Letter to the Editor

THE INCIDENCE OF ERYTHEMA NODOSUM LEPROSUM IN INDIA: A RETROSPECTIVE FOLLOW-UP OF THE INFIR COHORT

Dear Editor,

Erythema nodosum leprosum (ENL) is a debilitating, painful multisystem complication of borderline lepromatous (BL) leprosy and lepromatous leprosy (LL) characterised by fever, malaise and painful erythematous cutaneous nodules.\textsuperscript{1} ENL may occur before, during or after completion of multi-drug therapy (MDT) and is often recurrent or chronic in nature. ENL is a significant burden on individuals, their families and scarce health resources.\textsuperscript{2} A systematic review identified only five published studies reporting the incidence rate of ENL,\textsuperscript{3} none of which were conducted in India or Brazil the two countries with the greatest burden of leprosy.

We wished to determine the incident rate of ENL in the participants of the ILEP Nerve Function Impairment and Reaction (INFIR) Cohort Study and the course of the disease.

The INFIR Cohort Study recruited patients newly diagnosed with multibacillary (MB) leprosy at two centres in north India (Faizabad and Naini). Individuals with a bacterial index (BI) of 3 or more received 24 months of multi-drug therapy (MDT). Follow-up was monthly for 12 months and then every two months in the second year. Study subjects had clinical and detailed nerve function assessments.\textsuperscript{4} We conducted a retrospective review of the hospital records of the 303 study participants in January 2014. The maximum period of review was ten years from enrolment into the study. We used the data obtained from the retrospective review in conjunction with the original study data and obtained the following results. Approval was granted by The Leprosy Mission India.

One hundred and five of the 303 individuals recruited into the original study had BL leprosy or LL and were therefore at risk of ENL.\textsuperscript{5} Twelve of the 105 records were not available including three belonging to individuals diagnosed with ENL during the cohort study.

The clinical details of participants are summarised in Table 1.

The median age of those with and without ENL was 30 years. Seventeen (81\%) of the 21 individuals with ENL were male but this difference was not statistically significant. Six of the 21, one individual with BL leprosy and five with LL, were diagnosed with ENL at enrolment into the cohort study. Thirteen individuals (40·6\%) with LL and eight (11·0\%) with BL leprosy had ENL. The odds of LL patients developing ENL was 5·6 (2·0–15·4, \(P = 0·001\)) compared to individuals with BL leprosy; 38\% had acute ENL and 43\% chronic. One individual experienced ENL for more than 5 years.

Fourteen of the 21 individuals developed ENL during the 24 month period of the INFIR Cohort Study whilst taking MB MDT. One person with LL developed ENL 81 days after the completion of the study.

The total person-time at risk of the 105 individuals diagnosed with BL leprosy or LL in the study was 198 years. The incidence rate (IR) was 7·6 cases of ENL per 100 person years at risk (PYAR). Individuals with BL leprosy had an ENL IR of 4·6 cases/100 PYAR and those with LL 17·2 cases/100 PYAR.

The development of ENL during the 10 year period of this study is shown in Figure 1. The line at two years denotes the end of the prospective phase of the INFIR Cohort Study.

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All patients with ENL received oral prednisolone. Clofazimine was used in five individuals and thalidomide in four.

This is the first study to report the IR of ENL in India, the country with the largest burden of leprosy.6 We report a higher incidence rate than other studies identified by Voorend and Post3 shown in Table 2 which vary greatly in methodology.

We report the number of cases of ENL per 100 PYAR in individuals diagnosed with leprosy and commenced on MB MDT. Other studies have reported the IR of ENL in terms of the number of episodes of ENL rather than the number of cases making comparison difficult. Saunderson et al. reported an incidence rate of 6·9 episodes of ENL per 100 PYAR in 300 Ethiopian MB patients of which 286 were classified as having BL leprosy or LL using the modified classification of Jopling.7 The retrospective study from Nepal reports an overall IR of 3·2 episodes of ENL/100 PYAR in patients with BL leprosy or LL.

