Erythema nodosum leprosum in Nepal: a retrospective study of clinical features and response to treatment with prednisolone or thalidomide

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Summary

Introduction  Erythema nodosum leprosum (ENL) is an inflammatory reaction, which may occur in the course of leprosy and may result in nerve function impairment and subsequent disability.

Methods  This retrospective study explores demographic and disease specific parameters. Severity of ENL was assessed using the Reaction Severity Scale (RSS). Records of 94 patients were reviewed. The study reports also on the treatment of 76 of these patients who were treated with prednisolone alone or thalidomide in addition to prednisolone.

Results  Thirty percent of patients presented with ENL at time of diagnosis; 41% developed ENL-reaction in the first year of MDT. Forty-eight percent of patients were treated for ENL-reaction for less than 12 months; 13% for more than 5 years. High RSS-scores correlated with a longer duration of treatment. In group A (prednisolone) 51.7% and in group B (prednisolone and thalidomide) 76.6% of patients were male. Age, leprosy classification, delay of multidrug treatment (MDT) and interval between MDT and first ENL-symptoms did not differ significantly in both groups. Median duration of ENL-treatment was 15 months in group A versus 38 months in group B (P < 0.001). At the start of treatment, ENL-reaction was less severe in group A (RSS = 12) than in group B (RSS = 18; P = 0.003).
Discussion  ENL-symptoms may be of help in the early diagnosis and adequate treatment of ENL. Characterisation of (sub) groups of patients with ENL based on presence and severity of symptoms is important for future prospective studies to better evaluate the efficacy of interventions.

Introduction

Leprosy is an infectious disease affecting mainly the skin, by invasion of histiocytes, and the nerves by invasion of Schwann-cells. The latter process may lead to irreversible nerve function impairment (NFI) and subsequent chronic disabilities. In 2004, nearly 7000 new cases were detected in Nepal, a country with high endemicity of leprosy.1

Erythema nodosum leprosum (ENL), or type 2 reaction, is an acute inflammatory condition involving a TNF-α- and immune complex mediated immune response with infiltration with Th2-cells, that occurs most frequently in LL-patients, less frequently in BL patients and is more commonly seen in patients with a high bacterial index.2,3 ENL-reaction may occur during or after treatment but may also be the presenting feature in new patients presenting for diagnosis.3,4 Clinical symptoms include the typical crops of small painful red nodules on the skin. Other organs that can be involved in this systemic reaction are lymph nodes, liver, kidneys, spleen, nerves, eyes, testis and joints.5,6 Chronic and recurrent ENL may last for months or years and may cause chronic neuropathy and disability or even death if left untreated.7–10 Saunderson also found that ENL-reaction is an important risk factor for chronic and recurrent neuropathy, with a relative risk of 11.6 (3.1–43).

Although immunological reactions are very common and are considered a major source of morbidity in leprosy, little data has been published on the epidemiology of ENL. Manandhar et al. published an epidemiological study which included 108 ENL-patients.11 In 2004, Kumar reported on 2600 leprosy patients, of which 885 developed ENL-reaction and in 2006 Pocaterra reported on 116 patients.2,12 Other studies included much smaller numbers of patients with ENL.4,13,14 Thalidomide is an effective drug in treating the skin and systemic features of ENL, leading to rapid improvement. This has been shown in several double-blind clinical studies.15–19 Its main adverse effects are teratogenicity and neurotoxicity.20–24 Because of these effects, some countries and programmes will not, or can not, import or supply the drug.20,21,25,26 When used, it should be prescribed under strict precautions to prevent the unwanted side-effects.20,22,27–29 The drug’s mechanism of action is anti-inflammatory and thought to be through the selective inhibition of the production of the pro-inflammatory cytokine TNF-α by monocytes.

In Green Pastures Hospital and Rehabilitation Centre (GPH&RC), thalidomide is used as a second line drug: a) for patients suffering from chronic ENL; b) when high prolonged dose of prednisolone do not control the reaction; c) when patients develop side-effects to prednisolone, or d) when prednisolone is contra-indicated. The main aims of this study were: a) to determine the clinical features of ENL in this group of patients, b) to report on treatment outcome with prednisolone and thalidomide.

Methods and Patient Population

This was a retrospective study conducted at the Green Pastures Hospital and Rehabilitation Centre (GPH&RC) in Pokhara, Nepal. This is a referral hospital, run by the International
Nepal Fellowship (INF), that provides medical care for all leprosy patients in the Pokhara region and for referred patients from Western Nepal. All patients with new ENL, both in- and outpatient, registered at the GPH&RC neuritis clinic between April 15th 1996 and April 14th 2004 were included (n = 94).

