Blink reflex, H-reflex and nerve-conduction alterations in leprosy patients

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Summary Peripheral nerve lesions are the most important cause of disability in leprosy patients. Electrophysiological studies are used in the diagnosis and prognosis of neuropathy. Nerve conduction is the most frequently used electrophysiological test method to detect neuropathy, although it evaluates only a part of the peripheral nervous system. Blink reflex and H-reflex are electrophysiological tests which evaluate facial and trigeminal nerve function. This study determined the frequencies of blink reflex, H-reflex and motor and sensory nerve conduction alterations in twenty five heterogeneous, clinic patients with lepromatous leprosy and a control group of 20 healthy subjects. Study results showed a decrease in motor and sensory nerve conduction in 40% and 30%, respectively. In blink reflex (BR), right R1 was altered in latency in 20% of patients, left R1 in 20%, right ipsilateral R2 in 16%, left ipsilateral R2 in 20%, and right and left contralateral R2 were altered in 32% of patients. There was an absence of H-reflex in 16% (n = 4) and prolonged latency in 4% (n = 1).

Introduction

Neuropathy is one of the most frequent complications in leprosy patients, manifesting itself as motor, sensitive, or autonomic alterations.1,2 Neuropathy diagnosis is generally made through
physical examination or electrophysiological studies. Nerve conduction is the most frequently used electrophysiological study to diagnose neuropathy. However, it evaluates only a part of the peripheral nerve. Other electrophysiological methods such as blink reflex, H-reflex and F-wave are also used to evaluate the peripheral nervous system.3

The blink reflex (BR) is analogous to the corneal reflex, involving the stimulation of the trigeminal nerve through its ophthalmic branch (supraorbital), from where afferents travel to thepons, mesencephalon, and cerebral cortex to make final connections with the facial nerve).3,4 In response to stimulation, a blink reflex can be recorded ipsilateral or contralateral to the site of stimulation. Stimulation of the ophthalmic nerve branch produces two kinds of responses in the orbicular muscle of the eyelid: an early response, or R1, and a delayed response, or R2. Of these, R1 is evoked only on the stimulated side and is considered to be a pontine reflex. In contrast, R2 is recorded bilaterally following unilateral stimulation, and relies on a more complex pathway that includes interneurons at the level of the pons and the lateral medulla.3,4

The H-reflex (Hoffman reflex) is used to evaluate the velocity of conduction of motor and sensory neurons. It is particularly useful in evaluating spinal cord circuitry in a non-invasive manner.3,4 Because leprosy predominantly affects the peripheral nervous system, the objective of the present study was to determine H-reflex, blink reflex and motor and sensory nerve-conduction alterations in leprosy patients. To the best of our knowledge, there are no previous studies dealing to correlate simultaneously three electrophysiological test with clinical manifestations in LL patients.

Materials and methods

A cross-sectional study was carried out using patients presenting with lepromatous leprosy (LL). All patients registered as LL by Colima State health Institution (Secretaria de Salud, Sanitary Jurisdiction No. 1) were included in this study. LL was confirmed by histopathologic and immunological studies (not included). Patients presenting with chronic alcohol ingestion, antecedents of cervical trauma, cerebrovascular disease, cardiovascular disease, trigeminal neuralgia or facial paralysis were excluded from the study, as were patients with cardiac pacemakers or sensitivity afraid to electrical currents. The control group consisted of a group of 20 healthy volunteers (11 women, nine men; mean age 41 ± 10.2 years (range 27–60 years), which has been the basis for description of alterations in previous electrophysiological studies.5,6 None of these subjects had any evidence or history of diabetes, hypertension or cardiac or cerebral vascular disease. All subjects gave their written informed consent and the Hospital Ethics Committee approved the study. The electrophysiological study was carried out in the Clinical Electrophysiology Laboratory of the University Center for Biomedical Research of the University of Colima, Mexico.

