Lepr Rev (2007) **78,** 416–433

WORKSHOP REPORT

International workshop on neuropathology in leprosy – consensus report

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Accepted for publication 20 November 2007

Introduction

From 19–22 June 2007, an international workshop on neuropathology in leprosy was held at the Kontakt der Kontinenten conference centre, Soesterberg, the Netherlands. The workshop was organised by the Netherlands Leprosy Relief and the Synapse Consortium for research on nerve damage and reactions in leprosy. The workshop brought together 36 scientists and experts from 11 countries in North and South America, Europe, Africa and Asia (see Appendix 3) (Table A4). They represented many professional disciplines, including neurologists, neurosurgeons, neurophysiologists, neuropathologist, clinical immunologists, histopathologists, leprologists, epidemiologists, statisticians, a research physiotherapist and a dermatologist.

Structure of the Report

Part 1 of the report comprises a summary of salient points noted during the presentation of research findings and the plenary discussions that followed each presentation. Part 2 is made

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0305-7518/07/064053+18 $1.00

up of the consensus statements of the three working groups that met on Day 3 and 4 of the workshop. They attempted to reach consensus on current understanding and best practice based on available evidence, identify gaps in knowledge and prioritise research needs for the future. They addressed the following topics:

Group 1: Mechanisms of neuropathology in leprosy
Group 2: Screening and diagnostic testing of nerve function in leprosy
Group 3: Treatment of neuropathy in leprosy

Part 1 – Plenary Sessions' Report

The workshop started with a warm welcome by the convener, Dr Wim van Brakel, and by Mr. Kommer Braber, Director of Netherlands Leprosy Relief (NLR), the sponsoring agency. Although not able to be present in person, Dr Pannikar of the WHO Leprosy Unit expressed his full support for the effort to understand the neuropathology of leprosy more fully.

Prof. Cairns Smith reviewed the objectives of the workshop; he pointed out that the synthesis of neuro-immunopathological, clinical and epidemiological regarding the neuropathology of leprosy evidence was the key process in this workshop:

1. To bring together and discuss the evidence available from different studies on the neuro-immunopathology of leprosy and develop consensus on the current best model(s) of neuropathy in leprosy.
2. To bring together and discuss the evidence available from different clinical and epidemiological studies on the neuropathology of leprosy and develop consensus on the risk factors for and pattern of neuropathy in leprosy.
3. To integrate the conclusions from 1 and 2 and to discuss the implications of current knowledge for treatment and management of neurological complication in leprosy.
4. To produce a consensus report on 'the current model of neuropathology in leprosy and its implications for the treatment of nerve damage'.
5. To develop an agenda for future research and action regarding neurological aspects in leprosy.

Two reviews were presented, firstly of relevant clinical and epidemiological research by Dr Paul Saunderson and, secondly, of recent neuropathological research by Dr David Scollard. They are to be published separately. It is clear that previous studies have used different definitions for clinical aspects of neuropathy in leprosy, but recent papers by Nicholls and van Brakel should help to standardise these in future.[1] A review of the neuropathology showed that the relative importance of the immunological and non-immunological mechanisms of nerve damage is still poorly understood, which has important implications for treatment (Scollard, submitted). In addition, a number of processes, such as the development of oedema in and around the nerves, are known to be important, but have not been studied in any depth up to now.

New findings from the recently completed INFIR study were presented.[2] Approximately 300 MB leprosy patients were extensively investigated for risk factors for, and immunopathological features of, nerve damage. An interesting finding was that histology correlated rather poorly with the clinical features seen in patients in reaction (Lockwood *et al.*,

in preparation). Two-thirds of the reaction diagnoses were only histopathological reactions ('silent reaction'), which were not diagnosed clinically. It was suggested that the whole pathological process in leprosy is in fact an immunological reaction, which sometimes surfaces as a clinical 'reaction'. This is confirmed by immunohistochemical evidence showing that reactional markers (CD68, TNF-alpha, iNOS and TGF-beta) were present in the large majority of BT/BL patients, but were increased in Type 1 Reactions (T1R).

The use of various modalities for testing nerve function was also examined in the INFIR study. There was a presentation and discussion about the need to establish normative ranges or cut-offs for various tests and about the importance of taking into account simple confounding factors, such as age and sex. The widely-used standard tests of sensation, the graded monofilaments, generally reflected well the underlying severity of neuropathy (measured with sensory nerve conduction and temperature sensation), though sometimes with considerable delay (van Brakel *et al.*, submitted). The common test of muscle strength, the voluntary muscle test (VMT), reflected underlying neuropathy well in the ulnar nerve, but not in the median or peroneal nerve. In the latter two nerves, less severe degrees of weakness are being missed.[2] It was suggested in the discussion that extension of the big toe may be a more accurate test of peroneal nerve function than dorsiflexion of the foot. This requires further study. From a prospective comparison of tests, nerve conduction studies and warm perception testing appeared to be the most sensitive tests, allowing NFI to be detected early (van Brakel *et al.*, in preparation). Subclinical neuropathy was shown to be very extensive. Contrary to expectations, the study did not find consistent evidence that small fibre neuropathy generally precedes large fibre neuropathy.

Dr Peter Nicholls presented a novel graphical method of showing how nerve function and laboratory parameters of individual INFIR patients changed over time. This was regarded as very valuable, as it allowed insight into how different parameters related to each other in time.

A number of presentations from FIOCRUZ, Brazil, presented various modalities for testing, including the vasomotor reflex (VMR) as a test of autonomic nerve function.[3] In a group of 76 patients, autonomic nerve lesion was more frequent than somatic lesions and was strongly related to the immune-inflammatory reaction against *M. leprae*. Measured by laser Doppler fluxometry, household contacts of patients are at an increased risk of having peripheral autonomic neuropathy as compared to the general population, but the importance of this is unclear. One current study is evaluating the predictive value of abnormal VMRs and presence of PGL-1 antibodies with regard to the risk of developing leprosy in household contacts. Genetic studies have indicated a possible role of ninjurin as a predictive marker of neuropathy.