Twenty-nine patients with ENL were treated with prednisolone only (group A). Sixty five patients also received thalidomide. Patients receiving thalidomide for mild ENL without Nerve Function Impairment (NFI) (n = 12) and patients with side-effects of prednisolone (n = 2) or with contra-indications for prednisolone (n = 4) were excluded from the analysis. Contra-indications and side-effects included diabetes mellitus, gastro-intestinal bleeding, and tuberculosis. We reviewed the charts of the remaining 47 patients who received thalidomide following the development of new ENL-nodules on prednisolone (group B, n = 47). Demographic characteristics, symptoms, clinical course and treatment outcomes of group A were compared to group B to identify predictive factors for success of prednisolone-treatment. Relevant bio-data, and patients’ disease and treatment characteristics were extracted from the medical records.

**Case definitions**

*Case definition of ENL.* The appearance of typical erythematous skin lesions was the diagnostic criterion for ENL, with or without other less specific symptoms such as fever or neuritis. Patients with possible ENL-related symptoms but without the typical skin lesions were excluded.

*Management of ENL.* The standard treatment regimen consisted of 40 mg per day prednisolone, tapering off within 16 weeks. Recurrent severe ENL was additionally treated with higher doses of prednisolone up to 60 mg daily, clofazimine and/or thalidomide. Some patients with mild ENL received only thalidomide usually as monotherapy. All patients receiving thalidomide were treated as inpatients and female patients were put on strict contraceptive medication.

*Severity of ENL.* Data were taken from patients’ charts and were scored according the Reaction Severity Scale (RSS, appendix), excluding the reversal reaction related items, thus leading to a maximum score of 74. This scale was a ‘trial scale’ and is different from the scale as recently published in this journal which evolved from the scale used in our study. RSS-scores were calculated at the start and the end of ENL-treatment. The RSS-high-score was calculated by adding the highest scores of each RSS-item at any time during ENL-treatment.

*Nerve function assessment.* Standard nerve function assessment was conducted monthly, and consisted of Voluntary Muscle Test (VMT) and Sensory Testing (ST). Sensory testing was performed with the Semmes-Weinstein monofilaments and motor function was scored according the Medical Research Council-scale.

*Nerve function impairment (NFI).* This term described impaired sensory or motor nerve function at nerve function assessment. Recent loss was considered to be loss of less than 6 months duration. Impairment was defined as follows: VMT for any muscle grade 4 or less; ST see appendix RSS.

*Nerve palpation findings (NPF).* We used this term for what is often referred to as ‘neuritis’: enlarged or tender nerves on physical examination. We chose this term to prevent confusion with ‘neuritis’, which is sometimes also used for nerve function impairment.

*Duration of ENL.* To assess the duration of ENL, the dates from start to end of treatment with prednisolone and/or thalidomide were taken, thus including symptom-free periods. In this study, no distinction was made between chronic and recurrent ENL.
The median duration of ENL treatment was estimated by using the Kaplan–Meier procedure for censored survival data. Paired $t$-test was used to investigate the difference in severity of ENL-reaction between the start and the end of treatment. Simple linear regression analysis and the Pearson correlation coefficient were used to inspect the association between duration of ENL treatment and the RSS. To assess the significance of differences in incidence of symptoms in various groups, logistic regression is used. Significance of differences in percentages of dichotomous observations is assessed with the Chi square test or the Fisher exact test when appropriate.

To compare normally distributed variables the $t$-test for independent groups was used; for non-normally distributed variables Mann–Whitney $U$ was used. The log rank test was used to compare Kaplan–Meier survival curves. $P$-values less than 0.05 are considered to indicate significance. Statistical analysis of our data was performed using SPSS 14.0.

**Results**

**Characteristics of ENL Patients**

We reviewed the charts of 94 patients; 64 were male (68%). The age range was 11–70 with a median of 35 years (25th percentile: 26 years, 75th percentile: 45 years). Most patients had polar lepromatous leprosy (81%); BL leprosy was recorded in 19% of the patients. In one patient, referred some years after MDT treatment, the classification could not be determined.

The time between the onset of the first leprosy symptoms and start of MDT ranged from 1 month to 24 years (Figure 1). Only 48% of the patients were diagnosed within the first year after the first symptoms appeared; 20% within the first 6 months.

Approximately 30% of patients presented with ENL at the time of diagnosis (Figure 2). Most patients (41%) developed ENL in the first year of treatment.

