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The use of steroids and thalidomide in the management of Erythema Nodosum Leprosum; 17 years at the Hospital for Tropical Diseases, London

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Abstract
Objectives: Prednisolone and thalidomide are commonly used in the management of erythema nodosum leprosum (ENL) and bring relief to patients with this condition worldwide. However, both ENL and its treatments can cause significant morbidity. This study describes the spectrum of ENL seen at The Hospital for Tropical Diseases, London (HTD) the use of steroids and thalidomide in its management and the complications of their use.

Study Design: We conducted a retrospective audit of patients diagnosed with ENL between 1996 and 2013. Data were obtained from hospital records including severity and length of disease, together with treatments received and adverse effects.

Results: Between 1996 and 2013, 30 patients were diagnosed with ENL. The median bacillary index (BI) at diagnosis was 4.65, higher than in previous studies. Most patients developed ENL during leprosy treatment (67%) and had chronic ENL (57%). The median length of ENL was 60 months (range 9-192); patients with BI>4.5 had significantly longer duration of disease. 87% patients received prednisolone for median nine months; 35% developed adverse effects including diabetes and hypertension. 87% patients received thalidomide for median 16 months; 65% complained of side effects. There were no pregnancies or venous thromboembolisms. 77% patients stopped prednisolone within two months of starting thalidomide. There were no deaths in our cohort.

Conclusion: We describe the clinical course of ENL in a non-endemic country with access to thalidomide and prednisolone. ENL may last far longer than previously described and has significant impact on a patient’s health. In the UK, thalidomide is essential as a steroid-sparing agent, to prevent the adverse effects and mortality of long-term steroids which have been documented elsewhere.

Introduction
ENL is a multisystem, relapsing and remitting disorder occurring in patients with lepromatous and borderline lepromatous leprosy. Although its pathogenesis is not fully understood, it is characterized by immune complex deposition and T cell activation with high levels of TNFα and IL6. This manifests clinically as tender erythematous skin lesions with or without systemic symptoms such as fever, neuritis, orchitis and bone pain. The incidence of ENL varies from 5% to 49% in cohorts
worldwide. Risk factors include having lepromatous leprosy or a bacillary index (BI) over 4. The management of ENL is difficult. Anti-inflammatory agents are rarely sufficient for symptomatic control. Prednisolone rapidly controls symptoms but risks the complications of long-term steroid treatment. Thalidomide is effective but associated with side effects including tiredness, constipation and neuropathy. It is unavailable in many countries due to concern about teratogenic risk. Clofazimine can be effective as an anti-inflammatory agent at a dose of 300mg/day. However, it takes four weeks to work and the associated skin pigmentation can be stigmatizing for patients in leprosy endemic areas.

Other disease modifying agents have been tried with varying success. Case reports and a small case series suggest azathioprine may reduce the frequency and severity of ENL episodes and may be effective as a steroid sparing agent. Both etanercept and infliximab, tumour necrosis factor- alpha (TNFα) inhibitors, have been reported to be effective in individual patients with severe ENL. The utility and safety of expensive immunosuppressive agents in resource poor settings where tuberculosis is endemic has yet to be established.

The Hospital for Tropical Diseases, London, (HTD) is a tertiary centre for tropical disease and runs the leprosy referral clinic for the UK National Health Service. The majority of patients diagnosed with leprosy in the UK are referred to this clinic. Most patients receive the WHO recommended multidrug therapy (MDT) of rifampicin, clofazimine and dapsone in blister packs provided by WHO. Patients who have adverse effects to first line treatment are given alternative regimens, such as monthly rifampicin, ofloxacin and minocycline (ROM).

Prednisolone, clofazimine and azathioprine are available for the management of ENL. Thalidomide is prescribed through the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.). TNFα inhibitors are not currently available for patients with ENL.

This retrospective case note review aims to describe the spectrum of ENL seen at HTD, the use of steroids and thalidomide in its management and the complications of their use. Although this manuscript describes the side effects of drugs used in ENL treatment, we emphasise that these drugs bring relief to ENL patients worldwide.

