	12 months	
1+ to 3+	65	26·4 months	12 months	
4+ to 6+	98	27·9 months	18 months	
WHO grade				
0	2249	25·8 months	12 months	
1	256	31·3 months	12 months	
2	159	51·0 months	24 months	$P<0·01$
BCG scar				
Present	1324	26·8 months	12 months	
Absent	1340	26·9 months	12 months	
Intake reaction status				
Treated	128	18·8 months	12 months	
Not treated	2536	28·3 months	12 months	$P<0·01$
Nerve function status				
No sensory loss	2284	26·0 months	12 months	
1–5 points loss	187	38·7 months	18 months	
6+ points loss	193	39·2 months	24 months	$P<0·001$
No motor loss	2343	26·1 months	12 months	
1005 points loss	249	34·3 months	24 months	
6+ points loss	72	63·2 months	36 months	$P<0·001$

[a] Youngest cases not tested.

greatest amongst individuals presenting with definite motor loss (58 months for definite facial or ulnar loss, 71 months for median loss and 42 months for common peroneal loss).

We found differences in delay between groupings defined by nerve enlargement status at registration. For ulnar, common peroneal and posterior tibial nerves definite (2+ point) enlargement was associated with increased delay ($P<0·01$ in each nerve pair). For facial and median nerves the differences in means failed to reach statistical significance.

Table 3 presents disability rates according to reported delay. It is apparent that a minority of individuals develop significant impairments in a relatively short period.

DELAY IN PRESENTATION, COMPLIANCE AND OVERALL OUTCOME.

Failure to complete MDT is associated with traditional beliefs and behaviour that may also contribute to delay in presentation.[14] We might therefore expect to find an association

Table 3. Patients with disabilities at intake within selected patient groupings

	Delay up to 3 months	Delay 4–6 months	Delay 7–12 months	Delay 13–24 months
All cases				
Grade 1 disability rate	8% (13/159)	8% (34/445)	10% (86/847)	9% (47/513)
Grade 2 disability rate	1% (1/159)	2% (11/445)	4% (34/847)	7% (37/513)
MB cases				
Grade 1 disability rate	20% (2/10)	25% (12/48)	30% (44/148)	23% (28/120)
Grade 2 disability rate	10% (1/10)	8% (4/48)	13% (20/148)	17% (21/120)
PB cases				
Grade 1 disability rate	7% (11/149)	5% (22/397)	6% (42/699)	5% (19/393)
Grade 2 disability rate	0% (0/149)	2% (7/397)	2% (14/699)	4% (16/393)

between delay and incomplete treatment or late release from treatment (RFT). We defined late release from treatment as failure to complete PB MDT in 9 months or MB MDT in 36 months. These are the limits recommended by WHO.[1] Excluding individuals who died or transferred before the projected RFT date, we found that for MB cases the mean delay in presentation for individuals with late RFT or failing to complete MDT was 4 months longer than for cases who completed treatment on time. For PB cases the difference was 10 months. Both of these differences are in the expected direction, but neither reached statistical significance.

Similarly, delay in presentation may be associated with failure to complete follow-up. Again excluding individuals who died or were transferred, the observed differences were in the direction expected but failed to reach statistical significance.

In an earlier publication,[11] we identified leprosy grouping and a history of nerve function impairment (NFI) at registration as risk factors for a first event of NFI during the first 2 years of follow-up. The same publication also reported delay in presentation as a simple univariate risk factor for new NFI [hazard ratio (HR) = 2·1, 95% confidence interval 1·5–2·8]. For the present paper, we extended that analysis to explore relationships between delay and other follow-up events during the 5 years of follow-up data now available. Using a univariate logistic regression procedure we found delay in excess of 12 months to be a risk factor for any event of NFI during follow-up, not just a first event (HR 1·41, CI 1·1–1·8, $P < 0·05$). Delay is a risk factor for chronic NFI, the recurrence of symptoms within 3 months of the end of an earlier period of steroid treatment (HR 1·9, CI 1·2–23·8). Delay is also a risk factor for recurrent NFI, the recurrence of symptoms more than 3 months after the completion of earlier steroid treatment (HR 1·6, CI 1·1–2·3). While we found no evidence that delay is a risk factor for type 1 or type 2 reactions it is apparent that delay in presentation is an important indicator for changes in nerve function status during and after MDT treatment.