The duration of ENL could only be calculated in 63 cases, because both the date of the start and the end of ENL-treatment need to be known. In these patients duration of treatment ranged from 1 to 62 months. Fifteen patients were still on treatment after the closing date for intake of the study; in eight patients, the end of treatment was unknown because of referral to other treatment centres; two patients were lost to follow-up; in three cases (3%) treatment with prednisolone/thalidomide extended for longer than 5 years. To indicate median duration of ENL reaction, a Kaplan–Meier survival curve is presented in Figure 3.
The data contains 63 true measurements of which both starting date and final date of ENL-treatment are recorded, and 25 censored measurements of which the starting date is known but the patient was still on treatment at the last visit to the hospital. Censored measurements are measurements of patients who were still on treatment at the end of the study, patients referred while still on treatment or patients lost to follow up. Missing values ($n = 6$) are patients of which the starting date of the treatment is unknown. The estimated median duration of ENL is 30 months (95% confidence interval 21–39 months). The figure shows the survival of ENL-reaction, starting with all included measures at time = 0 (cumulative survival = 1) and decreasing as ENL-reactions subside.

![Figure 2. Relationship of ENL onset to treatment with multi-drug therapy ($n = 88$). Year refers to year since starting MDT.](image)

![Figure 3. Kaplan–Meier curve for the duration of ENL. The line represents for each duration of treatment the proportion of patients still on treatment for ENL. +: censored observations (see also text). The dotted lines correspond to the median duration of ENL: 50% of the patients experience ENL for more than 30 months.](image)
The severity of the ENL-reaction was assessed at the start and the end of ENL-treatment using the Reaction Severity Scale. We also calculated the ‘RSS-high score’, the sum of all the highest scores of each item of the RSS (Table 1).

We calculated this to indicate the severity of ENL, including all symptoms that were noted during the reaction. The mean scores and the standard deviation are summarised and the P-values given which show that mean RSS-score was lower at the end of treatment. This decrease in RSS, calculated over the 71 patients with known RSS scores at start and end of the ENL treatment, was 5·2 units on the RSS scale (95% confidence interval 3·9–6·6 RSS units). Only 10 of 72 cases for whom the relevant data were available recovered completely (RSS = 0 at the end of ENL-treatment).

Figure 4 gives a scatter plot with a linear regression line, indicating a positive association between severity of the ENL reaction (RSS-high score) and duration of ENL: Pearson correlation coefficient = 0·64, P < 0·001. For this calculation only the 63 cases with known starting date and final date of ENL-treatment could be used.

FEATURES OF ENL-REACTION

The diagnosis of ENL-reaction largely depends on the appearance of ENL-skin lesion, although the reaction often has systemic features and systemic involvement. Figure 5 shows the prevalence of symptoms of ENL-reactions as measures in our group.

The prevalence of orchitis was calculated from data of only male patients (n = 64). Missing data per symptom varied from two to five. The prevalence of symptoms in male and female patients or BL and LL patients did not differ significantly. The prevalence of symptoms was also calculated by age groups: 14 (15%) cases were under 20 years of age at presentation; 43 (46%) were 20 to 39 years old; 32 (34%) patients were 40 to 59 years and five patients were over 60 years old.

Age-related differences are noticeable in low prevalence of fever (P = 0·0086) in patients over 60 years, and the increase of oedema (P = 0·0332) with age. In the age groups < 20 years, 20–39 years, 40–59 years and > 60 years, the prevalence of fever was 58%, 91%, 76% and 20% respectively and the prevalence of oedema was 33%, 65%, 83% and 80% respectively.

TREATMENT OUTCOME

Group A (n = 29) included patients receiving prednisolone and group B (n = 47) included patients receiving thalidomide in addition to prednisolone because of insufficient response to prednisolone.

Table 1. Severity of ENL-reaction, as measured by Reaction Severity Scale (RSS), at start and end of ENL-treatment and RSS-high score during treatment

|                      | n  | Mean | SD  | P-value* |
|----------------------|----|------|-----|----------|
| RSS at start of treatment | 85 | 16   | 8·6 | <0·001   |
| RSS at end of treatment    | 72 | 7·4  | 6·0 |          |
| RSS-high score**         | 89 | 29·8 | 11·3|          |

* P-value resulting from paired t-test for the mean decrease in RSS in the 71 patients with known RSS scores at start and end of ENL-treatment.

** RSS-high score: sum of the maximum scores per item during ENL-treatment period.
Characteristics of groups. The groups differed in gender composition: 52% male patients in group A versus 77% in group B ($P = 0.025$) (Table 2).

There was no significant difference in age. In group A more patients were classified as BL (34.5% versus 15.2%; $P = 0.052$). Delay of leprosy treatment with MDT was longer in group A (16 and 11 months respectively; $P = 0.097$). The median time between the start of

Figure 4. Severity and duration of ENL-reaction. The severity of the ENL-reaction is given by means of the RSS high score which is defined as the sum of the highest scores of each RSS-item and is displayed on the vertical axis. This plot is based on the 63 cases with known start- and end-date of ENL. The line represents the linear regression line of RSS high score on ENL duration. Pearson correlation = 0.64, $P < 0.001$.

