Neurophysiological patterns of ulnar nerve neuropathy in leprosy reactions

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Summary

Background: Leprosy neuropathy, despite being primarily demyelinating, frequently leads to axonal loss. Neurophysiological examination of the nerves during Type 1 (T1R) and Type 2 reactions (T2R) may give some insight into the pathophysiological mechanisms.

Methods: Neurophysiological examinations were performed in 28 ulnar nerves during a clinical trial of steroid treatment effectiveness, 19 patients with T1R and nine with T2R. The nerves were monitored during a period of 6 months; there were eight assessments per nerve, for a total of 224 assessments. Nine neurophysiological parameters were assessed at three sites of the ulnar nerve. The compound motor action potential amplitudes elicited at wrist, elbow and above, as well as the conduction velocity and temporal dispersion across the elbow, were chosen to focus on the changes occurring in the parameters at the elbow tunnel.

Results and Conclusion: Neurophysiological changes indicating axonal and demyelinating processes during both T1R and T2R were detected across the elbow. Changes in demyelination, i.e. a Conduction Block, as a primary event present during T2R, occurring as an acute phenomenon, were observed regularly; in T1R Temporal Dispersion, a subacute phenomenon, was seen. During treatment remyelination occurred after both types of reactions.

Introduction

Leprosy neuropathy is a chronic condition, which begins as an infection of the Schwann cell and may end in a demyelinating neuropathy which increases during the inflammatory process accompanying the leprosy reactions. It frequently leads to significant axonal loss.
It is important to understand the neurophysiological status of the nerves during the inflammatory phenomena – the leprosy reaction.

There are two types of nerve damaging reactions: Type 1 leprosy reaction (T1R) or reversal reaction, in patients who have an active cell-mediated immune response against *M. leprae* antigenic determinants, i.e. polar tuberculoid (TT), borderline tuberculoid (BT), mid borderline (BB) and borderline lepromatous (BL) and Type 2 leprosy reaction (T2R) or erythema nodosum leprosum (ENL), which is predominantly immune-complex mediated and occurs only in patients with borderline lepromatous (BL) and lepromatous leprosy (LL). Oral steroid treatments\(^1\,^2\) are used to treat these reactions with variable outcomes. There are reports in the literature concerning the neurophysiological features of neuropathy in leprosy, particularly in nerve conduction studies, with abnormalities in motor and sensory potentials, focal CV reduction, increase of distal latencies and absence of sympathetic skin responses.\(^3\,^4\,^5\,^6\,^7\,^8\,^9\,^10\) But the patterns of nerve involvement are not clear since both demyelination and axonal degeneration are commonly found together in leprosy neuropathy.\(^11\) Moreover, there is little information about nerve conduction during and after reaction treatment.\(^12\,^13\)

To understand the mechanism of regeneration, the electrophysiological status of the nerve needs to be studied during oral steroid treatment in both types of reaction.\(^2\)

The high frequency of ulnar nerve involvement,\(^3\,^13\) its vulnerability at the elbow,\(^5\,^11\) and the neurophysiological findings associated with different clinical forms of leprosy\(^4\) mean that this nerve is an archetype of leprosy neuropathy. Different patterns in the findings may be expected since the duration and pathologic features of the reactions are distinct. This study aims to define the neurophysiologic patterns associated with ulnar nerve involvement in both types of leprosy reaction. Different patterns of lesion may be expected since the duration and pathologic features of reactions are distinct. The motor nerve conduction was chosen as the neurophysiological parameter because the motor fibres represent a wide sample of the myelinated fibres present in a mixed nerve.\(^14\) It can be measured in all segments of a nerve and it is reproducible, even in the most proximal segments.\(^15\)

**Method**

**Setting:** outpatient clinic of the Instituto Lauro de Souza Lima, in Bauru Brazil.

**Timing:** September 2003 to August 2005.

**Patient Selection:** Patients were being recruited for a study on the effectivity of steroid treatment of Type 1 and Type 2 leprosy reactions.

Patients with new ulnar nerve involvement, within 3 or 3–6 months’ duration, as defined by complaints such as loss of sensation and paraesthesia, sensory and/or motor impairment, ulnar nerve tenderness and/or enlargement were included. Of 163 patients recruited for the study, 21 were eligible for the neurophysiological study; 17 men and 4 women (ages 21–60, mean: 41.5). Twelve patients had T1R (3 BT and 9 BB) and nine T2R (all LL).

