Neuropathic pain in people treated for multibacillary leprosy more than ten years previously

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Summary
Objectives To identify patients with typical symptoms of neuropathic pain in a well-defined cohort of multibacillary patients being followed up as part of a relapse study in Ethiopia; to identify risk factors for the development of neuropathic pain.
Design 96 patients who had completed MDT more than 10 years previously participated in the study, through a questionnaire.
Results 28 (29%) had symptoms of neuropathic pain and it was reported as severe in 12. Because the past history of these subjects is well documented, a risk factor analysis was carried out. The presence of leprosy-related impairment was the only significant risk factor for neuropathic pain that was identified.
Conclusions Neuropathic pain is an important problem in a proportion of people previously treated for leprosy. Further research into the management of the condition is required.

Introduction

Neuropathic pain is described in a wide range of conditions involving either the central or peripheral nervous systems. It can be defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system.1 The underlying pathophysiological mechanisms are poorly understood,2 but the condition can develop in association with almost any type of nerve pathology. Leprosy causes some degree of peripheral nerve damage in a large proportion of cases. In the recent INFIR study, 39% of 188 multibacillary patients experienced a reaction, neuritis or new nerve function impairment during the 2-year follow-up period, while 50% had evidence of sub-clinical neuropathy.3 Reports of neuropathic pain in people treated for leprosy have, however, only recently started to appear,4 and a recent histopathological study of biopsies from 17 patients with neuropathic pain in India, showed evidence of chronic inflammation in the dermal...
Nerves. The current situation has been comprehensively reviewed by Haanpää et al. who point out the need for further research into the epidemiology of the condition and its treatment, in people affected by leprosy. Treatment is in principle neither difficult nor expensive, so there is a pressing need for greater awareness of the condition in people who, in other respects, are considered as no longer active cases.

In the largest study of neuropathic pain in leprosy published to date, Stump et al. interviewed and examined 358 patients in Brazil. While 201 (56%) patients had experienced pain at some time, only 53 (15%) complained of it as a current problem. That study described the characteristics of the pain in detail, but did not examine risk factors, apart from the leprosy classification: current pain occurred in 13% of lepromatous, 22% of borderline and 13% of tuberculoid cases.

A Neuropathic Pain Symptom Inventory has recently been developed and validated. We used components of this inventory to design a simple screening questionnaire to determine the baseline level of neuropathic pain in a group of multibacillary leprosy patients treated with WHO multi-drug therapy more than 10 years previously, whose clinical course, both during and after treatment, has been extensively documented. Risk factors for the development of neuropathic pain after leprosy could be examined.

Patients and Methods

The AMFES cohort included 660 people who were registered as new or relapsed cases of leprosy in central Ethiopia, between 1988 and 1992. The primary aim of the study was to examine the relapse rate after standard, fixed-duration multi-drug therapy (MDT: 6 months for PB cases and 24 months for MB cases). Follow-up continued until 1999, but after that, a sub-group of 141 multibacillary patients was followed until 2005. This sub-group included those with an initial BI of 3 or more, who were still attending for follow-up in 1999. The main purpose of this extended period of follow-up was to determine the incidence of late relapse in the group thought to be at highest risk.

Ninety-six patients were interviewed during the final round of annual examinations of the AMFES cohort in 2005. Twenty-six were originally enrolled as relapse cases, who had been treated with dapsone monotherapy prior to receiving MDT within the AMFES study; 70 were new cases at enrolment. All 96 patients had completed treatment with MDT prior to 1995; all had been closely monitored and some had received treatment for reactions during the intervening 10 or more years.

During the regular follow-up consultation, subjects were asked if they would be willing to fill in an additional questionnaire about symptoms of pain. The questionnaire was administered to all those who agreed. A nerve function assessment was carried out as part of the follow-up examination. Impairment was defined as any loss of sensation (inability to feel light touch from a ball-point pen) in the palms of the hands or soles of the feet, or any loss of voluntary muscle strength in muscles supplied by the nerves typically affected in leprosy (ulnar, median, common peroneal), or lagophthalmos. Voluntary muscle strength was assessed using a standardised method, as previously described, using a three-point scale (Strong [S], weak [W] or paralysed [P] – both partial or full loss of muscle strength [W or P] was described as impairment).

A simple screening questionnaire using components from The Neuropathic Pain Symptom Inventory was translated into Amharic and translated back as a check for accuracy.
(see Annex). This screening procedure did not include mapping the pain in relation to specific nerves affected by leprosy. As patients were seen in remote clinics without laboratory facilities, it was not possible to rule out other causes of neuropathic pain, such as diabetes, alcoholic polyneuropathy or depression.

Analysis was carried out using EpiInfo (v6). The Yates correction of the Chi-square test for significance was used.

Results

Twenty eight (29%) of the 96 patients reviewed stated that they were experiencing symptoms suggestive of neuropathic pain. The pain was stated to be severe in 12 (43%), moderate in 14 (50%) and mild in two (7%). The timing of the pain was daily in eight patients (29%), weekly in eight (29%) and only occasionally in 12 (43%). Table 1 indicates the lack of any close relationship between severity and timing of the pain.

In describing the pain, the majority of patients felt it as a burning (11 cases) or tingling (11 cases) sensation, or both (two cases). Three patients described it as pressure and one as a stabbing pain. Seventeen (61%) said that it sometimes felt like an electric shock, while 12 (43%) said that the pain could be provoked by light touch, a common feature of neuropathic pain, known as allodynia. Neither of these features of the pain correlated with severity or timing.