Figure 5. Incidence of symptoms; percentage of patients with specific symptoms.
MDT and the first symptom of ENL differed, but not significantly: 12 months in group A, 5 in group B ($P = 0.203$). In both groups, ENL occurred in 1 out of 3 patients before MDT was started.

**Duration of ENL.** Figure 6 shows survival curves for the length of ENL in each group, starting with all included measures at time 0 (cumulative survival = 1) and decreasing as ENL reactions subside.

The data contains 49 true measurements of which both starting date and final date of ENL-treatment are recorded, and 23 censored measurements of which the starting date is known but the patient was still on treatment at the last visit to the hospital. Censored measurements are measurements of patients who were still on treatment at the end of the study, patients referred while still on treatment or patients lost to follow up. Missing values ($n = 4$) are patients of which the starting date of the treatment is unknown. Group A contains 9 censored measures and two missing values and group B, 14 and 2 respectively. Significance is calculated using log rank test: $P < 0.001$.

**Reaction severity.** Table 3 shows that severity of ENL differed at start of ENL-treatment; in group A, median RSS was 12, compared to group B, in which median RSS was 18 ($P = 0.003$). The difference of severity at the end of treatment was not significant: in group A, median RSS was four and in group B, median RSS was 11 ($P = 0.092$). The RSS-high score in group A was 21 and differed significantly from the RSS high score in group B, which was 36 ($P < 0.001$).

Table 4 shows the differences in frequency of symptoms in both groups, pointing to significant higher incidence of most symptoms in group B, except nerve palpation findings, uveitis and orchitis.

To compare the effect of treatment in both groups, notes on ENL-skin lesions, NFI, NPF, RSS and fever at end of ENL-treatment of both groups were compared to those at the start of ENL-treatment (Table 5). The differences of treatment outcomes between the groups remain non-significant.

### Table 2. Characteristics of patients treated with thalidomide- and non-thalidomide regimens

| Variable | Group A ($n = 29$) | Group B ($n = 47$) | $P$-value |
|----------|---------------------|---------------------|------------|
| Sex      | Male  51.7% 76.6%   | Female 48.3% 23.4%  | 0.025      |
| Age (years) | 37.6 (12.5) | 36.8 (13.1)  | 0.79       |
| Classification (%) | 34.5% 15.2% | 65.5% 84.8%  | 0.052      |
| Delay (months) | | | 0.097 |
| Median (25%–75%-ile) | 16 (9–48) | 11 (6–34)  |     |
| Start ENL after start MDT in months | | |     |
| Median (25%–75%-ile) | 12 (0–27) | 5 (0–12)   | 0.203     |
| % ENL at start MDT | 33 | 33        |     |

* Erythema nodosum leprosum in Nepal

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**References**

[1] MDT and the first symptom of ENL differed, but not significantly: 12 months in group A, 5 in group B ($P = 0.203$). In both groups, ENL occurred in 1 out of 3 patients before MDT was started.

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| Start ENL after start MDT in months | | |     |
| Median (25%–75%-ile) | 12 (0–27) | 5 (0–12)   | 0.203     |
| % ENL at start MDT | 33 | 33        |     |
Discussion

The patients in this study may be unrepresentative of patients with ENL in general because patients with severe ENL are more likely to be referred to a specialist centre. Our group also includes patients that did not respond well to treatment with prednisolone, respectively group B, that experience ENL for more than t months. The curve for patients treated with prednisolone (group A) is below the curve for patients treated with prednisolone and thalidomide (group B), indicating a lower proportion of patients with ENL at any point in time after the beginning of ENL (log rank test: \( P < 0.001 \)).

Figure 6. Kaplan–Meier survival curves of duration of ENL. Solid line: group A; dotted line: group B; +: censored observation. The lines represent for each duration of t months of ENL the proportion of patients in group A, respectively group B, that experience ENL for more than t months. The curve for patients treated with prednisolone (group A) is below the curve for patients treated with prednisolone and thalidomide (group B), indicating a lower proportion of patients with ENL at any point in time after the beginning of ENL (log rank test: \( P < 0.001 \)).

Table 3. Differences in Reaction Severity Score in both groups (\( P \) values obtained by Mann–Whitney \( U \) test)

| RSS               | Group A (\( n = 29 \)) | Group B (\( n = 47 \)) | \( P \)-value |
|-------------------|------------------------|------------------------|--------------|
| At start of treatment | 12 10–17               | 18 13–23               | 0.003        |
| At end of treatment | 4 3–8                  | 11 3–14                | 0.092        |
| RSS-high score    | 21 14–25               | 36 30.5–42             | <0.001       |
The gender ratio in our group is similar to other clinical studies with a male:female ratio of 2:1.20,34 Thus gender does not seem to be a risk factor for developing ENL. This contrasts with a study from North India which showed that female patients were at a higher risk (male RR = 0.75 (0.59–0.95)), but concurs with two other studies in which gender was not found refer to as ‘Nerve Palpation Findings’, but also for NFI. In the literature there are also different definitions of ENL-reaction. Van Brakel defined ENL as ‘... crops of tender subcutaneous skin lesions’.33 For communication and research purposes there should be a common understanding about terms being used.