**Method**

We conducted a retrospective audit of the management of patients with ENL seen at the Hospital for Tropical Diseases, London, between January 1996 and December 2013. Ethical approval was not required as this was an audit of our current practice. Data were obtained from hospital records including case notes from consultations and in-patient admissions, electronic letters and laboratory records. Data collected included age, sex, country of origin, country where leprosy was acquired, Ridley-Jopling classification, BI at diagnosis, treatment regimen, treatment length and occurrence of ENL. Further data were collected about ENL including timing, pattern, severity and length of disease together with treatments used. Adverse effects of steroids were recorded including weight gain, diabetes, hypertension, osteoporosis, cataracts and occurrence of infections. Adverse effects of thalidomide were also recorded including tiredness, constipation, dizziness, abdominal pain, unplanned pregnancy and venous thromboembolism. The neurological outcomes of thalidomide treatment are currently being collected and will be reported separately. As these data were collected retrospectively from notes, letters
and laboratory records rather than from systematic patient interview, the occurrence of adverse events may be underestimated.

Table 1 details the case definitions used.

<Insert Table 1 near here>

**Results**

Between 1996 and 2014, 18 patients with BL and 46 patients with LL were seen at HTD. Four (22%) patients with BL and 26 (56%) patients with LL developed ENL. Of 30 patients with ENL, 20 (67%) were male. Ten (33%) patients acquired leprosy in South Asia, ten (33%) in South America and seven (23%) in West Africa. The median age at leprosy diagnosis was 33 years; 29 (97%) patients were of working age and 24 (80%) were between 20 and 40 years old. Patients had a median of 18 months of symptoms before the diagnosis of leprosy was made. The median BI at diagnosis was 4.65 (4.7 in patients with LL and 2.6 in patients with BL leprosy). Twenty-two (73%) patients had a BI over 4. All patients received multi-drug therapy (see Figure 1).

<Insert Figure 1 near here>

Nine (30%) patients developed ENL before starting leprosy treatment, 20 (67%) during treatment and one (3%) after treatment. Thirteen (43%) patients had recurrent ENL and 17 (57%) patients had chronic ENL. No patients had acute ENL.

The median length of ENL was 60 months (range: 9 to 192 months). Four (13%) patients had ENL for more than 10 years (see Figure 2).

<Insert Figure 2 near here>

Those with an initial BI over 4.5 had a median length of ENL of 76 months in comparison to 40 months in patients with a BI of 4.5 or less (Mann Whitney u test, P = 0.043). Sixteen (53%) patients had moderate disease with four (13%) experiencing severe disease. There were no deaths in this cohort.

Twenty six (87%) patients received prednisolone, 26 (87%) received thalidomide, five (17%) received high dose clofazimine and four (13%) received a further disease modifying agent. Figure 3 shows the combinations of treatments that patients received.

<Insert Figure 3 near here>

Prednisolone was given for a median of 9 months (range 1 week to 74 months) at a dose range of 5mg to 80mg/day. The median maximum dose of prednisolone was 40mg/day; patients were initially started at this dose and the dose was then reduced as their ENL was controlled. Of note, three (11%) patients were already on prednisolone for neuritis or Type 1 reaction when they developed symptoms of ENL. Nine (35%) patients developed side effects whilst on treatment; seven (27%) gained weight, four (15%) developed Cushingoid features and three (11%) developed steroid-induced diabetes. One patient developed a *Listeria monocytogenes* meningitis which was attributed to steroid use. Six (23%) had self-directed treatment at the end of therapy; these patients kept rescue packs of prednisolone at home and took a short course if they experienced an ENL flare-up.

Thalidomide was given for a median of 16 months (range 2 weeks to 175 months) at a dose range of 12.5mg to 500mg/day. The median maximum dose of thalidomide was 400mg per day. Twenty (77%) patients were on prednisolone when thalidomide was started. The median time from developing ENL to starting thalidomide was 5 months in men and 8 months in women. Twenty (77%) were weaned off prednisolone whilst taking thalidomide in a median of 2 months. Seventeen (65%) patients had side effects on thalidomide: 16 (61%) felt tired, four (15%) felt dizziness and four (15%)
complained of constipation. There were no unplanned pregnancies or venous thromboembolisms.

