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WORKSHOP REPORT

International workshop on erythema nodosum leprosum (ENL) – consensus report; the formation of ENLIST, the ENL International STudy Group

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Introduction

A workshop on erythema nodosum leprosum (ENL) took place at the Parklane Hotel, Cebu City, Philippines from 18th–20th February 2012. It was organised by the American Leprosy Missions, the Leonard Wood Memorial Center for Leprosy Research and the Leprosy Group at the London School of Hygiene and Tropical Medicine (LSHTM).

The workshop brought together 28 scientists and clinicians from a variety of disciplines and organisations. Thirteen countries in Asia, the Americas, Australasia, Africa and Europe were represented. A list of participants and their affiliations is given in the Appendix to this report.

Structure of the Report

Part 1 of the report comprises a summary of salient points noted during the presentation of research findings and disease profiles in the endemic countries represented. Part 2 is made up of the consensus statements of the two working groups. They attempted to reach consensus on current understanding, identify gaps in knowledge and prioritise research needs for the future. They addressed the following topics:

Group 1: Clinical issues
Group 2: Laboratory science and pathology issues

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Part 1 – Plenary Sessions' Report

Professor Diana Lockwood, one of the conveners of the workshop welcomed the participants and thanked the Leonard Wood Memorial Center for hosting it. She gave a brief overview of the clinical course of ENL and highlighted the challenges it poses:

1. Every centre has a relatively small number of patients, but ENL is an important cause of morbidity in leprosy.
2. Thalidomide is an effective drug, but is not available in all countries due to teratogenicity.
3. Previous treatment trials have been of poor quality and a more robust body of evidence is needed on which to base management recommendations.
4. The immunopathology of ENL remains obscure.

The Cochrane Review 'Interventions for erythema nodosum leprosum'showed that good quality data are lacking and that to improve this multicentre studies would need to be performed.[1]
Professor Lockwood outlined the aims of the workshop:

1. To critically review the published evidence on treatment of ENL
2. To identify research topics which could improve patient outcomes
3. To identify studies needed to improve the understanding of the pathogenesis of ENL
4. To highlight improvements in the design of future clinical trials of treatments for ENL
5. To develop an ENL research network

There were presentations on the clinical burden and the management of ENL by participants from the different endemic countries.

BRAZIL

Dr Anna Sales from Fiocruz, Rio de Janeiro, Brazil stated that between 1998 and 2010, 462 multibacillary (MB) patients were treated with 12 doses of WHO standard multi-drug therapy (MDT) and followed annually for up to 10 years. The Ridley-Jopling classification of these 462 patients was 99 with mid-borderline leprosy, 151 patients with BL leprosy and 212 patients with LL. 60% of the 462 developed ENL. ENL occurred before and up to 6 years after starting MDT.

The Brazilian Ministry of Health guidelines recommend the use of thalidomide or prednisolone. High dose clofazimine and pentoxifylline are also recommended.[2] At Fiocruz patients with ENL are usually treated with thalidomide. Prednisolone and pentoxifylline are used for individuals with recurrent ENL for whom thalidomide is not appropriate.

Dr Sales also presented cases of ENL which illustrated the varied clinical presentations of ENL at Fiocruz. This included patients with extensive necrotic skin lesions and unusual presentations such as parotid gland involvement.

Dr Jaison Barreto reported that at the Instituto Lauro de Souza Lima between 2006 and 2010, 397 patients were treated for ENL. 57% of LL patients had ENL. Thalidomide is used often to manage patients with ENL. Thalidomide has a rapid onset of action and is very effective. Dr Barreto reported that the effect of clofazimine and pentoxifylline was disappointing. Azathioprine seemed to be effective but is expensive. Dr Barreto showed some

unusual cases of ENL mimicking Sweet's syndrome and erythema multiforme and cases of necrotizing ENL.

ETHIOPIA

Dr Shimelis Doni described the recent experience at the All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre (ALERT) in Addis Ababa, Ethiopia where there were 327 new leprosy patients diagnosed in 2011and 2000 patients attending for reaction management. In the previous two months, 85 patients had attended with ENL. Thirteen were inpatients. 12% of patients had had ENL for more than 2 years and 68% of all individuals with ENL were classified as severe. 24% of patients had been taking prednisolone for more than 2 years. Thalidomide is not available in Ethiopia.