The two studies8,9 from Bangladesh used MB classifications10 and were likely to have included a large proportion of borderline tuberculoid (BT) patients who are not at risk of ENL.

The study by Scollard and colleagues from Thailand calculated the IR of ENL by including patients before and after the start of MDT. The overall IR was 3·9 cases of ENL/100 PYAR. Thirty patients

Table 1. The clinical details of participants with BL leprosy and LL in the INFIR Cohort (n = 105)

<table>
<thead>
<tr>
<th>Number</th>
<th>BL/LL participants without ENL</th>
<th>Individuals with ENL</th>
<th>Unadjusted Odds ratio and/or P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age [Range] (years)</td>
<td>30 [12–60]</td>
<td>30 [22–60]</td>
<td>ns</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>2·82:1</td>
<td>4·25:1</td>
<td>ns</td>
</tr>
<tr>
<td>BL leprosy</td>
<td>65</td>
<td>8</td>
<td>OR 5·6 (P = 0·001)</td>
</tr>
<tr>
<td>LL</td>
<td>19</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Median of Mean Bacterial Index [Range]</td>
<td>2·0 [0–5·33]</td>
<td>3·66 [0–4·66]</td>
<td></td>
</tr>
<tr>
<td>Mean duration of follow up (days) since enrolment in INFIR study [95% CI]</td>
<td>837·5 [675·5, 999·5033]</td>
<td>1357·6 [891·7, 1823·5]</td>
<td>0·0098</td>
</tr>
<tr>
<td>Mean Time (days) to ENL diagnosis after enrolment [95% CI]</td>
<td>– – –</td>
<td>308·5 [165·3,451·7]</td>
<td>– – –</td>
</tr>
</tbody>
</table>

Figure 1. The occurrence of ENL in patients with BL leprosy and LL in the INFIR Cohort
developed ENL after starting MDT and were followed for a total of 589 years. The IR of ENL in individuals diagnosed with BL leprosy or LL in this study is therefore 5.1 cases per 100 PYAR and is broadly comparable to the post-enrolment ENL IR of the INFIR cohort.

Our results provide information on the incidence of ENL in patients diagnosed with leprosy at referral centres in India. The figures should be interpreted cautiously because of the retrospective nature of the study, missing records and that on occasion individuals with higher BIs were selected for recruitment into the INFIR Cohort Study.4

ENL is often chronic and may require prolonged immunosuppression.1,14 Optimal management of ENL requires significant resources. An accurate estimate of the incidence of the condition in those at risk is important because it enables the burden on leprosy services to be predicted and thus the challenges of managing ENL to be better met.

The material contained in this work has not been published in its present form in any other scientific journal.

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Table 2. Studies of the incidence of ENL

<table>
<thead>
<tr>
<th>Study</th>
<th>Population at risk</th>
<th>Method of classification</th>
<th>Number of cases of ENL</th>
<th>Number at risk</th>
<th>Cases (Episodes*)/100 PYAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh8</td>
<td>Field</td>
<td>MB</td>
<td>Clinical and SSS</td>
<td>8</td>
<td>357</td>
</tr>
<tr>
<td>Ethiopia11</td>
<td>Field</td>
<td>MB</td>
<td>Clinical and SSS</td>
<td>16</td>
<td>300</td>
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<tr>
<td>Bangladesh29</td>
<td>Field (Retrospective)</td>
<td>MB</td>
<td>Clinical</td>
<td>10</td>
<td>471</td>
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<tr>
<td>Thailand12</td>
<td>Hospital</td>
<td>BL/LL</td>
<td>Skin biopsy</td>
<td>44</td>
<td>119</td>
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<tr>
<td>Nepal13</td>
<td>Hospital (Retrospective)</td>
<td>BL/LL</td>
<td>Skin biopsy</td>
<td>22</td>
<td>175</td>
</tr>
<tr>
<td>India (Current study INFIR)</td>
<td>Hospital</td>
<td>BL/LL</td>
<td>Skin biopsy</td>
<td>21</td>
<td>105</td>
</tr>
</tbody>
</table>

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References