

## **Pre-Congress Workshop on Reactions and Neuritis**

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### **ENL**

A pre-print of a paper in press, by Indira Kawahita and Diana Lockwood, was distributed. Presentations on pathology, immunology, and gene profiling were discussed. The requirement for PMN's and vasculitis as diagnostic criteria as a criterion of ENL were discussed, noting that in a series from India, only 44% of biopsies of clinical ENL showed vasculitis. The issue of timing of the biopsy was discussed, with particular reference to the use of PMN's as a criterion for diagnosis since their appearance in tissue lesions appears to be transient, and there was consensus that a re-evaluation and standardisation of pathologic criteria for ENL is advisable. The experience of ENL developing after experimental therapy with intracutaneous rIFN $\gamma$  was noted, and there was a discussion of the lack of understanding of mechanisms that trigger ENL. Some data from the Philippines indicates that the incidence of ENL is much higher in patients who received one year of MDT compared to those who received two years of MDT. Microchip analysis of mRNA from 13 biopsies from patients with ENL and controls, including two pairs of specimens, has demonstrated a large number of genes up- or down-regulated. Many of the up-regulated genes are notably associated with vascular and angiogenic factors or adhesion molecule expression. This is particularly interesting in view of the suggested role of thalidomide in modulating angiogenesis. It was noted that this technology has its own challenges regarding data analysis, and that while some may regard such studies as 'fishing expeditions', others see them as voyages of discovery. In addition to indications that ENL may be an immune complex phenomenon, the potential role of CMI in ENL was discussed, noting that for both theories the evidence remains interesting but not conclusive. Presentations on clinical aspects and risk factors, detection and management in the field, management in specialist centres, and research needs were discussed. Regarding clinical aspects, it was emphasised that:

- Clarification is needed regarding the frequency of the different features in patients developing ENL who have received MDT.
- Prednisolone and thalidomide are effective but may have different mechanisms of action, the former mainly suppressing inflammation while thalidomide may act on underlying mechanisms.
- Well designed clinical trials are required but difficult due to relapsing nature and numbers needed.

- Standardised and validated outcome measures and severity assessments are essential in assessing therapeutic interventions.

The need was emphasised for development of laboratory tests to assist in assessment of severity and resolution of ENL. The experience of using inhibitor of TNF $\alpha$ , infliximab, in the treatment of two patients with ENL was discussed, noting that it was highly effective but one patient relapsed and required thalidomide treatment to prevent recurrence. There is a theoretical risk that patients treated with infliximab may be at risk of relapse of their leprosy, since infliximab has been associated with the development of clinical leprosy in leprosy endemic areas. In the field, ENL may be divided into three categories: mild (single episode ENL), moderate or acute recurrent (multiple episodes of ENL for < 2 yr), and severe or chronic (continuous immunosuppression required). There is a need for good trial data on the management of mild ENL, although clofazimine is widely used. The general opinion was that clofazimine in higher doses helpful in moderate ENL. The importance of recognising iritis and other generalised involvement was discussed, as well as the need to emphasise to health workers the varied nature of ENL. Concern was expressed that ENL and its complications are less well recognised in 'integrated' health settings, where it might be judged as unimportant when health workers were unduly concerned about the overall collection of numbers of cases on treatment or released from treatment, etc. As summarised, some of the major challenges in the field are:

- Training and logistics: awareness of ENL and timely referral of cases;
- Recognition of nerve damage and iritis
- Supply of drugs – clofazimine and steroids are not always readily available.

#### TYPE 1 REACTIONS

The pathology and T1R and a study of correlations between pathologists in the histopathological diagnosis of T1R were presented. Data were reviewed concerning studies of histological features seen in standard H/E – stained sections, as well as studies using antibodies to evaluate the changes in HLA-DR expression, neuropeptides, and other markers, noting that none of these has, to this point, provided definitive markers for the diagnosis of T1R. An international double-blind study of the histopathological diagnosis of T1R by highly experienced pathologists demonstrated that edema, the presence of giant cells and the size of giant cells were all recognised as important features, but that other features were interpreted more selectively by individual pathologists. Overall, only 50% of reactions were clearly diagnosed histologically. The discussion highlighted the need for standardisation and validation of diagnostic histopathological criteria for T1R, research to understand the triggering mechanisms of T1R, and the need for criteria to distinguish between relapse and reactions involving nerves. It was noted that triggering mechanisms may involve factors 'outside of' the immune system itself, such as neuroendocrine influences.