Blink reflex test

A Nicolet Viking IV electromyograph was used and the patient was laid supine on a bed in a quiet, temperature-regulated (25–32°C) and electrically shielded room. A ground electrode was placed on the patient’s chin, and stimulation was performed via a cathode placed on the ophthalmic arch. The active recording electrode was placed between the lower and middle part of the inferior lid, and the reference electrode was placed on the forehead at 4 cm from
the external edge of the active electrode. The intensity of the stimulus was 80–100 V and 0-1 ms duration. The signal was filtered with a range of 5 kHz for high signals and 20 Hz for low signals. Scanning was 10 ms and gain was established at 200 mV. The frequency of pulses was 1–2 Hz. Four stimuli were applied to each side every 10 s. The results obtained were averaged and the parameter used for the analysis was latency to onset (measured from the stimulus artifact to the initial deflection for each response).

H-REFLEX OF THE TIBIAL POSTERIOR NERVE

With the patient in the prone position and with a knee flexion of 120°, a stimulus was applied in the popliteal fossa. The cathode electrode was placed proximal to the anode (for orthodromic stimulation) and stimulus intensity was in the range of 40–100 V, with 1 ms pulse duration. Recording electrodes were placed as follows: the active electrode at the ventral side of the right pelvic gastrocnemius muscle, and the reference electrode 4 cm away from the active one. An alteration was considered to be present when latency of the response was more than two standard deviations from the normal curve obtained from the control group measurements, or when the response was absent.

NERVE-CONDUCTION VELOCITY MEASUREMENTS IN ULNAR NERVE

With the patient in the supine position and the elbow at a flexion angle of 90°, the motor stimulation was performed at the wrist and the elbow (at 4 cm proximal to the epicondylus). A ground electrode was placed on the dorsal side of the right hand; an active electrode was placed at the level of the abductor muscle in the fifth finger of the hand, and a reference electrode was placed at 4 cm proximal to the same fifth finger. A supramaximal stimulation was applied in the range of 150 and 300 V, with 0-1 ms pulse duration. The parameters measured for the evoked responses were: amplitude, latency, and nerve-conduction velocity.

Ulnar sensory nerve measurement was performed with the patients in the position described above, and with a ring electrode (active) placed at the level of the interphalangic articulation, proximal to the fifth finger of the right hand, and the reference electrode placed at the level of the distal interphalangic articulation. Stimulation was applied at a distance of 14 cm (pulse duration: 0-1 ms; and range intensity: 80–140 V). The parameters measured in this response were latency, amplitude and nerve-conduction velocity. All measurements were done at room temperature (25–32°C).

STATISTICAL ANALYSIS

Means, standard deviation and percentages were used. Mean comparison of the two groups (leprosy group and healthy group) was carried out using the Student t-test or the Mann-Whitney U-test. Percentage comparison of the groups was made using the $\chi^2$ test with the Yates correction or the Fisher exact test. Tests were considered abnormal when latencies or amplitudes were greater or less than two standard deviations. A confidence interval (CI) 95% was used in all tests and statistical significance was considered when $P < 0.05$. 

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Results

Twenty-five lepromatous leprosy patients (14 men and 11 women) with a mean age of 46.9 ± 15.2 years (range from 25 to 84). Ten (40%) of the 25 examined patients had clinical manifestations of sensitive neuropathy ($n = 5$), motor neuropathy ($n = 3$) and mix neuropathy ($n = 2$). Disease evolution was 4.1 ± 2.6 years (range from 1 to 12 years). All patients received treatment upon entering the study. It was based in rifampicin (via oral 600 mg once a month), dapsone (via oral 100 mg once a day), and clofazimine (via oral 50 mg once a day plus 300 mg once a month), and the mean duration of treatment was 24.3 ± 13.8 months (range from 1 to 60 months).

The H-reflex was absent in 16% ($n = 4$) of the patients and prolonged latency in 4% ($n = 1$). M-wave latency was registered as normal in all cases, although amplitude was diminished in 68% ($n = 17$). H-reflex and M-wave peak amplitude mean comparison of the leprosy patients and healthy subjects was statistically different (Table 1) but there were no significant differences in mean latencies between the two groups. The mean age of the control subjects was 41 ± 10.2 years (range 27–60 years), and the mean height was 1·69 ± 0·07 m (range 1·59–1·88 m).

The following alterations were found in the blink reflex: prolonged latency of the right R1 in 20% ($n = 5$) of patients; left R1 in 20% ($n = 5$); right ipsilateral R2 in 16% ($n = 4$); left ipsilateral R2 in 20% ($n = 5$); right contralateral R2 in 32% ($n = 8$); left contralateral R2 in 32% ($n = 8$). There was an absence of left contralateral R2 in 8% ($n = 2$) of patients. There was a significant difference in right and left R1 and right contralateral R2 mean latency comparison of BR components in leprosy patients and healthy subjects (Table 2).