INDIA

Dr Vivek V. Pai described how the Bombay Leprosy Project (BLP) covers 23 health posts and is a referral centre. 265 patients with ENL were seen at the BLP from 2005 to 2011. Clinical data on 56 patients indicated that 39 patients had a BI of 3 + and above. 35 patients had multiple episodes of ENL. Patients are treated with clofazimine, prednisolone and thalidomide, and sometimes all three drugs in combination. Different brands of thalidomide are available and this competition has lead to a reduction in cost. Thalidomide has been used for approximately 6 years. The starting dose of thalidomide is 300 mg daily in divided doses. The dose is then tapered and the patient maintained on 50 mg daily. 35% of patients develop further ENL after stopping thalidomide.

NEPAL

Dr Mahesh Shah from Anandaban Hospital in Nepal described the experience in that referral centre. In 2011, 137 new cases of leprosy were diagnosed. There were more than 100 admissions for reactions. A retrospective review indicated that 114 of 174 (66%) ENL patients had LL. 51·3% of patients had ENL prior to the diagnosis of leprosy but others developed their first episode of ENL within 5 years of initiation of MDT. 50% of patients were still receiving treatment with prednisolone and/or thalidomide for their first episode of ENL 18 months after it was diagnosed. The retrospective data from Anandaban suggests that subsequent episodes of ENL are of shorter average duration than first episodes. Thalidomide is available but expensive and rarely used in females. An inpatient stay is required for patients while they are taking thalidomide. Dr Shah had found that MTX had some steroid sparing effect in severe chronic, prednisolone-dependent patients with ENL. He has also given azathioprine to some patients with ENL.

THE PHILIPPINES

Dr Marivic Balagon presented the experience of ENL at the Leonard Wood Memorial Center during the three year period 2009–2011. More than 26% of patients with BL and LL leprosy developed ENL. Approximately 45% had a BI greater than or equal to 4. 87% of cases of ENL presented at diagnosis or in the three years following the diagnosis of leprosy. The majority of patients were treated with prednisolone, thalidomide being unavailable in the

country. She also presented the recently published data comparing patients treated with 12 or 24 months of MB MDT.[3] Two separate cohorts of individuals, recruited in the periods 1985–1992 and 1998–2004, were followed for relapse. The individuals treated with the shorter course of MDT did not have an overall increased risk of developing ENL, but the severity appeared to be increased; BI greater than or equal to 4 was a significant risk factor. A placebo controlled trial of clofazimine prophylaxis after completion of 12 months MDT is now underway.

Professor Warwick Britton presented a review of ENL mechanisms which is to be published separately. This described the evolution of our understanding of the pathophysiology of ENL over the past four decades. ENL has long been known to be a distinct clinical entity, with a histopathological picture of neutrophil infiltration and small vessel vasculitis, but the underlying immune mechanisms are obscure. He outlined four phases in our more recent understanding of the pathophysiology of ENL.

Immune Complexes

ENL has features resembling a Type III hypersensitivity disorder due to immune complexes (IC).[4] IC are a combination of antibody, antigen and complement. There is a polyclonal antibody response in borderline lepromatous (BL) leprosy and lepromatous leprosy (LL).[5]

Skin blisters from ENL lesions contain IC,[6] but they can also be found in patients without ENL. *M. leprae* activates the complement pathway. However IC are not consistently identifiable in ENL and are not a complete explanation of ENL. In IC disease anti-B cell strategies or anti-antibody strategies are useful. In hepatitis C cryoglobulinaemia (an example of an infectious cause of IC disease) it is important to block B cells but also to remove antigen by treating the infection.

Tumour Necrosis Factor (TNF)

TNF was shown to be a critical cytokine in mediating ENL.[7,8] TNF is present in the serum and in ENL lesions.[8,9] C-reactive protein (CRP) is usually raised in ENL.[10,11] *M. leprae* and lipoarabinomannan stimulate TNF from monocytes.[12] Mononuclear cells from ENL patients spontaneously release TNF.[13]

Thalidomide can cause a rapid fall in plasma TNF[7] and blocks its release from monocytes although not all patients have increased levels of TNF.[14] Thalidomide has other mechanisms of action as exemplified by its effect on lymphocyte proliferation in myeloma.[15,16] TNF is a marker of the proinflammatory response in ENL but it is not clear what triggers the release of TNF and interleukin-6. The inhibition of TNF is a therapeutic aim, but some anti-TNF strategies significantly increase the risk of tuberculosis.[17] Blocking effector molecules such as NF-κB downstream of TNF may have a role.

