Late onset neuropathy in leprosy patients released from treatment: not all due to reactions?

FERNANDO DE MENDONÇA CARDOSO, MARCOS R.G DE FREITAS, TANIA MARIA ESCADA, MARIA TEREZA NEVARES & OSVALDO J. NASCIMENTO
Neuromuscular Diseases Service, Antonio Pedro University Hospital, Niterói, Rio De Janeiro, Brazil

Accepted for publication 31 May 2013

Summary
Objectives: To evaluate the clinical, neurophysiological and histological features of cases of neuropathy developing after completion of anti-leprosy treatment, where biopsy showed inflammatory changes.

Patients and Methods: Seven patients were evaluated by a single neurologist. Electro-neuro-myography and peripheral nerve biopsy were performed in all patients.

Results: Median age was 50.6 years. Time from release from treatment and onset of symptoms ranged from 1 to 12 years (median of 6.6 years). Sensory symptoms were the most common complaint, including pain (71%) and paresthesiae (71%). Muscle weakness was found in 51% and muscle atrophy in 43% of the subjects. Peripheral nerve thickening was present in all patients. Neurophysiological studies suggested sensory-motor polyneuropathy and multiple mono-neuropathy. Nerve biopsy showed inflammatory processes with fibrosis of endoneurium, perineurium and epineurium and total or partial loss of fibres. No bacilli were detected with Wade staining. Patients treated with corticosteroids had some relief of symptoms.

Conclusion: After release from treatment, leprosy patients may insidiously develop progressive peripheral nerve symptoms not fulfilling criteria for relapse or leprosy reactions. Sensory symptoms predominate and peripheral nerve thickening is an important finding. We speculate that these late onset symptoms are secondary to chronic immune-mediated processes in response to antigens of M. leprae.

Introduction

Leprosy is one of the most common primary causes of non-traumatic disease of the peripheral nerves worldwide.1 Although its prevalence is steadily declining, leprosy remains an important cause of infectious neuropathy in tropical and subtropical countries.2,3

Correspondence to: Fernando de Mendonça Cardoso, Av Almirante Ary Parreiras, n65, 1205, Icarai, Niteroi, Rio de Janeiro, Brasil (Tel: +55 021 98547179; e-mail: fdmcardoso@yahoo.com.br)
The burden of leprosy and the public perception of the disease have dramatically changed in recent years. The use of multi-drug therapy (MDT) for the treatment of leprosy, as recommended by the World Health Organization (WHO), changed the natural history of this disease and dramatically decreased disabilities. Concomitant attention to the follow-up of these patients translated into better identification of reactions and relapses. Nonetheless, leprosy continues to be a disabling and stigmatizing disease.

Some patients, after receiving the recommended WHO treatment, develop new chronic and progressive symptoms and signs of disorders of the peripheral nervous system (PNS), or have worsening of pre-existing neuropathies that are not due to leprosy reactions or relapse. The mechanisms of these neurological complications are, as yet, poorly understood.

Accordingly, herein we evaluated the clinical, neurophysiological and histological features of cases of neuropathy developing after completion of anti-leprosy treatment, where biopsy showed inflammatory changes. Manifestations were characterised as a function of demographics (age, gender), time since treatment end, as well as neurophysiological and histological aspects.

Patients and methods

Eligible patients had completed the treatment for leprosy and had symptoms or signs of disorders of the PNS not due to leprosy reactions, relapse or others causes of peripheral neuropathy. All had the multibacillary form (MB) of leprosy, were older than 18 years old, and were released from treatment as per the criteria of the WHO. All patients had been treated with MDT for 1 year. Onset of motor, sensory or autonomic symptoms and signs started after the end of therapy. Peripheral nerve biopsy failed to identify viable bacilli. Other causes of peripheral neuropathy, such as diabetes, alcoholism, metabolic diseases, intoxications, hereditary neuropathies, HIV, HTLV 1 or 2, vasculitis, paraproteinemias and other primary or secondary PNS diseases were also ruled-out. Exclusion criteria were: (i) incomplete treatment for leprosy, (ii) individuals fulfilling criteria for relapse or leprosy reactions.