Prof. Cairns Smith reviewed evidence from the ILEP Nerve Function Impairment and Reaction (INFIR) study on predicting new NFI in people with leprosy (Smith *et al.*, in preparation). Interestingly, different predictors were found for skin events and nerve events. Abnormalities in sensory nerve conduction parameters were the most sensitive predictors of new NFI. The apparent predictive effect of some other tests, such as warm and cold sensation, disappeared on adjusting for age. Of the serological markers, TNFα levels do show significant within-subject change prior to an event, but the variation between individuals is probably too great to allow a test to be developed.

Dr Jan Hendrik Richardus presented an analysis of data from the COLEP study, showing that PGL-1 positivity, in combination with MB classification, was a better predictor of future NFI than the previous clinical prediction rule from the BANDS study that combined MB

classification and NFI already present at diagnosis.[4] In discussion, it was pointed out that the meaning of PGL-1 positivity in this context is unclear. No such association was found in the INFIR study. This finding would need validation in other areas.

Electrophysiological data of nerve function in patients in the INFIR cohort treated with corticosteroids were presented by Dr Einar Wilder-Smith. He showed a good response to treatment with prednisolone in large fibre damage (sensory nerve conduction (SNC) amplitude), but little response in small fibres (warm detection thresholds (WDT)). The improvement was maximum after 6 months and was best in those with both amplitude and latency impairment. In contrast, in a study of electrophysiological parameters in pure neural leprosy patients treated with MDT and steroids in Brazil, presented by Dr Ximena Illarramendi, small fibres showed some recovery after 1 year (autonomic function, and pain and temperature sensation), while NC parameters did not, except for nerve conduction block. Wilson Marques Junior presented data on electrophysiological abnormalities found in 332 household contacts of leprosy patients. Thirteen were diagnosed with various types of neuropathy, but the predictive value of these findings for developing clinical leprosy is as yet unsure. No predictive value could be established until now in another study in Brazil investigating the risk of developing leprosy in contacts with abnormal vasomotor reflexes (VMR) and a positive PGL-1 test.

Surgical decompression of affected nerves is enthusiastically advocated by some authors. Published results were reviewed by Natasja van Veen, who showed that most studies were methodologically unsound (van Veen *et al.*, in preparation). Pain relief seems to be a definite benefit of surgery, but improvement in nerve function has not been demonstrated. For future studies, it was suggested that imaging of nerves and the measurement of intra-neural pressure may provide helpful indicators, in addition to routine tests of nerve function and nerve conduction studies.

Dr Elizabeth Bezuneh emphasised the importance of psychosocial issues in the management of NFI. Low self-esteem and depression can prevent recovery by blocking compliance with treatment. Counselling and the formation of self-care groups have been helpful in some settings.

Dr Vanaja Shetty reviewed her work on the pathogenesis of neuropathy. She suggested that atrophic changes in axons precede paranodal demyelination.[5] Electron microscopy studies showed a reduction in axon calibre. Hypophosphorylation of axons was consistently found in nerves of leprosy-affected persons. This was proposed to be the mechanism underlying axonal atrophy.

David Scollard presented recent work on the armadillo model of nerve damage, which now seems quite promising. Finally, the bank of serological, biopsy materials and blots, from the INFIR study, which are stored at BPRC, Hyderabad, India, was described by Prof. Indira Nath. Participants were invited to submit proposals to use these specimens for further study. The prospective nature of the study and the enormous database of clinical data, make this 'bank' a unique resource.

Part 2 – Consensus Statements of the Working Groups

MECHANISMS OF NEUROPATHY IN LEPROSY – GROUP 1

Three distinct mechanisms of nerve damage in leprosy are recognised:

Damage due to direct effects of M. leprae

Damage due to direct effects of *M. leprae* includes neurofilament damage of the type described by the models of Shetty *et al.*[5] mechanisms involving Schwann cell pathology,[6,7] and also the contact demyelination described by Rambukkana and colleagues.[8] Investigations of how and when demyelination occurs will need to involve the use of animal as well as *in vitro* model systems.

Damage mediated by inflammatory and immune-mediated processes

Damage mediated by inflammatory and immune-mediated processes is probably the most varied form of damage, and includes, but is not limited to, damage involving:[9–11]

a. binding of antibodies to neurofilaments
b. cytotoxicity
c. homing receptors to e.g. Schwann cells
d. alteration of the phosphorylation status of nerve proteins
e. binding of myelin-activated T-cells
f. molecular mimicry/autoimmunity

Experimental studies to investigate these forms of nerve damage would involve the use of Schwann cells, endothelial cell and macrophages in *in vitro* systems. The role of Schwann cells in nerve damage, whether as passive targets of *M. leprae* or in an active role, has been extensively studied, though many questions remain.[6,9,12–14]

Damage due to oedema and mechanical processes

a. Schwann cell damage can render nerve fibres more liable to mechanical injury.
b. Intercellular (and perhaps also intracellular) oedema in the nerve trunk, whether with or without protein ingress, can lead to compression of the nerve fibres. It is also likely that compression of the blood vessels occurs, leading to ischemia and further damage

Investigation of these processes may involve the use of CT guided probes to measure intraneural pressure in nerves *in vivo*.

It is possible that some clinically observed phenomena, such as variability of response to steroid treatment, may be due in part to these different processes of nerve damage working in different combinations in different people.