These findings are reflected in the observed differences in delay in groupings judged to have good or bad outcomes at final assessment. Two groupings were defined with good outcomes. 1869 individuals who presented and completed follow-up with no NFI reported a mean delay of 25·7 months (median 12 months). A further 57 individuals who presented with NFI but completed follow-up with no NFI reported mean delay of 25·3 months (median 12 months). Similarly, two groupings were defined with poor outcomes. 125 individuals presenting and completing follow-up with NFI reported a mean delay of 52·8 months

(median 24 months). 27 individuals presenting with no NFI but completing follow-up with NFI reported mean delays of 21·6 months (median 12 months). The experience of this last group may relate to the rapid development of symptoms in a minority of individuals. Excluding these, we note that delays amongst individuals with bad outcomes are double those for individuals with good outcomes.

Discussion

In presenting our findings, we are aware that the reliability of our assessment of duration of symptoms is of critical importance. Clinic procedures, described earlier, were designed to give a best estimate, encouraging us to consider the resulting assessments to be as reliable as those reported by others. However, the likelihood is that, as identified by WHO,[15] there is still a tendency to under-estimate rather than over-estimate delay.

We found delay to be associated with older age groups, MB disease and with grade 2 disability. In addition we note longer delays in pure neural leprosy. We found signs of reaction to be a trigger for early presentation and moderate or severe sensory or motor function loss to be associated with delay. Enlargement of ulnar, common peroneal and posterior tibial nerves was also associated with delay.

We found no evidence that within our study population, delay is a risk factor for late RFT or for the failure to complete follow-up. Since our analysis excluded people who transferred their treatment elsewhere, it may be that we excluded the people who were non-compliant.

Contact surveys and referrals by doctors and others were associated with reduced delay, while field survey was associated with longer delays, having a value in locating individuals not referred by other means. Our findings draw attention to the value of general and contact surveys, particularly at a time when, in the wider context, lack of resources and changes in administrative structure result in their discontinuation. In the absence of surveys, there will be much greater reliance on lay referral and the establishment of referral routes amongst health service providers. Raising awareness within the community and amongst medical professionals will be vital in achieving and maintaining effective control.

Our analysis confirms the importance of delay in presentation as a key aspect of leprosy control and leads us to consider if an agreed threshold defining early presentation has a role to play as an indicator of good practice. Such a threshold would be more demanding than the WHO disability grading which effectively sanctions lengthy delays not resulting in disability. We discuss four issues relating to the setting of such a threshold.

First, we suggest it is the experience of patients with fast-developing disease that is critical in setting a threshold defining early presentation. In the BANDS cohort, we note that five of 58 individuals diagnosed with MB leprosy and a reported delay of 6 months or less already had grade 2 disability (Table 3). Amongst individuals diagnosed with PB leprosy and reporting delays up to 6 months the rate was lower, nevertheless, the experience of the worst-case MB group suggests that the threshold should be set at no more than 6 months.

Second, affected individuals need time to become aware of the significance of their signs and symptoms and to eliminate the possibility of a simple skin disease. There is a tension here between allowing sufficient time for non-specific symptoms to resolve while avoiding an extended period when significant or fast-developing symptoms may result in irreversible nerve damage. The need is for a threshold that defines persistent symptoms requiring professional assessment to eliminate the possibility of leprosy. Evidence from the present

study suggests that prevention of potentially irreversible impairments requires a threshold of reported delay of no more than 6 months, allowing steroid treatment in response to loss of nerve function. Six months is also adequate to identify and treat simple skin conditions.

Third, there is the issue of transmission, which is central to efforts to eliminate leprosy. Delays in diagnosis and start of treatment mean that individuals may remain infectious for an extended period. Even while knowledge of transmission remains incomplete, there is a strong argument for the earliest possible diagnosis and start of treatment.

Finally, setting a threshold value of just a few months would largely avoid problems of subjectivity and digit preference in delays reported by patients. Staff would simply validate the patient's reported delay against recent calendar events and record whether the individual delayed for more or less than the agreed threshold.

The evidence from the BANDS study suggests that a threshold of no more than six months might be used to define early and late presentation. Such a threshold would draw attention to individuals who delay, prompting field staff to enquire about the causes of delay, whether failure to recognize the possibility of leprosy, ignorance of cure, time committed to alternative medicine or lack of awareness amongst health service providers. The resulting increased awareness of help-seeking actions contributing to delay would indicate priorities for health education and direct managers to appropriate problem-solving actions.

In conclusion, in the present research, we have reported an association between delay in presentation and diagnostic grouping, WHO grading of impairment and nerve status at registration. In turn, there is an association with changes in nerve status during MDT treatment and later follow-up and in aspects of overall outcome. As an important step towards achieving early detection and ultimate elimination of leprosy it is apparent that identifying and addressing the causes of delay should be a priority amongst leprosy health service providers. Agreeing an appropriate threshold defining early presentation would provide an important indicator for use in reporting and evaluating the effectiveness of control programmes and direct attention to individuals who delay and to their help-seeking behaviour.

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