The neurological examination was performed by a single neurologist from the service of neuromuscular disorders, Antonio Pedro University Hospital in Niterói, Rio de Janeiro state, Brazil. Assessment included a complete neurological examination (evaluation of the motor system, superficial and deep tendon reflexes, superficial and deep sensory examinations and assessment of the cranial nerves). Sensory perception was examined using graded monofilaments. The ulnar, radial and peroneal nerves were palpated at the elbow, wrist and behind the head of fibula. Others nerves were palpated when possible. All cranial nerves were clinically evaluated. For the exclusion of other causes of peripheral neuropathy, subsidiary tests were conducted, including: full blood count, erythrocyte sedimentation rate, C-reactive protein, fasting glucose and at 2 hours following 75 g of oral glucose; renal and hepatic function tests, TSH and free T4; B12 vitamin and homocystine; HIV and HTLV1 and 2, VDRL; cryoglobulin studies; serum protein electrophoresis; rheumatoid factor; anti-Ro (SS-A) and anti-Ro (SS-B).

Electrophysiological studies were performed using Nihon-Khoden Neuropack 8 equipment. Motor and sensory nerve conductions studies were performed for all patients. Motor nerve conduction was evaluated by distal latencies, conduction velocity and amplitude of muscle action potential of the median, ulnar, common peroneal and posterior tibial nerves. Sensory nerve conduction was evaluated by distal latencies, conduction velocity and
amplitude of the sensory nerve action potentials of the median, ulnar, radial, superficial fibular and sural nerves. In selected cases (patients with proximal symptoms), we analysed the F wave. Needle examination was done in the brachial, first interosseous, anterior tibialis and extensor digitorum brevis muscles.

Sensory peripheral nerve biopsy in symptomatic areas was performed. Specimens were fixed in 3% glutaraldehyde and stained with hematoxylin & eosin (H&E), Gomori’s trichrome, Congo red for amyloid and Wade’s for bacilli identification. Semi-thin sections were stained with toluidine blue.

This study was approved by the Ethics Committee of our Hospital. All patients gave their informed consent prior to inclusion in the study.

**Results**

Our sample consisted of seven patients (three men and four women) fulfilling the enrollment criteria. Age ranged from 37 to 61 years old. Table 1 displays the baseline characteristics of the patients.

Time from end of treatment to onset of new symptoms ranged from 2–12 years (mean = 6·6 years). Four patients had onset of symptoms 8 years after the end of treatment.

The following symptoms were reported by the patients: pain (n = 5), paresthesiae (n = 5), and weakness (n = 4). Lower limbs were most commonly affected. In four patients, symptoms consisted of unilateral or bilateral ulnar palsy. Cranial nerves were not affected. Table 2 summarizes the clinical characteristics of the patients.

Findings from the electroneuromyography were consistent with axonal polyneuropathy in three patients, ulnar nerve mono-neuropathy plus axonal polyneuropathy in two, multiple mono-neuropathy in one and in one it was normal with bilateral carpal tunnel syndrome (this patient had small fibre neuropathy).

All nerve biopsies displayed inflammatory cell infiltrate with vacuolated cells, fibrosis of the perineurium, endoneurium and endoneural vessels (Figure 1, Table 3).

Viable bacilli were not found. The semi-thin method demonstrated the decreased number of nerves fibres (Figure 2).

**Table 1.** Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Race</th>
<th>Age</th>
<th>TAET (years)</th>
<th>NT</th>
<th>ENMG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>W</td>
<td>61</td>
<td>12</td>
<td>Yes²</td>
<td>MM</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>W</td>
<td>37</td>
<td>1</td>
<td>Yes¹</td>
<td>PNP</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>W</td>
<td>61</td>
<td>9</td>
<td>Yes²</td>
<td>PNP</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>W</td>
<td>58</td>
<td>3</td>
<td>Yes¹</td>
<td>CTS</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>W</td>
<td>55</td>
<td>2</td>
<td>Yes¹</td>
<td>MN + PNP</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>A</td>
<td>39</td>
<td>10</td>
<td>Yes²</td>
<td>MN + PNP</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>W</td>
<td>43</td>
<td>9</td>
<td>Yes³</td>
<td>PNP</td>
</tr>
</tbody>
</table>

Five patients were treated with prednisone (40 mg/day for 8 weeks, followed by gradual tapering off), and all reported relief of pain, but no improvement of motor or sensory impairments. They continued using 10 mg of prednisone daily for 1 year.