Research Priorities

1. *Development of animal models*

   Mouse (both standard and generic knock-out (GKO)) and armadillo models should be further deployed in the investigation of the mechanisms of nerve damage. It is recognised that the use of these models will be limited to a small number of centres: collaboration between relevant centres should be encouraged.
2. *In vitro systems*

   The utilisation of culture systems in the investigation of leprosy nerve damage is becoming more widespread, and should be encouraged. Cross fertilisation with other areas

of *in vitro* research into neurological phenomena (e.g. nerve regeneration) will be especially beneficial. It should be noted that the application of data obtained from these systems to clinical questions may not always be straightforward. As *M. leprae* is essentially a human pathogen, the use of human cells and cell lines is strongly recommended. Variations in the viability status of bacteria within a population and the predilection of *M. leprae* for lower temperatures should all be taken into account when designing experiments.

3. *Early nerve damage*

   Electrophysiological assessments have identified household contacts of leprosy patients who have impaired nerve conduction and autonomic nerve function but no clinical symptoms. These individuals should be studied more closely, as they are postulated to represent the earliest detectable form of leprosy nerve damage. Novel techniques such as nerve imaging should be utilised in these studies, although the application of such technology in leprosy is still in the developmental stage. Standardised protocols for the selection and storage of samples (e.g. biopsies) should be developed. A statement on nerve biopsies is appended.

4. *Reaction-related nerve damage*

   As the INFIR studies have shown, the important clinical phenomenon of reaction lends itself to investigation, as many patients at risk of developing reaction are already under treatment. Protocols to compare samples taken at baseline with those from the same patients at the onset of a reactional event should be developed; novel techniques, such as Luminex (for changes in the cytokine milieu) or microarrays (to detect changes in host gene expression), allow the assessment of large numbers of parameters simultaneously, and should be considered for inclusion in such analyses. It should be noted that identification of markers of phenomena such as nerve damage and reaction is still required: it is recommended that another practical workshop should be organised to decide priorities in this area.

5. *Genetic variability*

   Much work has been done on the role of genetic susceptibility to leprosy *per se*, but the involvement of genetic variability in susceptibility to reaction or nerve injury needs to be more closely investigated. There are a number of existing databanks of material which should be studied in this regard. The technology for assessing genetic variability has evolved rapidly. Variability in *M. leprae* strains and its relation to nerve damage also needs to be investigated more fully.

IMPLICATIONS FOR SCREENING AND DIAGNOSTIC TESTING – GROUP 2

Nerve function assessment (NFA) is important for the diagnosis of leprosy *per se*, but has an even more crucial role in the prevention and early treatment of nerve function impairment (NFI) once specific multidrug therapy is started. The evidence available from different clinical and epidemiological studies, as well as from the experience of the participants, demonstrated that nerve function impairment and assessment is heterogeneous between and within the different endemic countries, time-consuming and, in some aspects, subjective.[2,15–18] To be able to compare the different studies and to draw more accurate conclusions, consensus regarding NFA is needed, including the number and type of nerves to be assessed and the minimum testing parameters that would give adequate sensitivity to detect NFI.

Nerve function testing will depend on the level of the health services. Two levels of evaluation were discussed. The first level is that of field programmes or integrated services. The second level is the referral centre or hospital where expertise is available to perform a more thorough evaluation of the patient with additional examination techniques.

PERIPHERAL LEVEL (FIELD PROGRAMMES)

For this level, the number of parameters assessed should be minimised.

CLINICAL EXAMINATION

(Table A1)

Skin lesions and anaesthetic areas

Tactile sensation: a light static touch with cotton wool is recommended.[19]
Pain sensation: pin prick using a disposable pin or tooth pick.[20]
Temperature sensation: testing is not considered practical in peripheral health centres.
Autonomic function: look for loss of hair growth and loss of sweating.

Nerve palpation

Although nerve palpation is subjective and requires expertise, it is still considered a valuable parameter for clinical evaluation of the patient. The only two studies available on reliability of nerve palpation (ulnar, and common peroneal) showed only moderate or poor reliability.[21] There is evidence that the common peroneal (CP) nerve is commonly affected distally on the dorsum of the foot. Likewise, there is evidence that the radial cutaneous (RC) and sural nerves are commonly affected (INFIR study).[2] These nerves are not routinely assessed in the clinical examination of leprosy patients. The group recommends that the following nerves should be palpated in diagnostic and follow up examinations: greater auricular, ulnar, RC and CP nerves. They should be evaluated for size, tenderness and consistency. Other nerves that may be included, depending on expertise and guidelines are median, posterior tibial (PT) and sural nerves.

NERVE FUNCTION ASSESSMENT (NFA)

(Table A2)

Autonomic function

Evaluate skin dryness, hair loss and skin colour and temperature of palms and soles.

Sensory function

Tactile sensation Testing of tactile sensation can be performed with a ballpoint pen, but if possible, the use of graded nylon monofilaments is preferred.[22–24]

Pain Pin prick using a disposable pin or tooth pick (the pin or tooth pick should be disposed after use to prevent accidental transmission of any infectious diseases).

Temperature Temperature sensation: testing is not considered practical in peripheral health centres.

For the three types of sensation, pain, temperature and tactile, it is recommended to evaluate two sites per nerve for ulnar, median, RC and sural nerves, and 4 sites for PT nerve. Note the presence of callous and scars and exclude these as testing sites.

Motor function

Evaluate the presence of muscle atrophy (thenar, hypothenar regions) and of the common paralytic deformities, such as foot or wrist drop, claw fingers, and lagophthalmos. Perform one voluntary muscle test (VMT) each for facial, ulnar, median and CP nerves using the 3 grades: Strong, Weak and Paralysed.

REFERRAL CENTRE LEVEL

At the referral centre, the patient should be evaluated by staff specialised in managing leprosy complications, if possible a neurologist and/or other specialists as required according to the patient's condition (Table A3).