**Exclusion criteria were:** patients at risk of a neuropathy other than leprosy, i.e. diabetes, alcoholism, risk group for HIV infection; patients with a family history of hereditary neuropathy, and patients over 60 years of age. Patients with inactive neuropathy and/or chronic neuropathic pain, nerve abscess and palpable nodules in nerves were excluded as well as patients who had undergone neurolysis in the past.\(^13\,^16\) Patients with a contraindication for steroid therapy were also not accepted.
All patients had general clinical and dermatological examination and routine laboratory tests done.

Reactions were diagnosed as:

- **Type 1 reaction (T1R) in TT, BT, BB and BL patients:**
  An increased inflammation in existing lesions which are not tender on palpation and/or the occurrence of new lesions and/or acro-edema. Nerves could be enlarged, tender and show loss of function.

- **Type 2 reaction (T2R) in BL and LL patients:**
  A sudden appearance of inflamed papules, nodules and plaques that are tender on palpation. The patient may be ill and run a mild fever and there may be signs of involvement of other organs, e.g. eyes, testicles, joints, lymph glands and periost. Nerves could be enlarged, tender and have pain and loss of function.

The patients were randomly assigned to one of two treatment groups, experimental or control, according to the type of reaction. Treatment doses at the start of treatment were 1 mg/kg/day in the control group and 2 mg/kg/day in the experimental group. In T1R the steroid was decreased gradually to 1 mg/kg/day at the end of the first month and thereafter 10 mg/month until the end of the sixth month. In T2R steroid was decreased gradually to 0.5 mg/kg/day at the end of first month. The patients were assessed immediately prior to treatment (1st assessment), after one week (2nd), after one month (3rd) and thereafter monthly. The last follow-up was done at the end of 6 months (8th assessment). The neurophysiological findings are reported.

**NEUROPHYSIOLOGICAL EVALUATION**

Motor nerve conduction studies were carried out over three segments of the ulnar nerve. The recording of the compound motor action potential (CMAP) was done with the recording electrode on the belly of the *abductor digiti minimi* muscle and the reference electrode on a tendon or a bony surface.15

1. The CMAP amplitude by supramaximal stimulation was measured from the base line to the negative spike.15
2. The distal latency was recorded over an 8 cm long segment from the recording electrode to the wrist.
3. The nerve was also stimulated just below the elbow and 11 cm above the elbow. The conduction velocities over the forearm segment and across the elbow were computed.
4. The CMAP temporal dispersion (TD), i.e. the duration of CMAP,15 was recorded below and above the elbow. Its values, in percentages compared to the duration of CMAP at the wrist, were summated.
5. The minimum value of the F wave latency, related to demyelination in all segments of the nerve from stimulating electrode to spine and back to the recording electrode, were calculated over a series of 20 stimuli.

The severity grades of the neurophysiological involvement were classified as: (a) Normal motor nerve conduction; (b) Slightly abnormal: CV reduced at the elbow segment; (c) moderate abnormal: pronounced reduction of CV at the elbow and reduction at the
forearm segment; (d) pronounced abnormal: CMAP and CV with diffuse pronounced reduction and; (e) complete paralysis: CMAP absent.

**ANALYSIS**

The CMAP amplitude at the three sites and the CV and TD across the elbow were analysed to focus on the ulnar nerve physiopathology at the elbow. The curves of the mean value of these variables, for the eight evaluations during the follow-up, were compared to nerves of patients in the T1R and T2R groups. The Student ‘t’ test was applied for the parameters CV and TD across the elbow comparing the first evaluation with the eighth in both reaction groups. The patients in the two treatment groups were combined since the treatment had similar outcomes.\(^1\)

**ETHICAL CONSIDERATIONS**

This study was approved by the Ethical Committee of the Lauro de Souza Lima Institute. Informed written consent was obtained from each patient.

**Results**

Forty-two ulnar nerves from 21 patients were studied (Table 1).

Eight nerves had nerve conduction studies that were within normal limits. Six nerves were completely damaged, and 28 nerves were followed during treatment using neurophysiological assessments. Seventeen nerves in patients with T1R and 11 nerves in patients with T2R were followed during steroid treatment. The nerve lesion severity grade

<table>
<thead>
<tr>
<th>T1R</th>
<th>T2R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Age</td>
</tr>
<tr>
<td>P1.1</td>
<td>29,6</td>
</tr>
<tr>
<td>P1.2</td>
<td>56,3</td>
</tr>
<tr>
<td>P1.3</td>
<td>57</td>
</tr>
<tr>
<td>P1.4</td>
<td>47,9</td>
</tr>
<tr>
<td>P1.5</td>
<td>32,7</td>
</tr>
<tr>
<td>P1.6</td>
<td>61</td>
</tr>
<tr>
<td>P1.7</td>
<td>38</td>
</tr>
<tr>
<td>P1.8</td>
<td>59,5</td>
</tr>
<tr>
<td>P1.9</td>
<td>23,9</td>
</tr>
<tr>
<td>P1.10</td>
<td>53,3</td>
</tr>
<tr>
<td>P1.11</td>
<td>59,3</td>
</tr>
<tr>
<td>P1.12</td>
<td>42,8</td>
</tr>
</tbody>
</table>