Ulnar nerve motor branch nerve-conduction showed prolonged latency in 40% of the ($n = 10$) and diminished amplitudes in 48% ($n = 12$). Sensory branch nerve-conduction showed prolonged latency in 38% of patients ($n = 9$) and diminished amplitude in 4% ($n = 1$). Table 3 presents the mean latency and amplitude comparisons of the ulnar nerve motor and sensitive branches in leprosy patients and healthy subjects, showing significant difference between the two groups.

Discussion

Leprosy is one of the principal causes of non-traumatic peripheral neuropathy and is clinically manifested as lesions of the skin and peripheral nervous system. Neuropathy may

<table>
<thead>
<tr>
<th>Electrophysiological test</th>
<th>Leprosy patients ($n = 25$)</th>
<th>Healthy subjects ($n = 20$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-reflex latency (ms)</td>
<td>29.2 ± 16.6</td>
<td>29.1 ± 4.3</td>
<td>0.9</td>
</tr>
<tr>
<td>H-reflex amplitude (mV)</td>
<td>0.99 ± 0.9</td>
<td>4.4 ± 2.5</td>
<td>0.01</td>
</tr>
<tr>
<td>M-wave latency (ms)</td>
<td>4.5 ± 1.0</td>
<td>5.0 ± 0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>M-wave amplitude (mV)</td>
<td>2.4 ± 1.5</td>
<td>7.5 ± 2.0</td>
<td>0.01</td>
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</tbody>
</table>
Develop before disease diagnosis or after therapy is begun and can manifest itself as motor, sensory, or autonomic alterations.\textsuperscript{8,9} Electrophysiological studies have been shown to be useful in the diagnosis and prognosis of patients presenting with leprotic neuropathy.\textsuperscript{1,3,7,9,11} Nerve-conduction is the most frequently used electrophysiological study, although it evaluates only segments of the peripheral nervous system (and only large nerve fibres).

On the other hand, other electrophysiological studies such as BR, F-wave, and H-reflex have been used since the 1970s. They are known as late responses because they make interconnections with other neurons and the response register is delayed.\textsuperscript{3,4}

In the present study, motor nerve-conduction was altered in 40% of patients and sensitive nerve-conduction was altered in 30%. Previous studies have mentioned alteration frequencies from 12% to 77%.\textsuperscript{9,10} Other researchers have reported sensorial alteration in 60–100% of patients. These differences from our results are probably a consequence of genetic differences and/or clinical and/or epidemiological characteristics of the patients. Future studies will need to be performed on better characterised patients.

In the present study, the blink reflex showed prolonged latency in right and left R1 in 20% of the patients. However, a recent study found alterations in the right early ipsilateral physical component (R1) in 75% of patients and left early ipsilateral R1 in 59%.\textsuperscript{11} The R1 component is the early BR response and responds ipsilaterally to the stimulus and is abnormal in pathological conditions involving the trigeminal and/or facial nerve at either the central or peripheral levels.\textsuperscript{3,4} On the other hand, 16% of our patients showed abnormalities in the right ipsilateral late bilateral tonic component (R2) and 20% in the left ipsilateral late bilateral tonic component; these results differed from those recently reported in which the frequency of left R2 alterations was 75%.\textsuperscript{11} The right and left contralateral bilateral components were altered in 16% and 12%, respectively.

<table>
<thead>
<tr>
<th>Blink reflex</th>
<th>Leprosy patients (n = 25)</th>
<th>Healthy subjects (n = 20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right R1 (ms)</td>
<td>12.3 ± 0.8</td>
<td>11.0 ± 0.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Left R1 (ms)</td>
<td>12.2 ± 0.9</td>
<td>11.0 ± 0.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Right R2 (ms)</td>
<td>31.7 ± 3.2</td>
<td>31.4 ± 2.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Left R2 (ms)</td>
<td>32.4 ± 3.2</td>
<td>31.4 ± 2.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Right contralateral R2 (ms)</td>
<td>33.2 ± 3.7</td>
<td>30.7 ± 2.3</td>
<td>0.01</td>
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<tr>
<td>Left contralateral R2 (ms)</td>
<td>30.6 ± 10.1</td>
<td>30.8 ± 2.3</td>
<td>0.9</td>
</tr>
</tbody>
</table>

| Table 2. Mean and statistical significance comparison of BR components in leprosy patients and healthy subjects |