CLINICAL EXAMINATION

As above

NERVE FUNCTION ASSESSMENT

Autonomic function

Evaluate skin dryness, hair loss and skin colour and temperature of palms and soles. If equipment is available, vasomotor reflexes may be tested with laser Doppler flowmetry.[25,26]

Sensory function

In addition to the nerves evaluated at the field level, the facial nerve and CP branch on the dorsum of the foot should be evaluated. Testing should be further refined and quantified by using several graded monofilaments.[27] Proprioception and tendon reflexes are only important for differential diagnosis.

Motor function

Voluntary muscle testing should include two strength tests each for facial, ulnar, median and common peroneal nerves using the 6-grade scale (0–5).[28] Consider adding tests for PT (big toe flexion) and CP nerves (toe extension). Dynamometry could be added to quantify muscle strength.

ELECTROPHYSIOLOGICAL TESTING

The minimum parameters and nerves that should be tested are amplitude, latency and velocity of sensory (ulnar, median, radial (cutaneous), sural) and motor (ulnar, median, radial, peroneal) action potentials. The technique should be standardized for all studies in leprosy, including standard test sites for each nerve.

FREQUENCY OF NERVE FUNCTION ASSESSMENT

NFA should be performed as part of the diagnostic examination and, subsequently, to monitor the response to treatment and occurrence of complications. Considering that early diagnosis of NFI is the main intervention available for prevention of permanent NFI, the minimum frequency of NFA should be standardised to monitor nerve function and allow early detection of NFI. The group concluded that NFA should be performed at different times and frequencies according to the type of leprosy, the presence of NFI and the context of the case management:

- NFA should be performed at leprosy diagnosis and at the end of treatment with MDT for all types of the disease.
- In case NFI is present at diagnosis, NFA should be performed at every visit.
- PB patients should be examined at least at diagnosis and at the time of release from treatment.
- In MB patients, the assessment should continue after MDT every 3 months for 2 years.
- MB patients with NFI should be referred when feasible for more detailed evaluation.

Research Priorities

1. *Diagnosis*

   The pathophysiology of nerve damage should be studied further. This may result in improvements in existing testing techniques and/or different techniques for the detection of (early, sub-clinical) leprosy and nerve involvement. A diagnostic algorithm for leprosy should be developed (definite, probably, possible, unlikely). The algorithm could include nerve conduction tests and, if possible, an EMG with needle electrodes, which would aid in differentiating leprosy from other neurological diseases, and acute neuritis from neuropathic pain.

   Research questions include:
   - What are the earliest neurological signs of leprosy, including in leprosy contacts?
   - What are the most sensitive (earliest affected) handheld sensory tests for diagnosing leprosy and NFI?
   - What is the value of nerve conduction studies (NCS) in the diagnosis of leprosy in contacts of patients?
2. *Clinical testing*

   To increase effectiveness of testing in the diagnosis of NFI and diagnosis of the disease, there is a need to establish a consensus of best combination of nerves to be included in clinical NFA. The possible role of vibrometry (including tuning fork(s)) and thermal sensation testing in the assessment of nerve function needs further research.

Research questions include:

- Are big toe flexion and extension strength tests useful in the assessment and evaluation of the PT and CP motor nerve function (intrinsic muscles of the foot)?
- What is the value of skin wrinkling and finger printing tests in assessing autonomic function?
- What is the clinical value of sensory testing of face, elbows and knees in the diagnosis (treatment follow-up) of leprosy?

3. *Complementary tests to validate clinical testing*

Nerve function

The place of dynamometry in evaluating motor function (e.g. RIHM, Rotterdam Intrinsic Hand Myometer) should be studied further in relation to VMT using the MRC scale. The question is: how findings on dynamometry correlate with VMT and with motor nerve conduction?

Nerve size (palpation)

Nerve enlargement is a fairly subjective finding and the reliability of nerve palpation is questioned. Therefore, findings of nerve palpation (size) need to be compared and validated with imaging techniques, such as ultrasound and MRI.

Electrophysiology

Several questions emerged that require further investigation regarding NCS.

- What is the correlation between NCS and histopathological findings?
- What is the value of Motor Unit Number Evaluation (MUNE) in leprosy? How does the MUNE technique that measures the approximate number of motor neurons innervating a single muscle or a small group of muscles, relate to clinical muscle testing? Can progressive motor unit loss produced by leprosy reactions be evaluated by MUNE?

4. *Treatment monitoring*

The prognostic advantage of early detection of sub-clinical neuropathy should be demonstrated in a double blind randomised controlled trial. Available evidence suggests that NCS and testing of thermal sensation should be included when monitoring any clinical trial of treatment of NFI, as well as in future cohort studies investigating neurological outcomes.

5. *Analysis of existing data*

Additional analysis of INFIR/BANDS/TRIPOD data, and possibly other studies, is recommended to a) provide additional justification for the inclusion of other nerves in NFA (field or research) and b) determine if the number of sensory test sites can be reduced without losing the sensitivity of the test (when compared to a reference test with 10 test sites).

IMPLICATIONS FOR TREATMENT – GROUP 3

Optimal steroid treatment (duration/dosage/delivery)

There is evidence that the WHO-recommended 12-week steroid regimen produces poorer nerve function impairment outcomes than a 20-week regimen.[29] A recent RCT has shown that for Type 1 Reactions, treatment for 20 weeks produced significantly better outcomes than the 12-week treatment.[30] There was no difference in outcomes between a high-dose regimen,

starting at 60 mg per day and a lower-dose regimen starting at 30 mg per day. For Type 2 Reactions it is probably better to start with higher initial doses of 60 mg.

There have been no RCTs of standardised or patient-tailored steroid regimens that have Nerve Function Impairment as the primary outcome or of a comparison between these two approaches. Steroid regimens have been shown to be beneficial for 'simple' one-episode neuritis, but disappointing for recurrent neuritis.[31] Furthermore, it is not clear whether a recurrent neuritis should be considered a treatment failure or an additional episode of neuritis. Long-term benefits of steroids on nerve function impairment measures are not well established. Another gap in current knowledge concerns the treatment of silent neuritis.