** CHARACTERISTICS OF ENL-PATIENTS **

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| Symptoms     | %  | n  | %  | n  | P-value |
|--------------|----|----|----|----|---------|
| NPF          | 96 | 25 | 100| 47 | 0.347   |
| NFI          | 76 | 25 | 96 | 46 | 0.019   |
| Fever        | 56 | 25 | 89 | 47 | <0.001  |
| Joint pain   | 57 | 28 | 94 | 47 | <0.001  |
| Oedema       | 40 | 28 | 74 | 47 | 0.004   |
| Nerve pain   | 21 | 28 | 66 | 47 | <0.001  |
| Eye involvement | 11 | 28 | 53 | 47 | <0.001  |
| Uveitis      | 7  | 28 | 19 | 47 | 0.158   |
| Bone pain    | 14 | 28 | 49 | 47 | 0.002   |
| Lymphadenitis| 4  | 28 | 28 | 47 | 0.010   |
| Orchitis     | 13 | 15 | 31 | 36 | 0.297   |
| Muscle pain  | 0  | 28 | 15 | 47 | 0.041   |

P values obtained by logistic regression analysis (NPF: Nerve Palpation Findings. NFI: Nerve Function Impairment).

** Table 4. Incidence of symptoms in both groups **

| N  | Better % | Equal % | Worse % | Mean progress on RSS scale | P-value |
|----|----------|---------|---------|-----------------------------|---------|
| Skin | Group A | 21 | 90 | 10 | 0 | 2.05 | 0.34 |
|     | Group B | 36 | 89 | 6 | 6 | 2.56 |       |
| NFI | Group A | 21 | 29 | 57 | 14 | 0.52 | 0.07 |
|     | Group B | 36 | 11 | 64 | 25 | –0.25 |       |
| NPF | Group A | 21 | 38 | 52 | 10 | 0.95 | 0.15 |
|     | Group B | 36 | 64 | 28 | 8 | 1.78 |       |
| Fever | Group A | 17 | 41 | 59 | 0 | 0.41 | 0.56 |
|      | Group B | 30 | 37 | 60 | 3 | 0.57 |       |
| RSS | Group A | 21 | 86 | 5 | 10 | 7.38 | 0.22 |
|      | Group B | 36 | 94 | 0 | 6 | 9.78 |       |

** Table 5. Comparison of progress during treatment of both groups on different items of Reaction Severity Scale (P values based on t tests for independent groups)**
to be a risk factor. However, the ratio we found could be the result of referral bias, with more men being referred or coming to GPH&RC, and fewer women considered for treatment with Thalidomide.

This study shows a long interval between the first symptoms of leprosy and the start of MDT. The frequency of ENL-reaction might be reduced with timely diagnosis, lower bacillary load, and adequate treatment. Van Brakel et al. showed that ENL was present in 30% of BL-LL cases at diagnosis. This was probably the reason for seeking health care. In our study hospital registered group, 41% of patients developed ENL in the first 12 months of taking MDT. Another study from Nepal had similar findings with 34% of patients presenting with ENL before starting MDT and 45% developing it during the first 12 months of taking MDT. A study from Ethiopia included 40 ENL-patients, of whom 9 (22.5%) presented with ENL at the start of treatment, and 14 (35%) in the first year of MDT. A study from north India reported that 20% of patients presented with ENL before starting MDT, and that 30% developed ENL-reaction during the first year of taking MDT. Van Brakel et al. conducted a study in Pokhara, Nepal, in 2004 and found a prevalence of 5.7% (10 of 175) in BL/LL patients at registration and 3.2 ENL episodes per 100 person years at risk during follow-up. In the AMFES-group in Ethiopia, all 16 ENL-patients developed ENL-reaction after the start of MDT; the majority of cases first presented with ENL in the second and third year after the start of MDT.

In our study treatment of ENL was limited to 1 year in 33% of the cases. Kumar et al. reported that 64.3% of all ENL-patients suffered from recurrent reaction and that treatment duration averaged 34 months (range: 5 to 96 months). In the AMFES-group (Ethiopia), 63% of all cases had more than one episode, and 31% developed five or more episodes over a period of more than 2 years. In a study from Thailand, 34 (77%) of 44 ENL-patients had multiple episodes with ENL. These results underscore the fact that ENL-reaction should be regarded as a relapsing-remitting condition.