T Lymphocyte Activation

T cell responses may be relevant in ENL although they are normally minimal or absent in BL and LL leprosy.[18] Modlin showed an increase in the number of CD4 T cells in ENL compared with other LL cases.[19] Prolonged interferon-γ therapy induced ENL in LL patients.[20] There may be a place for T cell inhibition with agents such as cyclophosphamide, pulse

methylprednisolone or methotrexate (MTX). However the evidence is not strong enough to explain the pathophysiology of ENL completely.

Neutrophil Recruitment

Gene expression in ENL lesions has recently been reported.[21] Neutrophil recruitment genes, including E-selectin, are upregulated and their expression increased compared to LL lesions.

Studies have repeatedly demonstrated that a high bacterial index (BI) is a risk factor for the development of ENL which strongly suggests that the process is antigen driven.[22,23] Slit skin smears (SSS) are important for predicting those at highest risk but where SSS are not done, another simple measure of antigen load is needed, such as phenolic glycolipid-1in blood or urine.

In conclusion, Professor Britton emphasised the fact that ENL is a clearly recognised clinical entity, but that there seems to a marked heterogeneity in the underlying immunopathology. Thalidomide is certainly very effective in mitigating the condition, but the search for safe alternatives has not so far been successful.

Dr Gigi Ebenezer gave a presentation on the pathology of ENL. The classical histopathological features in ENL lesions are infiltration of neutrophils within pre−existing macrophagic granulomas of lepromatous lesions often associated with vasculitis, panniculitis, and macrophages with fragmented bacilli. Histological evidence of endothelial damage with necrotizing vascular changes and thrombus formation reflect the heterogeneous clinical presentation of ENL lesions. The role of B cells in the pathogenesis of ENL is unclear and new studies are needed on the role of B cells in ENL because of the lack of contemporary data. Gene expression in ENL lesions provides evidence of a local inflammatory mechanism linking IL-1β, E-selectin and neutrophil recruitment. This is an important pathway for tissue injury and thalidomide inhibits this neutrophil recruitment.[21] E-selectin is a transmembrane protein involved in neutrophil binding to endothelium, an initial step in neutrophil recruitment. Alpha-1-acid glycoprotein levels were high in patients with ENL compared to those with LL. The level of this acute phase protein decreased to normal levels after treatment of ENL with thalidomide.[24] The authors suggested this may be a useful biomarker of ENL.

Dr Barreto discussed some preliminary work concerning angiogenesis in leprosy. There is increased expression of CD31 and CD105 in the skin lesions of patients with ENL compared to other LL patients. CD31 is a marker of endothelial cells and lymphatics and CD105 a marker of proliferating endothelial cells.[25] These data indicate that further studies of CD105 in ENL might be useful.

Professor Lockwood discussed the treatment of ENL in detail emphasising its recurrent nature.

The WHO Operational Guidelines mention steroids and ‘other drugs’ in the management of ENL.[26] The ILEP guidelines refer to the use of prednisolone, clofazimine and thalidomide but do not address the issue of how to manage patients with chronic, recurrent ENL.[27] The Cochrane Review identified only 13 trials with 445 participants, most conducted prior to the introduction of MDT.[1] The review highlighted the methodological problems in the studies including the absence of scales, no intention-to-treat (ITT) analyses and poorly defined endpoints. The authors concluded that thalidomide has a significant effect. A further conclusion was that clofazimine is better than prednisolone but this is counter to clinical experience.

The outcome measure in most studies is acute symptom control. The studies on clofazimine in ENL are very short with data recorded for only 4-6 weeks. The time to the next clinical episode was not reported. There has been one further randomised study comparing thalidomide and prednisolone treatments published since the publication of the Cochrane Review.[28] Although thalidomide is known to be neurotoxic no systematic data has been collected on this complication in leprosy patients. There is a paucity of data concerning other potential agents for treating ENL which need further assessment in systematic studies Azathioprine has not been studied in a randomised controlled trial (RCT) but a case series of nine patients from Brazil has been reported.[29]

Ciclosporin is being used in a pilot study in Ethiopia. There is a report of ciclosporin in three individuals who were not responsive to thalidomide.[30] The use of the TNF inhibitors infliximab and etanercept has been reported in one patient each.[31,32]

The recurrent nature of ENL results in many patients being treated with high doses of corticosteroids for prolonged periods which exposes them to significant adverse effects. Thalidomide is not available in all countries and is not suitable for all patients with ENL. Effective treatments need to be identified, for those patients with recurrent ENL or those with contraindication, which can be used instead of prednisolone and thalidomide. Another useful approach would be the ability to identify patients at risk of ENL which would allow selection of those who might benefit from prophylaxis.