P1: Patient with T1R; P2: Patient with T2R; MDT: multidrug therapy; PB: paucibacilar; MB: multibacilar; BT: borderline tuberculoiide; BB: borderline borderline.
was: normal (8), slight (10), moderate (9), pronounced (9). Six nerves were completely paralysed. The most frequent abnormal findings observed before treatment were: diminished CV across the elbow (83%), increased F wave latency (69%) and increased TD at the elbow and above (across the elbow) (53%), followed by a diminished CV along the forearm (39%) and increased distal latency (31%), (Table 2).

The distal latency was increased in 31% of the nerves. These findings were mainly seen in nerves with a higher grade of severity (9/26, 47%). Each neurophysiological parameter was analysed in time for both Type 1 and Type 2 reaction groups. The parameters with the highest frequency of involvement were analysed, i.e. CV across the elbow; CMAP – TD across the elbow and the CMAP amplitude below and above the elbow. In Figure 1, the curves of the CV in T1R and T2R, were similar, but at the beginning in T1R the CV reduction was greater.

However, the CMAPs TD across elbow curves showed a marked difference as follows: In the T1R nerves the CMAPs TD across elbow curve variation was significant; while in the nerves with T2R there was no change in the CMAPs TD across elbow (Figure 2).

Significant differences between the two types of reaction were not only seen in the improvement of the CV ($P = 0.015$) but also in the CMAPs TD across elbow ($P = 0.033$)

Table 2. Abnormal and normal neurophysiologic findings from 36 ulnar nerves of 21 patients, including the eight nerves without active neuropathy, before treatment. Nerve conduction parameters at the wrist, forearm, across elbow and along the nerve

<table>
<thead>
<tr>
<th>Type of leprosy reaction</th>
<th>Abnormal</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1R</td>
<td>T2R</td>
</tr>
<tr>
<td>Distal latency</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>CV forearm</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>CV across elbow</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>TD at elbow and above</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>F wave</td>
<td>16</td>
<td>9</td>
</tr>
</tbody>
</table>

CV: conduction velocity; TD: Temporal dispersion.

![Figure 1](image_url). Mean value of CV across the elbow measured in nerves of patients in T1R and T2R ($n = 28$). The first CV was measured before treatment and the second was measured at the end of the first week, the third at the end of the first month and thereafter monthly until the last measurement at the end of the sixth month.
The mean CMAPs amplitude curves below elbow were similar for the nerves of both T1R and T2R. Above the elbow there were differences in the first 2 months, the CMAPs were more prominently reduced in T1R nerves. Figures 3 and 4 show that most of the improvement in amplitude occurred between the first week and the second month for both reaction groups.

The F wave latency improvement accompanied the evolution of the other parameters during the study for each nerve group, i.e. in both T1R and T2R.

Discussion

The study demonstrates novel pathophysiological characteristics of leprosy reactions Type 1 and 2 and provides new insights for treatment concerning the timing related to drug use, expected recovery and the general prognosis in each type of reaction.

Patients’ clinical features in this sample were similar and confirmed the purpose of the study, despite the small number of nerves studied (\( n = 28 \)). Prior to treatment, the pathology over the 6 months of this study. The mean CMAPs amplitude curves below elbow were similar for the nerves of both T1R and T2R. Above the elbow there were differences in the first 2 months, the CMAPs were more prominently reduced in T1R nerves. Figures 3 and 4 show that most of the improvement in amplitude occurred between the first week and the second month for both reaction groups.