Ten women received thalidomide. Two of these women were post-menopausal and thus did not require contraception. Of seven patients whose contraception was documented, six (86%) used condoms, four (57%) used the oral contraceptive pill, three (43%) used a coil and one (14%) used the Depo contraceptive injection. One patient was documented to be using contraception but the type was not recorded in the patient’s records. Of five women who received thalidomide after the introduction of the S.T.E.P.S. programme, all had a negative pregnancy test documented at over 90% of appointments at which thalidomide was prescribed.

Four patients received clofazimine at doses between 100mg and 300mg per day. Three patients received azathioprine for between 8 and 44 months at a dose between 200mg and 300mg per day. These three patients had ENL of moderate severity that was not controlled on 40mg prednisolone per day. In the first patient, introduction of azathioprine allowed a reduction in prednisolone to 10mg per day at 2 months but the patient continued to require 2.5-10mg prednisolone daily for a further 22 months before prednisolone could be stopped permanently. In the second patient, prednisolone was reduced to less than 10mg per day at 11 months and then stopped completely at 23 months. The third patient did not respond to 8 months of azathioprine and required increased doses of prednisolone to control the symptoms of ENL.

The median length of follow up after ENL had terminated was 29 months (range 1-144 months). In 10 patients for whom electronic documentation of outpatient appointments was available, the median number of attended appointments was 49. Figures 4 and 5 show the clinical course of two patients with ENL.

Discussion

This is the first study to describe the clinical course of ENL in a clinic where patients can be treated with thalidomide and prednisolone in a non-endemic region.

Compared to other cohorts, the rate of ENL in our study is high: 56% of our patients with LL leprosy developed ENL compared to 49% of LL patients in a hospital-based study with similar inclusion criteria and case definitions in Hyderabad, India. Other studies have found lower rates of ENL; 31% in multibacillary patients in Brazil and 5% in field studies of multibacillary patients in Ethiopia. The differing inclusion criteria, case definitions and clinical settings may account for the variation between studies. However, the median BI at diagnosis in our cohort was 4.65 compared to 3.5 in Hyderabad; 63% of our patients had over 12 months of symptoms before being diagnosed with leprosy compared to 52% of patients in Nepal. We postulate that delay in diagnosis may result in a higher BI and, as a high BI is a known risk factor for ENL, increased rates of ENL in our cohort. The UK is a non-endemic area with an average of 10 new leprosy diagnoses per year. Awareness of leprosy is low outside the specialties of dermatology, infectious disease and neurology. This may contribute to delays in diagnosis.

As in previous studies, most of our patients developed ENL whilst on leprosy treatment. However, our patients had a longer duration of ENL (median 60 months, range 9-192 months) than previously reported. In Hyderabad, the median duration of ENL was 18.5 months. In Nepal, the range was 1 to 62 months. The longest case of ENL previously documented in the literature is 96 months, far shorter than our
maximum ENL duration of 192 months. Figure 5 shows the clinical course and
treatment of a patient with chronic severe ENL for 105 months.

It is unclear why our cohort has a longer median duration of ENL than previously
recorded but we suspect that it is a combination of three factors. Firstly, it may be due
to delay in leprosy diagnosis; our patients had a higher BI at diagnosis resulting in a
longer time to clear M. leprae antigen from skin, thus a prolonged period of immune
complex deposition causing symptoms of ENL. In our cohort, patients with a BI over
4.5 had a significantly longer duration of disease than those with a BI of 4.5 or less.

Secondly, there may be some patients with no adverse effects from thalidomide who
received extended courses of treatment because thalidomide kept them symptom free,
thus artificially prolonging the estimated duration of their ENL. Finally, it may be due
to the prolonged follow up of our patients. We reviewed patients for a median 29
months after their last episode of ENL hence we would expect to identify late
recurrences or prolonged mild ENL. As HTD is the main leprosy clinic in the UK,
loss to follow-up is rare and patients who developed recurrent ENL after discharge
would be referred back to our clinic. Previous studies have not documented duration
of follow-up or number of patients lost to follow-up so may have underestimated
the true duration of disease.

The extended duration of ENL has both social and medical implications for patients.
Most of our patients were of child-bearing and working age. In the UK, people whose
health is poor earn 7-15% less and are 34% less likely to be in employment than those
in average health. In West Bengal, the household cost of ENL was 28% of monthly
income and 11% of households faced catastrophic health expenditure.