Presentations regarding animal models and *in vitro* models for nerve injury were discussed. The armadillo offers the first good animal model of neuritis in leprosy, with the opportunity to follow functional parameters such as nerve conduction together with morphologic and molecular analyses of nerve trunks at different times during the course of infection. Sequencing of the armadillo genome has begun to provide the molecular tools needed to study this model in depth; such studies are now underway. Discussion noted that it

is still necessary to delineate the limitations of this model of neuritis as compared to leprosy neuropathy in man. Hope was expressed that new studies of the armadillo model might generate an animal model for reactions, as well. Technical advances now enable gene expression analysis using microarrays to explore the changes induced in primary human Schwann cells *in vitro* after infection with *M. leprae*. Some of these experiments have been done; over 200 genes show significant up- or down-regulation 24 h after infection, but analysis of the large database from this experiment has only begun. Studies of the role of Schwann cells in promoting chemotaxis of *M. leprae*-infected and uninfected monocytes is also of interest. It was emphasised that such studies *in vitro* should be done at cooler temperatures than usual (i.e., 33°C) to examine the effects of live *M. leprae*, with dies rapidly at 37°C.

Clinical aspects and risk factors for T1R and neuritis, the evidence base for therapeutic interventions, detection of T1R in the field, and detection in specialist centres were discussed. Studies have now demonstrated that the major risk factors for nerve function impairment are: 1) MB leprosy and 2) NFI before the patient is diagnosed. From these studies, it is evident that approximately 1/3 of MB patients will be affected by NFI under current circumstances of diagnosis and treatment. Evidence suggests that the best predictor of T1R is prior T1R. An evidence-based review of the treatment of reactions noted that long-term administration of corticosteroids is problematic due to many side-effects, and opened the question as to whether there is an optimal corticosteroid regimen. Many participants felt that there is not yet convincing evidence of an optimal regimen, and opted for individually tailored treatment. The discussion highlighted the need for randomised controlled trials of corticosteroid regimens alone and in combination with other agents. Preliminary evidence from 13 countries with widely differing characteristics, concerning the detection of T1R and neuritis in the field, suggests that knowledge of T1R and skills to detect T1R are not good in most field sites, largely due to poor supervision and emphasis in training programs on detection of leprosy without regard for detection of reactions. Prevention of disability appears to be discounted as an important issue in many countries, and often health workers are alerted only if pain is an issue. Discussion highlighted the need for a simple, easy to use assessment tool for health workers, and for a clear mechanism of referral to specialised centres when indicated. New studies on the use of ultrasonography using colour Doppler technology for the evaluation of neuritis was discussed, and the participants agreed that it was important to extend clinical research into such advanced-technology areas in specialty centres, in addition to continuing field research using simpler techniques.

#### TYPE 1 REACTIONS AND NEURITIS

Management of T1R and neuritis in the field continues to present many challenges. Reactions and neuritis remain major burdens for leprosy control programmes, and assessment methods at present are too subjective and are prone to misinterpretation. Some areas noted a decline in PB patients overall, but no decline the MB patients with Reactions. The need continues to develop good programs for management of these complications in integrated settings, and the use of newly available technology such as mobile phones to facilitate communication between field clinics and referral centres. As the total number of known patients declines in several countries, additional effort must be made to promote education and awareness of health workers about the dangers of reactions and neuritis. There is serious concern that alternatives to prolonged corticosteroid use should be developed. It was also noted that

neuropathic pain is not well recognised, with no data on the epidemiology or management of this problem.

Considerations of future research needs regarding T1R and neuritis emphasised that priority should be given to identifying factors that trigger reactions, and that promising areas of investigation might include endocrine influences, the effect of co-infections with other bacteria or parasites, and genetic markers of predisposition to reactions. Speakers noted some promising markers of reaction using PCR primers developed (and patented) in India; preliminary evidence that the plasma level of IP10 might be a useful marker were noted. An overview emphasised that these research needs must be prioritised for those that have the biggest impact, best feasibility, and likelihood of funding.

### **Research priorities: reactions & neuritis**

Clinical field experience indicates that Reactions and Neuritis remain major issues in leprosy.

ENL:

- Epidemiology & Risk Factors
  - Short-term MDT: higher incidence of later ENL?
  - Severity assessment scale
- Pathology
  - Criteria for histopathological diagnosis
  - Role of vasculitis
  - Triggering mechanisms
  - Mechanisms of ENL and triggering of the reaction
- Management
  - Assessment of second-line drugs

Type 1 Reactions

- Pathology/pathologic diagnosis
  - Criteria, e.g. better assessment of tissue edema
  - Standardisation of diagnosis
  - New markers; e.g. neuropeptides, specific antigens
  - Mechanisms of T1R and triggers for reaction
- Clinical Risk Factors need to be identified, in addition to those for neuritis

Neuritis

- Prediction rule (BANDS)
  - Assessment in other settings
  - Implementation in general field settings
- Awareness and recognition by health workers
- Management
  - Optimise steroid regimens
  - New drugs
  - Controlled trials of surgical decompression
- Neuropathic pain
  - Extent of the problem?
  - Management

- Pathogenesis
  - Mechanisms of nerve injury

Models

- Armadillo
  - Validation of model of neuropathy
  - ?Development of reaction model
- *In vitro* models
  - Culture conditions (e.g. 33° C) to preserve viability of *M. leprae*
  - Correlation of *in-vitro* findings with clinical & pathological features of leprosy