Based on current evidence we recommend giving a minimum of 20 weeks steroids for leprosy reactions, with a starting dose of 0·5–1 mg/kg body weight (in most leprosy-endemic countries usually between 30–60 mg), and then slowly reducing the dose. The patient's nerve function is monitored at least every 4 weeks.

Other immunosuppressants

The role of other immunosuppressants is currently being defined in relation to:

- Efficacy in improving nerve function
- Efficacy in treating patients not responding to steroids
- Patients with contra-indications to steroids

Clinical trials have shown the usefulness of azathioprine and cyclosporine,[32,33] and there is an ongoing study in Nepal using methylprednisolone-pulse-therapy at the start of treatment for reactions. A large RCT using azathioprine in Type 1 reactions is starting in India. Studies are being planned for Ethiopia; including trials concerning the usefulness of treatment with single immunosuppressants; others looking at the effect of combinations of immunosuppressants. RCTs are needed to establish their efficacy in the treatment of acute neuritis.

The role of other immunosuppressants in the management of Type 2 reactions is also being investigated. Several studies are in early stages or being planned, azathioprine in India, cyclosporine in the Philippines and methotrexate in Sri Lanka.

Neuropathic pain

Neuropathic pain is pain due to a primary lesion or dysfunction in the peripheral or central nervous system. The term neurogenic pain is sometimes used if the dysfunction causing pain is reversible. Hence, neuropathic pain always indicates permanent abnormality. It was observed that, although a frequent clinical problem, neuropathic pain in leprosy, particularly chronic post-inflammatory pain, has received insufficient attention.[34–37] Pain related to acute neuritis is neurogenic pain because it is usually reversible. Little is known about the mechanisms of neuropathic pain in leprosy. No Randomised Controlled Trials (RCT) have been done for the treatment of leprosy-related neuropathic pain.

Several interventions were identified that may relieve neuropathic pain in leprosy, such as pain medication, physiotherapy, surgery and patient counselling. Studies should also be designed to ensure that the potential placebo effects can be detected.

Based on general management of neuropathic pain and recommendations in Brazil for treatment of neuropathic pain in leprosy, the following medical treatments may be beneficial:[38]

- Amitriptyline 10–150 mg/day
- Nortriptyline: 10–150 mg/day
- Gabapentin: 900–3600 mg/day, divided over 3 doses
- Carbamazepine 200–600 mg/day, divided over 2–3 doses

We recommend starting treatment with either amitriptyline or nortriptyline as a first line drug if there are no contraindications. Patients with narrow-angle glaucoma, prostatic hyperplasia and heart disease should be treated with caution. The drug is started at a low dose, 10–25 mg in the evening, and the dose is increased in steps of 10–25 mg after 3–7 days to an adequate level of pain relief, with a maximum dose up to 150 mg/day.

Gabapentin is administered three times a day, and the target dose in the treatment of pain is 900–3600 mg/day. The initial dose is 300 mg at bedtime, and the dose can be increased with 300 mg in 1–3 days. Carbamazepine may be useful in throbbing or electric shock-like pain. It is started with 100 mg at bedtime and increased in steps of 100 mg after 3–5 days. The maintenance dose in neuropathic pain is usually 400–600 mg/day, divided into two doses when a slow-release preparation is used and into three doses when an ordinary preparation is used. Blood count and sodium and transaminase levels should be monitored, at least at the start of treatment.

Identification of high-risk groups for neuritis

Research shows that some leprosy patients are at higher risk of developing NFI, especially patients with MB leprosy, those with NFI at diagnosis and those with detectable PGL-1 antibodies.

Current knowledge shows that the following patients should have their nerve function closely monitored during and after MDT:[4]

- PB patients with pre-existing NFI
- MB patients without NFI (1 year monitoring after registration)
- MB patients with pre-existing NFI (2 year monitoring after registration)

At present, prophylaxis with steroids to prevent NFI cannot be recommended, as current evidence shows that 20 mg of prednisolone per day given for 16 weeks, although beneficial at 16 weeks, was not beneficial at the end of one year (TRIPOD trials).[39] Therefore, further studies are desirable. In such studies the possible benefit of using prophylaxis with steroid must be carefully balanced against possible risks of using steroids.

Surgery

In the literature there is anecdotal evidence that surgery might have a role in the management of acute and chronic neuropathic pain.[40] Its indications, however, are not standardised, nor have there been conclusive clinical trials to prove its efficacy. Notwithstanding, we see a possible role for surgery for patients with severe nerve pain who do not respond to medical

treatment and for those whose nerve function has not improved or is deteriorating during or after steroid treatment. To make further progress in this area, the mechanisms of pain in leprosy should be better understood, and hypotheses developed as to which types of pain might benefit from surgery.

Other questions

Many other questions are still left to be answered, e.g., what is the potential of nerve regeneration factors in the treatment of nerve damage in leprosy? Is there any rationale for using different treatment approaches for neuritis caused by Type 1 or Type 2 reaction? What are the options for the management of recurrent neuritis?