A number of factors were examined in the search for risk factors for the development of neuropathic pain, but only one showed a significant association. The factors examined are shown in Table 2.

The presence of leprosy-related impairment (either sensory loss or decreased voluntary muscle strength) at the time of completing the questionnaire more than 12 years after diagnosis, was the only factor found to be significantly associated with the occurrence of pain (odds ratio 7.7; 95% CI 2.5–25). These subjects were under regular review, so it was known that the impairments were not of recent onset, and thus not suggestive of an ongoing leprosy reaction.

On the other hand, six patients without impairment at follow-up complained of symptoms suggestive of neuropathic pain. Three of these had had thickened nerves at diagnosis, three had reactions and two were treated with steroids at some point during their follow-up. Only one patient had no thickened nerves at diagnosis, never had a reaction and was never treated with steroids – he had been 23 years old at diagnosis in 1992 and now complained of severe

| Table 1. Timing and severity of pain experienced by 28 patients |
|-----------------|--------|--------|--------|--------|
| Severity        | Daily  | Weekly | Occasionally | Total  |
| Mild            | 0      | 1      | 1       | 2 (7%) |
| Moderate        | 5      | 5      | 4       | 14 (50%) |
| Severe          | 3      | 2      | 7       | 12 (43%) |
| Total           | 8 (29%)| 8 (29%)| 12 (43%)| 28     |
pain, burning in nature, but only occurring occasionally; he described it as like an electric shock and said it could be brought on by light touch.

There was no evidence that earlier treatment with dapsone monotherapy and subsequent relapse increased the risk of experiencing neuropathic pain.

**Discussion**

Neuropathic pain is a neglected problem in people who have previously been treated for leprosy. Control programmes have rightly been concerned above all with case finding and chemotherapy, followed by the management of reactions and neuritis, and the prevention of disability. It is interesting to note that in this group of 96 MB cases, 62 (65%) had some impairment at diagnosis, while only 44 (46%) had impairment more than 12 years later ($P < 0.05$). Now that neuropathic pain is being increasingly recognised as an important late complication of leprosy, strategies for its effective management need to be developed.

Treatment of neuropathic pain is well established in other fields, but less so in leprosy. Because of cost and availability, a tricyclic antidepressant (for example imipramine or amitriptyline) may be tried first; if this is ineffective, or if side-effects are troublesome,
carbamazepine may be used.\textsuperscript{1} Trails of treatment in leprosy are needed, as there is at present no published evidence of efficacy in this context.

It is clear that neuropathic pain is common. Up to 56\% of patients experienced it at some point in Brazil,\textsuperscript{7} while it was a current problem in 29\% of cases in the present study in Ethiopia. In Brazil it was more common in borderline patients, while in Ethiopia it occurred with equal frequency in BL and LL cases. While severity of pain was a component of the questionnaire, it was not the main focus of the study and a more sophisticated assessment of pain severity was not considered necessary.

The analysis of risk factors identified only the presence of leprosy-related impairments as a significant factor. Nevertheless, in a clinical setting this could be a useful marker for identifying those at most risk. As this study only looked at multibacillary cases, further research is needed to examine the risk in paucibacillary cases.

Leprosy reactions occur most commonly soon after the start of effective treatment and decline steadily in frequency over the next 3–5 years.\textsuperscript{11} The diagnosis of neuropathic pain depends on identifying typical symptoms (see the questionnaire in the Annex) in patients without signs of other pathology, in particular, signs of a leprosy reaction, such as inflammatory skin lesions and new nerve function impairment. Although it was not possible to rule out other causes of neuropathic pain in this study, the possibility of other underlying conditions, especially diabetes and depression, should be borne in mind.

In conclusion, neuropathic pain is a common late complication in leprosy. The diagnosis is based on a history of typical symptoms occurring after treatment with MDT. It is important to determine the severity of the symptoms, as severity will serve as an objective indicator for evaluation of the effectiveness of treatment. Treatment is well-established for neuropathic pain due to other causes, although patients respond differently and care is needed to get the best results in each case.

Acknowledgements

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References

\textsuperscript{1} Haanpää M, Lockwood DNJ, Hietaharju A. Neuropathic pain in leprosy. Lepr Rev, 2004; 75: 7–18.
Annex

**AMFES: QUESTIONNAIRE ON CHRONIC PAIN IN LEPROSY**

<table>
<thead>
<tr>
<th>Name</th>
<th>AMFES number – SEN</th>
<th>Date</th>
<th>Clinic</th>
</tr>
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</table>

This is a questionnaire about pain that may be felt by some people long after they have been cured of leprosy.

A. Looking at yourself now, do you consider that you have some pain in your body most of the time, because of the leprosy you had years ago?

Yes.........................  No.........................

*If the answer to (A) is “No” there is no need to ask any more questions – this is the end of the questionnaire. If the answer to (A) is “Yes”, answer the other questions:*

B. How severe is your pain?

Mild .......................  Moderate ....................  Severe .......................  Very severe .......................  Extreme .......................  

C. Which type of pain do you feel most of the time?

Burning .....................  Pressure .....................  Tingling .....................  Stabbing .....................  Other........................................

D. When do you feel the pain?

All the time .................  Some hours every day .................  At least once a week .................  Only occasionally .................

E. Do you get short attacks of pain like electric shocks?

Yes.........................  No.........................

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F. Is your pain provoked by touching or brushing the skin?
   Yes.......................... No..........................

G. Is your pain relieved by medical treatment?
   Yes.......................... No..........................
   If yes, which drugs?..............................

H. Does the pain stop you sleeping?
   Yes.......................... No..........................