SYMPTOMS AND ORGAN INVOLVEMENT IN ENL-REACTION

At present, often only the typical ENL skin lesions are considered the main diagnostic criterion of an ENL-reaction. Research on the first symptoms before the appearance of ENL-lesions might be of clinical importance in order to help early diagnosis and improve treatment outcome. Other highly prevalent symptoms such as NPF, NFI, fever and joint pain could be helpful to improve early recognition and treatment of ENL in patients at risk.

Although ENL is widely known as a reaction with systemic symptoms in which many organs may be involved, little is known about the incidence of these symptoms. In our study the incidence of symptoms are extracted from the charts. Absence of notes on symptoms in patients’ charts were considered negative findings, thus our data may underestimate neuropathy. Symptoms may also have appeared due to side-effects of treatment, thus leading to an overestimation in our study. For example, neuropathy may also occur as a side-effect of thalidomide. There seems to be much more NFI in our study than would be expected. This overestimation could be because NFI may have been recorded on the RSS as present when patients reported to the hospital with NFI and it could not be established if this was recent NFI due to ENL or ‘old’ NFI not necessarily related to ENL. No reliable data from prospective studies are available on the possible progress of NFI in patients diagnosed with lepromatous leprosy, with or without ENL.
The two subgroups of ENL-patients had significant differences in severity of reaction, duration of treatment, frequency of symptoms and organ involvement (Table 3). The presence of certain symptoms may have been the reason for considering treatment with thalidomide.

We found that female patients were less likely to be treated with thalidomide than male patients. This may be due to the clinician being unwilling to expose women to the risk of phocomelia if they take thalidomide whilst in the early stages of pregnancy, although using contraceptives protects women from this risk. Social factors such as an unwillingness to be admitted may also decrease women’s access to thalidomide. The median age of the women in our study was 35 (15–54). Most women were of child-bearing age and received ‘depot’ contraceptive treatment.

Figure 6 shows a significant difference in duration of treatment in both groups, which was expected as group B is treated with thalidomide, indicative of a difficult-to-manage ENL-reaction. The more severe ENL at start of treatment and higher high-scores in group B indicates that patients presenting with severe ENL are at a higher risk of insufficient response to prednisolone.

Table 5 shows no significant differences of treatment outcomes, but the difference in outcome of NFI between RSS-item scores at the start and the end of treatment (improvement of 0.52 point of the RSS in group A and worsening of 0.25 points in group B) may suggest a worse NFI-outcome of nerve function in patients additionally receiving thalidomide ($P = 0.07$). This difference could be explained by the longer duration and more severe ENL-reaction in group B, but also to neuropathy as a possible side-effect of thalidomide-treatment.

In our study, thalidomide was often prescribed in addition to prednisolone. Standard treatment for severe ENL-reaction usually starts with 40 mg prednisolone. Longer duration (low doses) is recommended for type 1 reaction leprosy reactions. We were not able to compare prednisolone-treatment to thalidomide-treatment because the population of both groups (thalidomide versus non-thalidomide) differed in many important variables. In addition, many patients in both groups received additional drugs like pentoxyfillin, cyclosporine or clofazimine.

Various studies support the use of thalidomide in ENL. It may reduce the need for steroids and usually leads to quick improvement. Thalidomide has been shown to be more effective than pentoxifylline. Treatment with infliximab has been reported to be highly effective in a case of recurrent ENL in which prednisolone, thalidomide and pentoxifylline failed. Azathioprine may also be a safe drug to prevent recurrence of ENL.

**Limitation of the Study**

This was not a randomised clinical study comparing prednisolone with thalidomide (either alone or together with prednisolone). In both groups patients sometimes also received other drugs, especially in the ‘chronic’ ENL group e.g. clofazimine, cyclosporine or pentoxyfillin. No firm conclusions can be made on the basis of our study and between the groups as group assignment has also been influenced by the availability of thalidomide and/or presence of the primary treating physician.

Lockwood summarised 4 double-blind studies that all showed benefits of thalidomide. But these studies were done more than 30 years ago. Patients were treated with different
doses, for different lengths of time and different outcome measures were used. These patients most likely also differed in the severity of ENL.

CONCLUDING REMARKS AND RECOMMENDATIONS

ENL-related symptoms like enlarged or painful nerves, NFI, fever, and arthralgia may help in the early diagnosis of ENL and should be taken into account when making (sub) groups of patients in order to investigate the efficacy of drug treatments.

In this study, male patients, and patients presenting with severe ENL-reaction were more likely to receive thalidomide in addition to prednisolone.