In addition, ENL is often treated with long courses of steroids putting patients at
considerable risk of adverse events; 13% of patients treated with steroids developed
steroid-induced diabetes (SID) compared to 21% and 26% in two studies in India. The increased rate may be due to a higher incidence of Type 2 diabetes in South Asia.

However, until recently we did not routinely check patients’ blood sugars or HbA1C,
hence our data may underestimate the true incidence of SID in our cohort.

Sugurmaman investigated complications of steroid therapy in leprosy reactions and
found that 23% of patients developed cataracts and 3% developed TB. These
complications were not seen in our small cohort. However, this highlights the
importance of systematic recording of side-effects in patients on steroids, particularly
in areas without access to thalidomide. Figure 4 shows the clinical course and
treatment of a patient with ENL and a Type 1 reaction. She developed SID and
hypertension, gained weight and developed a Cushingoid habitus, which she found
particularly distressing.

There were no deaths in our cohort. Walker et al. found a mortality rate of 7.9% in
patients hospitalised for ENL in Ethiopia, where thalidomide is not available. In 50%
of deaths, steroids were identified as a definite contributing factor; these patients died
of TB or septic shock. We postulate that the zero mortality in our cohort was due to
the availability of thalidomide.

Thalidomide allowed 75% of patients to be weaned off steroids in a median of 2
months. However, it may need to be taken for years and many patients complain of
side-effects, particularly tiredness, which negatively affects their working and social
lives. Thalidomide is prothrombotic; the risk of deep vein thrombosis (DVT) in
patients with myeloma on thalidomide and dexamethasone is 17% and there are
increasing reports amongst leprosy patients on thalidomide. None of our patients
developed DVT. The occurrence of thalidomide-induced neuropathy in this cohort is
currently being investigated and will be reported separately.
Eighty percent of female patients were of childbearing age. Use of thalidomide precludes pregnancy and the S.T.E.P.S. programme mandates that women use two forms of contraception and attend clinic monthly for pregnancy testing. Although this is effective at reducing unplanned pregnancy it is disruptive to the patient’s working and family life.

Finally, the length of ENL has implications for health care provision. Patients with ENL attended many outpatient appointments and eight patients required hospital stay. They received long courses of treatment, some of which resulted in adverse events which themselves required treatment. As it is impossible to predict the likely length or severity of ENL at the outset, it is difficult to plan healthcare provision for these patients. Although this is unlikely to be problematic in the UK where the number of patients with ENL is small, it may have a significant impact on health care provision in countries where leprosy is highly endemic.

There were a number of limitations to our study. Notably the small sample size and non-randomised nature of this study limit the potential to generalise the data to other cohorts of patients. Most patients received both thalidomide and prednisolone and so it was not possible to evaluate their individual therapeutic effect. Furthermore, we have not discussed the neurological toxicity of thalidomide. This will be reported in a separate paper due to the large amount of data and complexity of this important topic.

As this was a retrospective review of patient records, it was limited by clinical documentation. In particular, side-effects of treatment were not systematically documented in notes but only documented if they occurred. Furthermore, our patients did not routinely have blood sugar, HbA1C and blood pressure measurements performed in clinic and so we may have underestimated treatment related side-effects.

**Conclusion**

This study highlights the significant effect that ENL has on patients’ lives even in a developed country with access to prednisolone, thalidomide and other disease modifying agents. In particular, it shows that ENL can last far longer than was previously suspected. This has implications on the working, social and family life of our patients and on health care provision. It underscores the importance of using thalidomide as a steroid-sparing agent to prevent adverse events associated with long-term steroid use. Further work is needed to investigate predictors of ENL severity and length of disease so that patients can be started on appropriate therapy early on in the illness. In addition, ongoing investigations into effective steroid-sparing agents in ENL should be supported and further advocacy is needed in leprosy endemic regions where thalidomide is not available.

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Competing Interests: Diana Lockwood is on the editorial board of Leprosy Review. All authors declare that the answer to the question on competing interest form are all ‘No’, and therefore have nothing to declare.

Contributorship
LEB Nabarro designed the study, collected and analysed the data and wrote the manuscript. D Aggarwal and M Armstrong collected data. DNJ Lockwood conceived of and designed the study, reviewed the data and helped to write the final manuscript.