Dr Saba Lambert from ALERT and LSHTM discussed the use of ENL severity scales. Assessing clinical signs and severity of ENL is necessary for diagnosis and treatment. A validated scale would empower researchers with an instrument for comparing their patients' outcomes. The lack of comparable data has hindered the development of internationally accepted treatment protocols and guidelines. A validated scale would aid the comparison of therapeutic agents.

The items that have been used to assess the severity of ENL in different scoring systems include the number of skin lesions, the presence of ENL lesion ulceration, the degree of fever, the presence of neuritis and other extra-cutaneous manifestations.[3,27,33–35] A standard approach is required in order to measure a complex multi-system disorder such as ENL.

Dr Lambert discussed the preliminary findings of using a severity scale with 21 items. Tender skin nodules, bone tenderness and peripheral oedema were the most common features of ENL and fever ($>37{\cdot}5^{\circ}C$) occurred in just 50% of patients classified as having severe ENL. Nerve tenderness and ENL associated nerve function impairment (NFI) was common in these Ethiopian patients. She advocated the development of a reliable severity scale, validated in different populations which might be composed of: symptoms and signs, the patient's assessment of their pain severity, the duration of ENL and the ENL treatment required. Dr Lambert also indicated that a scale useful as a research tool may differ significantly from one used in routine clinical practice.

Dr Peter Nicholls presented a secondary analysis of ENL in the INFIR Cohort which enrolled 303 MB patients.[36] In total 16 patients were diagnosed with ENL. Five were diagnosed using clinical criteria and a further 11 following a skin biopsy. Interestingly, only two of the individuals diagnosed clinically had the histological features of ENL in their skin biopsies. This has implications for the confirmation of ENL using histology as the gold standard. The factors that were predictive of a diagnosis of ENL were the presence of fever and a positive slit skin smear. Individuals with ENL appeared to have only modest NFI as assessed by voluntary muscle testing or sensory testing with monofilaments, but there was

evidence of significant subclinical nerve involvement using sensory and motor nerve conduction and warm detection threshold.

Dr Steve Walker gave a presentation concerning design issues for RCTs in ENL. The context for this was an interpretation of the findings of the four RCTs performed in the MDT era (Table 1).

The pilot study by Girdhar and colleagues compared 10 patients randomly allocated to receive intravenous betamethasone or placebo and oral steroids.[37] The authors concluded that there was no increased benefit of intravenous steroids compared with oral. Villahermosa compared two different thalidomide regimens in 22 Filippino patients and noted rapid symptom resolution.[38] However 95% of patients had recurrence within eight weeks of stopping thalidomide and 68% experienced mild or moderate adverse effects due to the drug. A double blind RCT comparing pentoxifylline and thalidomide in 44 Brazilian patients for 30 days also demonstrated rapid symptom resolution with thalidomide.[39] However recurrence was not reported and 25% experienced adverse effects by day 7. The only study to compare thalidomide and prednisolone was performed in India and enrolled 60 patients.[28] The treatment allocation was not concealed from the participants or the observers and thalidomide was given for a longer period than prednisolone. Thalidomide had a quicker onset of action and there was a very low rate of ENL recurrence of 6% in the thalidomide treated group during the one year follow up period. This contrasted with 25% of the prednisolone treated group experiencing recurrence on reducing to a dose of 10 mg daily. Adverse effects attributed to thalidomide occurred in more than 30% of individuals. The adverse effects of thalidomide reported in these studies were; somnolence, constipation, nausea, headache, vertigo, pruritus, tremors, inability to concentrate and rash.

There are many possible interventions that might be studied as pilot projects or in larger RCTs. A chosen intervention should be likely to have some effect, be widely available, affordable and acceptable to patients. Having selected a study intervention choosing a suitable control is essential. Thalidomide is considered to be the gold standard and there might be ethical issues in designing a study that did not include a thalidomide arm. However thalidomide is not considered effective in ENL associated neuritis and these patients have often been excluded from studies. It would be useful to know the proportion of patients who receive thalidomide as a first line agent in the management of ENL.