Research Priorities

1. *Steroid treatment*
   - A multi-centre RCT that compares different durations and dosages of steroids with nerve function as primary outcome. It is important to have a large enough study to permit sub-group analysis, especially for differing nerve status at entry.
   - An RCT comparing patient tailored steroid schemes with a standardised steroid regimen of at least 20 weeks (see above).
2. *Neuropathic pain*
   - Epidemiological studies on neuropathic pain in leprosy patients
   - Clinical trials to assess the efficacy of the general pain management, as indicated above, in the management of leprosy-associated neuropathic pain.
3. *Steroid prophylaxis*
   - A multi-centre RCT to see whether subgroups of patients can be identified who would benefit from prophylaxis with steroids to prevent NFI.
   - A multi-centre RCT to investigate whether prophylaxis of longer duration would be beneficial in defined subgroups.
4. *Other immunosuppressants*

   RCTs are needed to establish the efficacy of immunosuppressants, such as azathioprine and cyclosporine, in the treatment of acute neuritis.
5. *Neurolysis*

   A multi-centre RCT to investigate the efficacy of neurolysis surgery in patients with NFI >6 months, non-responders to steroids and other inclusion criteria are needed with a clear consensus about treatment outcome measures. These might include monofilament assessments of sensory function, nerve conduction studies and measuring of intra-neural pressure.

Acknowledgements

We are very grateful to the Netherlands Leprosy Relief (NLR), who kindly agreed to sponsor and organise this workshop. We are thankful also to the organisations and institutes that have contributed through sponsoring their representatives, and to the WHO Global Leprosy

Programme for endorsing the workshop. Last but not least we wish to thank all participants for giving their valuable time and efforts to make this workshop successful.

References

[1] van Brakel WH, Nicholls PG, Das L, Barkataki P, Suneetha SK, Jadhav RS *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.

[2] van Brakel WH, Nicholls PG, Das L, Barkataki P, Maddali P, Lockwood DN *et al.* The INFIR Cohort Study: assessment of sensory and motor neuropathy in leprosy at baseline. *Lepr Rev*, 2005; **76**: 277–295.

[3] Illarramendi X, Buhrer-Sekula S, Sales AM, Bakker MI, Oliveira A, Nery JA *et al.* High prevalence of vasomotor reflex impairment in newly diagnosed leprosy patients. *Eur J Clin Invest*, 2005; **35**: 658–665.

[4] Croft RP, Nicholls PG, Steyerberg EW, Richardus JH, Cairns W, Smith S. A clinical prediction rule for nerve-function impairment in leprosy patients. *Lancet*, 2000; **355**(9215): 1603–1606.

[5] Save MP, Shetty VP, Shetty KT, Antia NH. Alterations in neurofilament protein(s) in human leprous nerves: morphology, immunohistochemistry and western immunoblot correlative study. *Neuropathol Appl Neurobiol*, 2004; **30**: 635–650.

[6] Spierings E, de Boer T, Wieles B, Adams LB, Marani E, Ottenhoff TH. *Mycobacterium leprae*-specific, HLA class II-restricted killing of human Schwann cells by CD4 + Th1 cells: a novel immunopathogenic mechanism of nerve damage in leprosy. *J Immunol*, 2001; **166**: 5883–5888.

[7] Birdi TJ, Antia NH. Mechanisms involved in peripheral nerve damage in leprosy with special reference to insights obtained from *in vitro* studies and the experimental mouse model. *Int J Lepr Other Mycobact Dis*, 2003; **71**: 345–354.

[8] Rambukkana A, Zanazzi G, Tapinos N, Salzer JL. Contact-dependent demyelination by *Mycobacterium leprae* in the absence of immune cells. *Science*, 2002; **296**(5569): 927–931.

[9] Harboe M, Aseffa A, Leekassa R. Challenges presented by nerve damage in leprosy. *Lepr Rev*, 2005; **76**: 5–13.

[10] Siddiqui MR, Moreira AL, Negesse Y, Taye GA, Hanekom WA, Haslett PA *et al.* Local nerve damage in leprosy does not lead to an impaired cellular immune response or decreased wound healing in the skin. *Ethiop Med J*, 2004; **42**(Suppl 1): 55–62.

[11] Sarno EN, Santos AR, Jardim MR, Suffys PN, Almeida AS, Nery JA *et al.* Pathogenesis of nerve damage in leprosy: genetic polymorphism regulates the production of TNF alpha. *Lepr Rev*, 2000; **71** (Suppl): S154–S158.

[12] Barker LP. *Mycobacterium leprae* interactions with the host cell: recent advances. *Indian J Med Res*, 2006; **123**: 748–759.

[13] Oliveira RB, Sampaio EP, Aarestrup F, Teles RM, Silva TP, Oliveira AL *et al.* Cytokines and *Mycobacterium leprae* induce apoptosis in human Schwann cells. *J Neuropathol Exp Neurol*, 2005; **64**: 882–890.

[14] Spierings E, de Boer T, Zulianello L, Ottenhoff TH. Novel mechanisms in the immunopathogenesis of leprosy nerve damage: the role of Schwann cells. T cells and *Mycobacterium leprae*. *Immunol Cell Biol*, 2000; **78**: 349–355.

[15] Schreuder PA. The occurrence of reactions and impairments in leprosy: experience in the leprosy control program of three provinces in northeastern Thailand, 1987–1995 [correction of 1978–1995]. III. Neural and other impairments. *Int J Lepr Other Mycobact Dis*, 1998; **66**: 170–181.

[16] Croft RP, Nicholls PG, Richardus JH, Smith WC. Incidence rates of acute nerve function impairment in leprosy: a prospective cohort analysis after 24 months (The Bangladesh Acute Nerve Damage Study). *Lepr Rev*, 2000; **71**: 18–33.

[17] Saunderson P, Gebre S, Desta K, Byass P, Lockwood DN. The pattern of leprosy-related neuropathy in the AMFES patients in Ethiopia: definitions, incidence, risk factors and outcome. *Lepr Rev*, 2000; **71**: 285–308.

[18] Solomon S, Kurian N, Ramadas P, Rao PS. Incidence of nerve damage in leprosy patients treated with MDT. *Int J Lepr Other Mycobact Dis*, 1998; **66**: 451–456.

[19] ILEP. *How to diagnose and treat leprosy*. International Federation of Anti-Leprosy Associations (ILEP), London, 2001.