References


Figure 1: Treatment regimens of patients with ENL

30 patients

- 28 received rifampicin, clofazimine and dapsone.
- 1 received rifampicin, ofloxacin and minocycline
- 1 received rifampicin and dapsone

- 22 completed therapy
- 6 changed regimen

3 received rifampicin, ofloxacin and minocycline
1 received rifampicin, ofloxacin, minocycline and clofazimine
1 received rifampicin and clofazimine
1 received rifampicin, dapsone, ofloxacin
1 received rifampicin, dapsone and minocycline

Median length of treatment 30 months

This patient had previously been partially treated in India but had developed severe clofazimine pigmentation hence was started on a clofazimine free regimen.
This patient received rifampicin and dapsone alone as treatment that had been started elsewhere and the BI was low.
6 (20%) patients changed regimen due to complications of therapy; 5 due to severe clofazimine pigmentation and one to enable directly observed treatment with the ROM regimen.
The median duration of treatment is longer than advised by the WHO as patients with a BI ≥4 are treated for 2 years or until their BI falls below 2, due to the higher rate of relapse in these patients.
Table 1: Case definitions. Type and severity of ENL have been adapted from previous studies looking at the clinical course of ENL in Ethiopia and India.

<table>
<thead>
<tr>
<th>Case Definitions</th>
<th>Erythema nodosum leprosum</th>
<th>The presence of tender skin nodules with or without other systemic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of ENL</strong></td>
<td>Acute</td>
<td>Episode of ENL lasting less than 6 months in which treatment was slowly withdrawn with no recurrence of ENL whilst on treatment</td>
</tr>
<tr>
<td></td>
<td>Recurrent</td>
<td>At least one further episode of ENL occurring 28 days or more after withdrawal of treatment for ENL</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>Episode of ENL lasting longer than 6 months during which patient is on continuous ENL treatment or any treatment free periods are less than 28 days.</td>
</tr>
<tr>
<td><strong>Severity of ENL</strong></td>
<td>Mild</td>
<td>A few mildly tender lesions with or without mild aches and pain or low grade fevers without neuritis</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Mild ENL with neuritis or with more than three systemic symptoms such as joint pain, bone pain, anorexia, malaise, lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>Multiple skin nodules with high grade fever and organ involvement (iritis, orchitis, severe neuritis)</td>
</tr>
<tr>
<td><strong>Onset of ENL</strong></td>
<td>Before MDT</td>
<td>History of ENL onset before MDT was started or presence of ENL when MDT was started</td>
</tr>
<tr>
<td></td>
<td>During MDT</td>
<td>ENL which started during MDT</td>
</tr>
<tr>
<td></td>
<td>After MDT</td>
<td>ENL which started after MDT had finished</td>
</tr>
<tr>
<td><strong>ENL treatment</strong></td>
<td>High dose clofazimine</td>
<td>More than 50mg per day of clofazimine OR clofazimine prescribed independently of MDT.</td>
</tr>
<tr>
<td></td>
<td>Self-directed therapy</td>
<td>Rescue packs of prednisolone or thalidomide kept by the patient and taken in short course when the patient experienced a flare-up of ENL.</td>
</tr>
<tr>
<td><strong>Duration of ENL treatment</strong></td>
<td>Time from initial ENL symptoms until termination of symptoms OR the patient stopped taking treatment for ENL (whichever was latest)</td>
<td></td>
</tr>
<tr>
<td><strong>Complications of steroid use</strong></td>
<td>Hypertension, steroid induced diabetes, cataracts, osteoporosis, weight gain, infection</td>
<td></td>
</tr>
<tr>
<td><strong>Complications of thalidomide use</strong></td>
<td>Tiredness, constipation, unplanned pregnancy, dizziness, abdominal pain, venous thromboembolism</td>
<td></td>
</tr>
</tbody>
</table>
Figure 2: Duration of ENL

- Median length: 60 months
- Range: 9-192 months

- BI > 4.5: median length 76 months
- BI < 4.5: median length 40 months (P = 0.0043)
Figure 3: Combinations of treatments that patients received
Figure 4: The clinical course of a patient with ENL, type 1 reaction and neuritis. The patient was treated with prednisolone and thalidomide and developed steroid induced diabetes and hypertension as a complication of treatment.
Figure 5: The clinical course of a patient with chronic severe ENL maintained on thalidomide with intermittent prednisolone.