Table 1. Randomised controlled treatment trials in MDT treated leprosy patients with ENL

Study	Intervention	Number	Recurrence rate	Adverse events	Comments
Girdhar[37]	Intravenous betamethasone versus placebo and oral steroids	10	Unclear	No significant differences reported	Authors reported no benefit of intravenous therapy
Villahermosa[38]	Thalidomide	22	95% recurred within 8 weeks	68%	No females.
Sales[39]	Thalidomide versus pentoxifylline	44	Not reported	25% by day 7	Neuritis excluded 6 females.
Kaur[28]	Thalidomide versus prednisolone	60	Thalidomide 6%. Prednisolone 25% at a dose of 10 mg	Thalidomide >30%. Prednisolone more than thalidomide.	Neuritis excluded. No blinding.

The following points are important for improving the design of future RCTs:

1. There are no prospective studies documenting the frequency of the clinical features of ENL. This should be addressed.
2. Study inclusion criteria and robust clinical definitions are required
3. Future treatment studies also require well defined outcome measures and these should include some measure of ENL recurrence.

Part 2 – Consensus Statements of the Working Groups

Dr Indira Kahawita gave feedback from Discussion Group 1 on Clinical Issues. The group identified the following research priorities:

1. Second line drugs – steroid sparing agents and alternatives to thalidomide. There is a pressing need to identify affordable and effective treatments of ENL. This will improve outcomes for patients who only have access to prednisolone or in whom thalidomide is contraindicated.
2. Natural history. In order to assess treatments and determine prognosis for patients we need to define more clearly the following:
   a. The range of clinical lesions seen in ENL cases
   b. The geographical variations in incidence and clinical picture
   c. Changes in the clinical picture over time (recurrent and chronic cases)
3. Validate a severity scale in order to have a quantitative outcome measure for assessing efficacy of trial interventions. The weighting of some items may be necessary.
4. Identify risk factors for the development of ENL which might facilitate the use of prophylaxis
   a. Clinical parameters that parallel BI
   b. CRP as a predictor of ENL
   c. The role of stress and other psychosocial issues
5. Identify current management practices for ENL. There is widespread variation in availability of treatments and how they are employed.
6. Best outcome measures for RCTs include:
   a. Relief of acute symptoms
   b. Time to recurrence of ENL
   c. Total prednisolone dose used
   d. Reduction in a validated ENL severity score
   e. Quality of life assessment

What are the requirements for becoming a collaborating centre?

A descriptive study of the clinical features of ENL could include many centres, but it was felt best to limit the group to present participants, at least initially. Prospective studies, whether descriptive studies or clinical trials, will need a minimum number of patients diagnosed with ENL each year. Collaborating centres would formally agree to share data.

Feedback from Group 2 on Laboratory issues was given by Dr Deanna Hagge. The Group identified three themes for ENL laboratory research

1. Studies of ENL pathogenesis
2. Studies elucidating predictors of ENL
3. Studies to improve ENL monitoring

These studies would ideally lead to field feasible tests with clinical relevance such as simple blood, serum or urine assays. Potential biomarkers that could be investigated include CRP, angiogenesis markers (CD105, vascular endothelial growth factor), cytokines, chemokines and blood metabolites such as vitamin D, fatty acids and lipid mediators.

Investigation of pathogen specific indicators would be useful. Is there an epitope-antibody shift associated with ENL? This might be investigated using B cell and T cell assays. Is there a threshold or quantity of systemically available antigen that could be measured and associated with ENL? Immunohistological studies could focus on the cellular infiltrate in ENL but also examine epidermal nerve fibres as a potential marker of thalidomide toxicity. Other ideas for potential research were the role of re-infection or persistent exposure, ENL phenotype and *M. leprae* genotype correlation studies, differential expression in relation to MDT exposure and genome wide scanning for host markers.

ENLIST GROUP INITIAL RESEARCH EXERCISE

It was agreed to collect prospective data on the clinical features of ENL in patients at first presentation or those experiencing a recurrence or an exacerbation of ENL. This will be done during 2012 and 2013 using agreed definitions and standardised data collection forms. The objectives of this exercise are to:

1. Describe the clinical features of ENL
2. Describe the natural history of ENL
3. Determine current management practices
4. Determine features of severity

The initial data will be presented by each centre at the International Leprosy Congress in 2013 with publication of the pooled data in a peer-reviewed journal in early 2014.

Conclusion

The long-term goal of the ENLIST group is to conduct clinical trials of alternative treatments for ENL and thus provide evidence for the rational treatment of the condition. In the short-term, there is a need for a clearer definition of the clinical picture and course of ENL; correlation of the clinical findings with histopathological findings and other biomarkers; the development of a severity scale which could be used to monitor patients enrolled in a clinical trial; and the development of a network of centres able to recruit, investigate and follow-up significant numbers of ENL patients, as part of a multi-centre study.

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