[20] van Brakel WH, Shute J, Dixon JA, Arzet H. Evaluation of sensibility in leprosy – comparison of various clinical methods. *Lepr Rev*, 1994; **65**: 106–121.

[21] Chen S, Wang Q, Chu T, Zheng M. Inter-observer reliability in assessment of sensation of skin lesion and enlargement of peripheral nerves in leprosy patients. *Lepr Rev*, 2006; **77**: 371–376.

[22] Watson JM, Lehman LF, Schreuder PA, van Brakel WH. Ballpoint pen testing: light touch versus deep pressure. *Lepr Rev*, 2002; **73**: 392–393.

[23] Anderson AM, Croft RP. Reliability of Semmes Weinstein monofilament and ballpoint sensory testing, and voluntary muscle testing in Bangladesh. *Lepr Rev*, 1999; **70**: 305–313.

[24] van Brakel WH, Khawas IB, Gurung KS, Kets CM, van Leerdam ME, Drever W. Intra- and inter-tester reliability of sensibility testing in leprosy. *Int J Lepr Other Mycobact Dis*, 1996; **64**: 287–298.
[25] Wilder-Smith E, Wilder-Smith A, van Brakel WH, Egger M. Vasomotor reflex testing in leprosy patients, healthy contacts and controls: a cross-sectional study in western Nepal. *Lepr Rev*, 1996; **67**: 306–317.
[26] Beck JS, Abbot NC, Samson PD, Butlin CR, Grange JM, Cree IA *et al.* Impairment of vasomotor reflexes in the fingertips of leprosy patients. *J Neurol Neurosurg Psychiatry*, 1991; **54**: 965–971.
[27] Bell-Krotoski J. 'Pocket filaments' and specifications for the Semmes-Weinstein monofilaments. *J Hand Ther*, 1990; 26–31.
[28] Brandsma JW. Monitoring motor nerve function in leprosy patients. *Lepr Rev*, 2000; **71**: 258–267.
[29] Becx-Bleumink M, Berhe D, Mannetje W. The management of nerve damage in the leprosy control services. *Lepr Rev*, 1990; **61**: 1–11.
[30] Rao PS, Sugamaran DS, Richard J, Smith WC. Multi-centre, double blind, randomized trial of three steroid regimens in the treatment of type-1 reactions in leprosy. *Lepr Rev*, 2006; **77**: 25–33.
[31] Saunderson P. The epidemiology of reactions and nerve damage. *Lepr Rev*, 2000; **71** (Suppl): S106–S110.
[32] Marlowe SN, Leekassa R, Bizuneh E, Knuutilla J, Ale P, Bhattarai B *et al.* Response to ciclosporin treatment in Ethiopian and Nepali patients with severe leprosy Type 1 reactions. *Trans R Soc Trop Med Hyg*, 2007; **101**: 1004–1012.
[33] Marlowe SN, Hawksworth RA, Butlin CR, Nicholls PG, Lockwood DN. Clinical outcomes in a randomized controlled study comparing azathioprine and prednisolone versus prednisolone alone in the treatment of severe leprosy type 1 reactions in Nepal. *Trans R Soc Trop Med Hyg*, 2004; **98**: 602–609.
[34] Hietaharju A, Croft R, Alam R, Birch P, Mong A, Haanpaa M. Chronic neuropathic pain in treated leprosy. *Lancet*, 2000; **356**(9235): 1080–1081.
[35] Stump PR, Baccarelli R, Marciano LH, Lauris JR, Teixeira MJ, Ura S *et al.* Neuropathic pain in leprosy patients. *Int J Lepr Other Mycobact Dis*, 2004; **72**: 134–138.
[36] Croft R. Neuropathic pain in leprosy. *Int J Lepr Other Mycobact Dis*, 2004; **72**: 171–172.
[37] Haanpaa M, Lockwood DN, Hietaharju A. Neuropathic pain in leprosy. *Lepr Rev*, 2004; **75**: 7–18.
[38] Garbino JA, Nery JA, Virmond M, Stump PRNA, Baccarelli R, Marques W, Jr Hanseníase: Diagnóstico e Tratamento da Neuropatia. In: Jatene FB, Cutait R, Cuce Nobre MR, Marques Bernardo W (eds). *Projeto diretrizes* Associação Médica Brasileira/Conselho Federal de Medicina, Sao Paulo, 2005; pp. 147–159.
[39] Smith WC, Anderson AM, Withington SG, van Brakel WH, Croft RP, Nicholls PG *et al.* Steroid prophylaxis for prevention of nerve function impairment in leprosy: randomised placebo controlled trial (TRIPOD 1). *BMJ*, 2004; **328**(7454): 1459.
[40] Malaviya GN. Shall we continue with nerve trunk decompression in leprosy? *Indian J Lepr*, 2004; **76**: 331–342.

Appendix 1 – Consensus statement on handling of nerve biopsies

The following is a guideline, not a protocol.

Nerve biopsies (1–1·5 cm) should be processed immediately as follows. The specimen should be divided into 4 pieces: The two end pieces should be placed in 10% buffered formalin for routine histopathology; a central piece (approx 2 mm) in EM fixative for electron microscopy; and the last piece snap frozen for histochemical, biochemical, or molecular studies. Projects planning to obtain nerve biopsies routinely should consult a pathologist experienced with nerve biopsies to finalize a detailed protocol for the study.