<table>
<thead>
<tr>
<th>Ulnar nerve</th>
<th>Leprosy patients (n = 25)</th>
<th>Healthy subjects (n = 20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor latency (ms)</td>
<td>6.3 ± 1.7</td>
<td>3.2 ± 0.3</td>
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<tr>
<td>Motor amplitude (mV)</td>
<td>3.4 ± 2.6</td>
<td>10.8 ± 1.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Motor nerve-conduction (m/s)</td>
<td>54.4 ± 13.7</td>
<td>38.3 ± 8.4</td>
<td>0.01</td>
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<tr>
<td>Sensitive latency (ms)</td>
<td>6.3 ± 2.0</td>
<td>2.9 ± 0.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Sensitive amplitude (mV)</td>
<td>16.4 ± 22.5</td>
<td>24.8 ± 18.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Sensory nerve-conduction (m/s)</td>
<td>50.0 ± 10.0</td>
<td>59.7 ± 4.9</td>
<td>0.01</td>
</tr>
</tbody>
</table>

| Table 3. Mean and statistical significance comparison of action potential components of the sensitive and motor ulnar nerve in leprosy patients and healthy subjects |
altered in 32% of our patients, while the most recent study showed alteration of the left contralateral R2 in 83% of patients.11 The R2 component is the late ipsilateral (direct) or contralateral (indirect) response that is mediated by the ipsilateral nuclei of the trigeminal nerve and the ipso- and contralateral nuclei of the facial nerve. R2 constitutes a multi- or polysynaptic pathway in the bridge and bulb. This component helps to determine whether the lesion affects the afferent pathway (trigeminal nerve) or the efferent pathway (facial nerve) of the reflex. A trigeminal nerve lesion delays or diminishes R2 bilaterally when the affected side is stimulated, while a facial nerve lesion alters R2 only on the affected side.3,4 BR has been found to be altered in pathologies such as cerebral ischemia or brainstem infarcts and it has been demonstrated that R2 alterations can indicate brain damage.12–14 On the other hand, there are several influences that can modulate BR: the noradrenergic system,15 pain fibres,16 and the dopaminergic system.17 Even though BR final cerebral circuits are still unknown, the results of our study lead one to ask the following question: Is it possible that leprosy patients present with central and peripheral nerve lesions? Testing this hypothesis is a subject for future research. As previously mentioned, BR has been studied very little and our review of the literature has produced only one recently published article which evaluates blink reflex in leprosy patients.11 For this reason, the majority of our discussion was contrasted with this study.

The H-reflex, or Hoffmann reflex, or monosynaptic spinal reflex, was originally described by Hoffmann in 1918 and later studied by Magladery and collaborators. H-reflex evaluates conduction velocity of the complete axon and is equivalent in many aspects to the monosynaptic hammer reflex at the Achilles tendon (T-reflex). Therefore, the H-reflex appears when there is integrity of the arch reflex. It is performed by stimulating the nerve at a sub-maximum level to produce sensitive activation. This impulse travels in afferent form and makes monosynaptic connections with the motor neurons, which are then activated and responsible for the said reflex. Presently, there are few studies to determine H-reflex alterations in leprosy patients. Our study found an absence of H-reflex in 20% of patients. This differs from findings reported by Gupta and colleagues,10 who found alterations in 64% of patients. However, they analyzed both lepromatous leprosy and tuberculoid leprosy patients, which could help to explain the difference.

By using three electrophysiological tests (nerve conduction, BR and H-reflex) the present study was able to integrally evaluate leprosy patients. Ulnar nerve nerve-conduction detected peripheral motor and sensitive lesions in the superior limbs, H-reflex evaluated motor and sensitive functioning of the inferior limbs, and the blink reflex indicated the existence of cranial neuropathy.

It is probable that the percentage differences in electrophysiological alterations found between our study and others could be due to differences in the characteristics and backgrounds of patients.

References