There are no recently published high-quality randomised clinical studies on the effectiveness of thalidomide in the treatment of ENL. Such studies are needed. There are also no generally agreed recommended guidelines for the treatment of ENL as there are for the treatment of reversal reaction. Further research is recommended to confirm and identify other possible risk factors for the development of ENL. It is also recommended that in future studies on ENL the Reaction Severity Scale is used to quantify severity of ENL (mild, moderate, severe) and to follow patients in clinical trials.3,30

Further research is also recommended to be able to identify patients that may not adequately respond to prednisolone.

We hope that our study will be helpful in the design of future studies looking into the efficacy of thalidomide, and other drugs, in the treatment of (chronic) ENL. Based on our study patient treatment groups should be, and can be better characterised with the use of the RSS scale.

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References

1 World Health Organization. Global leprosy situation. Weekly Epidem Rec, 2005; 80: 289–296.
2 Pocaterra L, Jain S, Reddy R et al. Clinical course of erythema nodosum leprosum: an 11-year cohort study in Hyderabad, India. Am J Trop Med, 2006; 74: 868–879.
3 Walker SL, Lockwood DNJ. Leprosy. Clin Dermat, 2007; 25: 165–172.
4 Van Brakel WH, Khawas IB, Lucas SB. Reactions in leprosy: an epidemiological study of 386 patients in West Nepal. Lepr Rev, 1994; 65: 190–203.
5 Ridley DS. Reactions in leprosy. Lepr Rev, 1969; 40: 77–81.
6 Gawalkar S. Leprosy for medical practitioners and paramedical workers 7th edn, 2002, Ciba Geigy, Basle.
7 Bjune G. Reactions in leprosy. Lepr Rev, 1983; 61: S61–S67.
8 Saunderson P, Gebre S, Desta K et al. The pattern of leprosy-related neuropathy in the AMFES patients: definitions, risk factors and outcome. Lepr Rev, 2000; 71: 285–308.
Erythema nodosum leprosum in Nepal

Saunderson P, Gehre S, Byass P. ENL reactions in the multibacillary cases of the AMFES cohort in central Ethiopia: incidence and risk factors. *Lepr Rev*, 2000; 71: 318–324.

Saunderson P. Epidemiology of reactions and nerve damage. *Lepr Rev*, 2000; 71: S106–S110.

Manandhar R, LeMaster JW, Roche PW. Risk factors for erythema nodosum leprosum. *Int J Lepr*, 1999; 67: 270–278.

Kumar B, Dogra S, Kaur I. Epidemiological characteristics of leprosy reactions: 15 years experience from North India. *Int J Lepr*, 2004; 72: 125–133.

Becx-Bleumink M. Occurrence of reactions, their diagnosis and management in leprosy patients treated with multidrug therapy: experience in the leprosy control program of the all Africa Leprosy and Rehabilitation Training Centre (ALERT) in Ethiopia. *Int J Lepr*, 1992; 60: 173–184.

Brakel WH, Nicholls PG, Das L et al. The INFIR cohort study: investigating prediction, detection and pathogenesis of neuropathy and reactions in leprosy. Methods and baseline results of a cohort of multibacillary leprosy patients in North India. *Lepr Rev*, 2005; 76: 14–34.

Sheskin J, Convit J. Results of a double blind study of the influence of thalidomide on the lepra reaction. *Int J Lepr*, 1969; 37: 135–146.

Pearson JMH, Vedagiri M. Treatment of moderately severe erythema nodosum leprosum with thalidomide – a double blind controlled trial. *Lepr Rev*, 1969; 40: 111–116.

Waters MFR. An internally controlled double blind trial of thalidomide in severe erythema nodosum leprosum. *Lepr Rev*, 1971; 42: 26–42.

Iyer CGS, Languillon J, Ramanujam K et al. WHO co-ordinated short-term double-blind trial with thalidomide in the treatment of acute lepra reactions in male lepromatous patients. *Bull World Health Org*, 1971; 45: 719–732.

Sales AM, Matos de HJ, Nery JAC et al. Comparison of pentoxifylline, thalidomide and prednisolone in the treatment of type-2 reaction in leprosy. *Braz J Med Biol Res*, 2007; 40: 243–248.

Lockwood DJN. The management of erythema leprosum nodosum: current and future options. *Lepr Rev*, 1996; 67: 253–259.

Pannikar VC. The return of thalidomide: new uses and renewed concerns. *Lepr Rev*, 2003; 74: 286–288.

Teo SK, Resztak KE, Scheffer MA et al. Thalidomide in the treatment of leprosy. *Microbes Inf*, 2002; 4: 1193–1202.

Tadesse A, Shannon EJ. Concerns regarding in vitro and in vivo uses of thalidomide. *Lepr Rev*, 2005; 76: 94–96.

Moreira AL, Kaplan G, Villahermosa LG et al. Comparison of pentoxifylline, thalidomide and prednisolone in the treatment of ENL. *Int J Lepr*, 1998; 66: 61–65.