Discussion

Although the global prevalence of Hansen’s disease has decreased following the introduction of MDT, its overall incidence remains unchanged, being one of the main causes of peripheral neuropathy worldwide.9,10

Our patients had symptoms and signs that developed insidiously, in a progressive pattern that was compatible with the involvement of the PNS. This involvement was confirmed by nerve conduction studies. Although ENMG findings were not specific, six patients had peripheral neuropathy with axonal features, three had involvement of the ulnar nerve at the elbow. Nerve conduction was normal in one patient, suggesting small fibre polyneuropathy. Sensory symptoms, such as paresthesiae and hypoesthesiae were reported by all patients. Motor impairment was not reported as a symptom, but was identified at neurological examination in three patients (ulnar paresis). Only one patient has a normal neurological exam, despite the symptoms, reflecting a small fibre polyneuropathy. New cutaneous manifestations or worsening of previous lesions were not seen or reported. The sural nerve was biopsied in five patients, while the ulnar nerve was chosen in two. Inflammatory cell infiltrate, fibrosis of the epineurium, perineurium, endoneurium, loss of fibres and absence of bacilli were found in all patients.

It is well established that patients released from leprosy treatment may, sometimes and after a variable range of time, develop new neurological or cutaneous symptoms. In the INFIR study, 38% of MB patients developed neurological symptomatology, neuritis or leprosy reactions during a follow-up period of 2 years after the end of treatment.11 These findings frequently reflect the relapse of disease or leprosy reactions. In patients with the paucibacillary form (PB) of disease, the identification of these reactions may be difficult. Accordingly, patients with leprosy should be regularly followed even after being considered

Table 2. Clinical features

<table>
<thead>
<tr>
<th>Patient</th>
<th>Symptoms and neurologic exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paresthesias in lower limbs and weakness of left hand; interosseous and hypothenar atrophy, paresis in abduction of left fingers (MRC 3), touch, pain and temperature hipoesthesia on lateral aspect of left leg.</td>
</tr>
<tr>
<td>2</td>
<td>Pain in upper and lower limbs and normal neurological exam.</td>
</tr>
<tr>
<td>3</td>
<td>Burning pain in lower limbs; touch, pain and temperature hipoesthesia (stock pattern).</td>
</tr>
<tr>
<td>4</td>
<td>Pain and paresthesias in lower limbs; pain and temperature hipoesthesia (stock pattern).</td>
</tr>
<tr>
<td>5</td>
<td>Paresthesias in lower limbs and left hand; paresis in abduction of fingers (MRC 3), touch, pain and temperature hipoesthesia (stock and glove pattern).</td>
</tr>
<tr>
<td>6</td>
<td>Pain and paresthesias lower limbs and left hand; interosseous and hypothenar atrophy, paresis in abduction of fingers (MRC 3), touch, pain and temperature hipoesthesia (stock pattern) and hipoesthesia in median aspect of left hand and forearm.</td>
</tr>
<tr>
<td>7</td>
<td>Pain and paresthesias in hands and weakness in lower limbs; interosseous and hypothenar atrophy, paresis in abduction of fingers (MRC 2), touch, pain and temperature hipoesthesia (stock and glove pattern).</td>
</tr>
</tbody>
</table>
cured, and proper documentation of the clinical and histological characteristics of relapse and reversal reactions is mandatory, in order to proceed to the differential diagnosis.

In MB leprosy, relapse may be defined as the multiplication of *M. leprae*, demonstrated by an increase of at least two log units of the bacillary index at any single site, usually with evidence of clinical deterioration (new skin patches or nodules and/or new nerve damage), after the completion of treatment. According to the WHO, ‘cure’ happens after treatment completion (1 year for multibacillary patients and 6 months for paucibacillary patients), improvement of skin lesions and negative bacilloscopy for acid-fast bacilli for 3 consecutive months for MB patients. For PB patients, ‘cure’ requires resolution of skin lesions, no infiltration or erythema, and resolution of pain or sensitivity of the nerves.12