The F wave latency improvement accompanied the evolution of the other parameters during the study for each nerve group, i.e. in both T1R and T2R.
was predominantly found across the elbow and less frequently along the forearm or distally at the wrist (Table 2). These findings are in agreement with several other studies on nerve conduction.3–6,11,12 The increased distal latency found in 30% of the nerves was generally encountered in nerves with a severe degree of damage, i.e. in nerves with abnormal CV (9/26; 47%) along the forearm segment. This correlation might indicate that the increase in distal latency is a secondary phenomenon and is not the result of a primary compression at the wrist. The F wave latency also improved after the first week. This parameter is not specific for one nerve segment only, but for the nerve as a whole, from the cord to the muscle. It reflects a general improvement in nerve conduction during the study period that accompanied the segmental improvement. All the parameters with higher frequency of involvement in this experiment, i.e. CV across the elbow; CMAP – TD across the elbow and the CMAP amplitude below and above the elbow, had improved during the first week to the second month, but sooner in nerves involved in T2R. In a similar study on nerves in patients experiencing both types of reactions Thacker (1996), analysing only one segment of the ulnar nerve, showed that CV reduction was more pronounced in nerves of patients with T1R when compared to patients with T2R. Related to conduction recovery, most nerves that deteriorated following steroid treatment were in T2R patients.13 These authors suggested that there are differences in the immunopathogenesis of both reactions which could lead to demyelination in both, but the type of demyelination process in T1R and T2R was not identified. The speed with which edema occurred in each reaction was not considered, nor was the segment across the elbow utilised for measurements. The improvement in the first week to first month is most likely due to the reduction of intraneural edema.10,16 When comparing T1R and T2R nerves, the curve of CV across the elbow differed slightly but in T1R it was more reduced than in T2R during the first months (Figure 1). However, in the CMAP – TD across the elbow curve there was a definite difference, i.e. the T1R nerves showed a marked change and T2R did not (Figure 2). The CMAP – TD is a result of acquired segmental demyelination and, as the reduction of CV, reflects the involvement of Schwann cells.15 The absence of CMAP – TD in T2R suggests that here another mechanism occurs at the elbow segment. In order to understand the differences, it is necessary to compare the CMAPs amplitude curves, below and above the elbow, Figures 3 and 4, in which there are no considerable differences in both reactions groups.

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**Figure 4.** Median of CMAPs above the elbow measured in nerves of patients in T1R and T2R (n = 28). The first CMAP median above the elbow before treatment and the second measured at the end of the first week, the third at the end of the first month and thereafter monthly until the last measurement at the end of the sixth month.
The presence of a diminished amplitude at or proximally to the site of lesion, without TD is defined as conduction block (Figures 5 and 6).

There are two distinct pathological myelin findings and two distinct regeneration processes in the reaction groups: (a) In T2R a conduction block occurred as the central process; there is a more acute and focal phenomenon. (b) In the T1R the main process was TD – diffuse subacute and chronic segmental demyelination at the site of lesion. These two different pathophysiologic behaviors during the different types of reactions may reflect two aspects of the Schwann cell pathology when facing compression, depending on the time each reaction requires to develop edema. During the first, conduction block, the nerve is acutely submitted to mechanical force on the inflamed tissues. The myelin sheath is displaced to sites of lower pressure. This is similar to the acute compression that occurs during: ‘Saturday night palsy’, surgical retraction and tourniquet compression. During the second, TD, occurring in cases of T1R, the segmental demyelination is analogous to chronic compression (entrapment syndrome). The mechanical forces act quietly within anatomical tunnels as a consequence of

![Figure 5](image-url)

**Figure 5.** (a) Ulnar nerve motor conduction in the first evaluation of a patient from group T2R. The CMAPs at wrist, elbow and above elbow are depicted. In the third line the CMAP has an amplitude reduction of more than 50%, which characterizes a conduction block. (b) Last evaluation of the same nerve with a normal CMAP (third line), making evident the resolution of the CB.
the chronic inflammation during a T1R, leading to a restriction of gliding at the entrapment sites. The Ranvier node then loses its connection and the myelin its lamellar structure followed by demyelination and remyelination. In leprosy these compression phenomena are related to nerve enlargement due to intraneural edema in the anatomic tunnels. This insidious entrapment plus inflammation, if not treated, may lead to axonal loss in varying degrees. In the T1R group, the TD improved over time (Figure 2), following the same curve pattern as the changes in the cellular infiltrate and cytokines profile during steroid treatment demonstrated by an immunohistopathological study of the T1R skin lesions. The concordance between the improvement of the cytokine profile and cellularity and the motor nerve conduction data indicate a high specificity of this parameter for the inflammatory demyelination in leprosy.

Conclusions

1. Temporal Dispersion was associated with the involvement of the Schwann cell during the subacute inflammation occurring during a T1R. The improvement in the TD continues during the reduction of the steroids if the steroids are not discontinued too quickly.
2. Conduction Block during a T2R was associated with a focal and more acute intraneural edema at the elbow tunnel.
3. These parameters may help to differentiate between T1R and T2R and may be used as signs of neuropathological activity, indicating that the nerve may still respond to treatment.

4. The motor nerve conduction proved to be a reliable and trustworthy parameter for nerve function monitoring at different sites during anti-reaction treatment in leprosy.

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References