Shannon EJ. Thalidomide: will the past overshadow a promising future? *The Star*, 2000; 59: 10–13.

Naafs B. Treatment of leprosy: science or politics? *Trop Med Int Health*, 2006; 11: 268–278.

Lockwood DJN, Brycecon A. The return of thalidomide: new uses and renewed concerns. *Lepr Rev*, 2003; 74: 290–294.

Naafs B. The return of thalidomide: new uses and renewed concerns. *Lepr Rev*, 2003; 74: 294–295.

Pereira GF. On thalidomide and WHO policies. *Lepr Rev*, 2003; 74: 288–290.

van Brakel WH, Nicholls PG, Lockwood DJN et al. A scale to assess the severity of leprosy reactions. *Lepr Rev*, 2007; 78: 161–164.

Brunsma JW. Monitoring motor nerve function in leprosy patients. *Lepr Rev*, 2000; 71: 258–267.

Birke JA, Brandma JW, Schreuders TAR, Piefer A. Sensory testing with monofilaments in Hansen’s disease and normal control subjects. *Int J Lepr*, 2000; 68: 291–298.

Brakel WH, Nicholls PG, Das L et al. The INFIR cohort study: assessment of sensory and motor neuropathy at baseline. *Lepr Rev*, 2005; 76: 277–295.

Britton WJ, Lockwood DJN. Leprosy. *Lancet*, 2004; 363: 1209–1219.

Scollard DM, Smith T, Bhooapat L et al. Epidemiologic characteristics of leprosy reactions. *Int J Lepr*, 1994; 62: 559–567.

Schreuder PAM. The occurrence of reactions and impairments in leprosy: experience in the leprosy control program of three provinces in north-eastern Thailand, 1978–1995. I. Overview of the study. *Int J Lepr*, 1998; 66: 149–158.

Faber WR, Jensen SA, Goldschmidt WFM. Treatment of erythema nodosum leprosum with infliximab. *N Engl J Med*, 2006; 355: 739.

Verma KK, Srivasta P, Minz A, Verma K. Role of azathioprine in preventing recurrent erythema nodosum leprosum. *Lepr Rev*, 2006; 77: 225–229.
## Appendix. Reaction Severity Scale (please refer to van Brakel et al. Lepr Rev 2007, for recent version of Reaction Severity Assessment Form)

| Score | 0     | 1     | 3     | 5     |
|-------|-------|-------|-------|-------|
| For type 1 reaction |       |       |       |       |
| A1    | Degree of inflammation of skin lesion | None | Erythema | Erythema, raised lesion, painful/plaques | Ulceration |
| A2    | Number of inflamed lesions | None | 1 to 3 | 4 to 10 | >10 |
| For type 2 reaction |       |       |       |       |
| A3    | Degree of inflammation of nodules | None | Tender nodule(s) | Painful nodule(s) | Ulceration |
| A4    | Number of nodules | None | ≤10 | >10 | >50/uncountable |
| A5    | Inflammation of lymph nodes due to current reaction | None | Chronic | Mild, acute | Definite |
| A6    | Inflammation of joints due to current reaction | None | Chronic | Mild, acute | Definite |
| A7    | Inflammation of eye due to current reaction | None | Chronic | Mild, acute | Definite |
| A8    | Inflammation of testes due to current reaction | None | Chronic | Mild, acute | Definite |
| A9    | Bone pain due to current reaction | None | Chronic | Mild, acute | Definite |
| For both type 1 and 2 reaction |       |       |       |       |
| A10   | Fever due to reaction | <37.5 | 37.6–38.9 | >39.0 | – |
| A11   | Peripheral oedema due to reaction | None | Oedema not affecting function | Oedema affecting function | – |
| A12   | Number of limbs with peripheral oedema due to reaction | None | 1 | 2 or more | – |
| A13   | Nerve pain | None | Mild, does not limit activity | Sleep or activity disturbed | Incapacitating |
| A14   | Nerve tenderness on gentle palpation | None | Mild tenderness or paraesthesia, absent if attention is distracted | Present, even if attention is distracted | Severe, patient withdraws limb forcibly |
### Appendix, continued

| Score | 0 | 1 | 3 | 5 |
|-------|---|---|---|---|
| A15   | No new enlargement or borderline | Definite new enlargement | – | Nerve abscess |
| A16   | None | 1–2 levels lost | 3–9 levels lost | 9–15 levels lost |
| A17   | None (MRC 5) | MRC 4 | MRC 3 | MRC < 3 |
| A18   | None | 1 | 2 or 3 | More than 3 |

RSS-score: cumulative of scores.
RSS-high score: cumulative of highest scores at any time during treatment.