Appendix 2 – Tables of recommended neurological tests

Table A1. Neurological tests recommended for a diagnostic examination of leprosy in peripheral health centres

Function	Tools/tests	Site	Grading
Sensory	Pinprick: toothpick or disposable pin	Skin	Yes/no
	Ballpoint pen	Skin	Yes/no
	Cotton wool	Skin	Yes/no
Motor	Presence of atrophy	Thenar area	Yes/no
		Hypothenar area	Yes/no
		First web space	Yes/no
		Foot dorsum	Yes/no
	Contractures	Eyes/hands/feet	Yes/no
	Voluntary muscle testing	Facial, ulnar, median, radial and common peroneal nerves	Strong/weak/paralysed
Autonomic	Hair loss	Skin	Yes/no
	Dryness	Skin	Yes/no
Nerve palpation	Enlarged/tender	Greater auricular, ulnar, radial cutaneous, common peroneal and posterior tibial nerves	Yes/no

Table A2. Neurological tests recommended for nerve function assessment of leprosy patients in peripheral health centres

Function	Tools/tests	Site	Grading
Sensory	Ballpoint pen or Cotton wool (or monofilaments when available)	2 sites per nerve for ulnar, median, radial cutaneous	Yes/no
		4 sites for posterior tibial	Yes/no
		2 sites for sural	Yes/no
Motor	Presence of atrophy	As above	Yes/no
	Contractures	Eyes/hands/feet	Yes/no
	Voluntary muscle testing	Facial, ulnar, median, radial and common peroneal nerves	Strong/weak/paralysed
Autonomic	Feel for dryness	Palms and soles	Yes/no
Nerve palpation	Enlarged/tender	Greater auricular, ulnar, radial cutaneous, common peroneal and posterior tibial nerves	Yes/no

Table A3. Neurological tests recommended for nerve function assessment of leprosy patients in referral centres

Function	Tools/tests	Site	Grading
Sensory	Pain with pin-prick	Dermatomes and nerves (ulnar, median, radial, posterior tibial, sural)	Yes/no/diminished
	Cold/warm	Dermatomes and nerves (ulnar, median, radial, posterior tibial, sural)	Yes/no/diminished
	Light touch with cotton wool	Dermatomes and nerves (ulnar, median, radial, posterior tibial, sural)	Yes/no/diminished
	Vibrometry: tuning fork	Wrists, elbows, clavicles medial malleoli, patellas	Yes/no/diminished
	Deep tendon reflexes	Biceps, triceps, brachioradialis, patellar, achillean	0–4
	Monofilaments	3 sites per nerve for ulnar, median, radial, and sural; 4 sites for posterior tibial	0–5
	Nerve conduction studies	Facial, ulnar, radial, median, sural	Amplitude Latency Velocity Temporal dispersion
Motor	Blink reflex	Facial nerve	Latency
	Voluntary muscle testing	Ulnar, median, radial, posterior tibial, common peroneal	0–5
	Nerve conduction studies	Facial, ulnar, median, radial, common peroneal, tibial	Amplitude Latency Velocity Temporal dispersion
Autonomic	Laser Doppler fluxometry	Fingertips and toes	Vasomotor reflexes
Nerve palpation	Enlarged/tender	Greater auricular, ulnar, radial cutaneous, common peroneal and posterior tibial nerves	Yes/no

Appendix 3: Workshop participants

Table A4.

	Name	Affiliation and country
1	Dr Ximena Illarramendi	Oswaldo Cruz Institute, FIOCRUZ, Brasil
2	Dr Sérgio Luiz Gomes Antunes	Oswaldo Cruz Institute, FIOCRUZ, Brasil
3	Dr Wilson Marques Junior	Universidade de São Paulo, Brasil
4	Dr Marcos Raimundo Gomes de Freitas	Universidade Federal Fluminense, Brasil
5	Dr José Antônio Garbino	Instituto Lauro de Souza Lima, Brasil
6	Dr J. Wim Brandsma	ALERT, Ethiopia
7	Dr Elizabeth Bizuneh	ALERT, Ethiopia
8	Dr P.S.S. Sundar Rao	The Leprosy Mission Trust India
9	Dr Rupendra Jadav	Stanley Browne Labs, India
10	Dr Lavanya Suneetha	Nireekshana-acet Narayanaguda, India
11	Dr Sujai Suneetha	Nireekshana, India
12	Prof Indira Nath	Blue Peter Research Centre, India
13	Dr Vanaja Shetty	The Foundation for Medical Research, India
14	Dr Sajid Husain	Central JALMA Institute for Leprosy, India
15	Dr Amit Agrawal	Datta Meghe Institute of Medical Sciences, India
16	Dr Mary Jacob	Christian Medical College, India
17	Dr Murdo Macdonald	Mycobacterial Research Laboratory, Nepal
18	Dr Einar Wilder-Smith	National University Hospital, Singapore
19	Dr David Pahan	Rural health programmes DBLM, Bangladesh
20	Dr David Scollard	National Hansen's Disease Programs, USA
21	Dr Paul Saunderson	ALM, Norway
22	Dr Erik Post	DAHW (GLRA), Germany
23	Prof W. Cairns S. Smith	University of Aberdeen, UK
24	Prof Diana N.J. Lockwood	London School of Hygiene and Tropical Medicine, UK
25	Dr Steve Walker	London School of Hygiene and Tropical Medicine, UK
26	Dr Indira Kahawita	London School of Hygiene and Tropical Medicine, UK
27	Mr Jason Mcknight	London School of Hygiene and Tropical Medicine, UK
28	Dr Peter Nicholls	University of Southampton, UK
29	Dr Aki Hietaharju	Tampere University Hospital, Finland
30	Dr Wim van Brakel	Royal Tropical Institute (KIT), Netherlands
31	Dr Remke Jellema	Netherlands Leprosy Relief, Netherlands
32	Dr Jan Hendrik Richardus	Erasmus MC, University Medical Center Rotterdam, Netherlands
33	Ms Natasja van Veen	Erasmus MC, University Medical Center Rotterdam, Netherlands
34	Prof Tom Ottenhoff	Leiden University Medical College, Netherlands
35	Dr Ben Naafs	Netherlands
36	Dr Erik Slim	Amsterdam Medical College, Netherlands
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