Apart from the slowly progressive lesions, sudden (acute or subacute) impairments of neurological function may happen and are defined as leprosy reactions.13 They represent an important cause of clinical deterioration and disability, and may occur before, during or after treatment. Two types of leprosy reactions are described: Type 1 (reversal reactions) and Type 2
Reversal reactions (RR) represent the acute activity of cellular immunity precipitated by the removal of bacterial antigens located in the skin and peripheral nerves. This is accompanied by tissue injury, neuritis and acute inflammation of skin lesions. Risk is highest during the first year after the beginning of MDT, but neurological signs may occur later. In 2000, Bowen et al. described a patient considered to be cured of leprosy, who developed an acute pattern of multifocal sensory disturbance beginning around 25 years after the end of treatment. Detailed clinical, electroneuromyographic and histological evaluations were performed. Leprosy reactions and relapse were excluded, as well as other possible causes for neurological impairment. Subsequently, in 2003, Rosenberg et al. evaluated and followed 14 patients with leprosy who developed progressive neurologic impairment after treatment end. Symptoms were not explained by relapse or leprosy reactions, and developed from 1 to 22 years after the diagnosis of leprosy. Nerve conduction studies showed a reduction in the motor or sensory action potential amplitude with normal or slow conduction velocity. The response to corticosteroids was unsatisfactory. Histological analyses of the skin or of the damaged nerves were not performed. More recently, Nascimento et al. studied three patients with painful neuropathy of the lower limbs with onset happening years after treatment end. Superficial nerve biopsy performed in two patients demonstrated inflammatory and ischemic lesions without the bacilli. The authors considered that the neuropathy was the result of a chronic immune process, suggesting prolonged treatment with immunosuppressive drugs.

In our study, patients had insidious pain, more frequent in the lower limbs. The gradual onset and the histological findings allowed us to exclude leprosy reactions, in particular RR, which is characterised by acute exacerbation of cellular immunity in response to bacterial antigens. As a result, it produces acute or sub-acute clinical manifestations with cutaneous lesions and inflammatory neuritis, with predominantly sensory symptoms. Systemic manifestations (fever, malaise, weight loss) are frequent. Our patients did not have acute or subacute symptoms, worsening of existing skin lesions or onset of new ones. In addition, RR occurs more frequently during or within 1 year after the treatment. The histological features described in RR, edema, hyperemia and granulomas, were not identified in our biopsies.

Our patients also did not meet the essential criteria for relapse. They had progressive neurological symptoms without cutaneous involvement and no histological evidence of active disease. Our patients had been treated for a period equal to or greater than 1 year and had a diagnosis of the MB form of the disease. In relapsing cases, the histological findings are typical, characterised by mononuclear cell infiltration, with replacement of nerve fibres by

---

**Table 3. Histological aspects of peripheral nerve biopsy**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Biopsied Nerve</th>
<th>Inflammatory infiltrate</th>
<th>Perivascular inflammatory infiltrate</th>
<th>Vasculitis</th>
<th>Fibrosis</th>
<th>Loss of fibres</th>
<th>Bacilli</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SU</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>S</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>S</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>S</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>S</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>S</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>SU</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>0</td>
</tr>
</tbody>
</table>

0: absence, +: mild, ++ moderate, +++ intense, SU: superficial ulnar, S: sural
connective tissue and demonstration of viable bacilli to the techniques of Wade and Fite. We found inflammatory reactions in nerve biopsies, but no viable bacilli.

Thus, based on clinical, epidemiological and histopathological aspects we suggest that our patients portray a new clinical form of leprosy neuropathy that is not yet fully recognised. Because pain disappeared with corticosteroids, despite the persistence of motor and sensory impairment, we suggest an inflammatory basis for this affection. We suggest that this late-onset of peripheral neuropathy is probably due to a chronic immune-mediated process in response to antigens of *M. leprae*.

**Final considerations**

Leprosy is one of the major causes of peripheral nervous system disease in Brazil. If left untreated, it can lead to clinical deformities and functional disability.
Our study has limitations, the most important being the small sample size, which limited the possibility for more sophisticated analyses. Accordingly, in order to better understand and recognise this form of disease, further multi-centre research is necessary. Detailed histological analyses with the identification of cell type and antigens are a prelude for understanding the pathogenic mechanisms, which will guide the proper selection of therapy. Thus, peripheral nerve biopsy remains an essential tool in the evaluation of leprosy patients who develop new symptoms.

Acknowledgements

We would like to express our special thanks to Mrs Janaina Bigal for her assistance in the translation of the manuscript.

References