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CLINICAL RESEARCH SHORT REPORT

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A-waves are associated with neuropathic pain in leprosy

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Abstract

Introduction/Aims: The A-wave is a late response related either to demyelination or early axonal regeneration. It may be helpful in the evaluation of some peripheral neuropathies. In leprosy, previous studies suggested that A-waves could be a neurophysiological marker of pain in patients during reactions. Herein we have attempted to further assess the profile and clinical correlates of A-waves by exploring a large leprosy cohort.

Methods: Between 2015 and 2018, 63 patients with leprosy (47 men and 16 women) had A-waves in nerve conduction studies and were included in this study. We included patients regardless of whether they were experiencing leprosy reactions or not. We then compared clinical features in nerves with and without A-waves.

Results: The mean age of study participants was 46.5 ± 12.3 years and most had borderline leprosy. From this cohort, we assessed separately 83 motor nerves that demonstrated A-waves (group A^+) and 29 motor nerves that did not demonstrate A-waves (group A^-). Neuropathic pain (NP) was found in 66 of 83 nerves in group A^+, but only 5 of 29 in group A^- (79.5 vs 17.2%, $P < .001$). In contrast, no significant between-group difference emerged regarding presence of reactions, sensory function (based on Semmes-Weinstein evaluations), or muscle strength. A-waves were found in nerves with neuropathic pain experiencing (39 of 66 = 59%) or not experiencing (27 of 66 = 41%) leprosy reactions.

Discussion: These results show that A-waves are associated with neuropathic pain in leprosy patients, regardless of the nerves affected and the immune status (in reaction or not).

KEYWORDS
A-waves, late response, leprosy neuropathy, nerve conduction study, neuropathic pain

INTRODUCTION

A-waves are late responses recorded during motor nerve conduction studies that may be observed in axonal and demyelinating peripheral neuropathies.[1–8] A-waves are considered an early sign of motor fiber damage or dysfunction.[3] The physiological basis of this electrodiagnostic sign is not fully understood, but two phenomena play key roles: ectopic or ephaptic motor action potentials and collateral reinnervation in partially denervated muscles.[9,10]

Although leprosy is endemic in many countries and represents one of the leading causes of neuropathy in Brazil, few studies have assessed A-waves in patients with this disease.[8,11] In one of these studies, Garbino et al identified A-waves as a marker of neuropathic pain in leprosy patients with type 1 and type 2 reactions.[8] It remains to be established whether A-waves are still associated with pain in

Abbreviations: CMAP, compound muscle action potential; NCS, nerve conduction studies; NP, neuropathic pain.

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patients not experiencing reaction episodes. Beyond pain, other clinical correlates of A-waves in leprosy still deserve investigation, such as sensory loss or weakness.

The aim of this study was to determine whether A-waves were associated with neuropathic pain, sensory loss, or weakness in patients with leprosy.

METHODS

Patients

The Lauro de Souza Lima institute is a national leprosy reference center in Brazil. From April 2015 to October 2018, we collected data from all patients with leprosy attending the neurophysiology service at the institute who underwent nerve conduction studies (NCS) and demonstrated A-waves. Patients were included regardless of whether they were experiencing reactions. Among these patients, we identified all nerves that demonstrated A-waves (group A^+). To enable comparisons, we also designated another group (group A^-), which included nerves from the same cohort of patients that did not demonstrate A-waves. The latter were selected as nerves located contralateral to nerves with A-waves for which tracings were available and which were not associated with unrelated disorders such as entrapment neuropathies.

Patients with underlying comorbidities or taking drugs capable of causing peripheral nerve damage were excluded from the analyses.

This study was approved by the institutional ethics committee of Lauro de Souza Lima. All patients provided informed consent.

Clinical evaluation

For every patient, we recorded information on disease duration and clinic-immunological subtype (according to the Ridley & Jopling classification).[12] Most patients had tissue confirmation; however, for the remaining few without pathological analyses, the diagnosis was established according to clinical features and bacilloscopy.

Clinical evaluation was performed on the same day as the electrodiagnostic tests. Sensation and presence of neuropathic pain were then assessed in the territory of each individual nerve. We used Semmes-Weinstein monofilaments to evaluate tactile sensation[13] and, from there, divided nerves into two groups---those with normal/mild abnormalities vs those with moderate/severe abnormalities in the innervation territory. The Brazilian Portuguese validated version of the DN4 questionnaire was employed to diagnose neuropathic pain (NP).[14] Whenever DN4 scores were higher than 3 in the innervation territory of a specific nerve, we considered NP to be present locally.

Motor function was also evaluated following Brazilian guidelines for simplified leprosy evaluation.[15] For median, ulnar, and peroneal nerves, we used the Medical Research Council scale to assess muscle strength in a pair of distal muscles innervated by each nerve (ulnar: first dorsal interosseous and abductor digiti minimi; median: abductor pollicis brevis and opponens pollicis brevis; peroneal: extensor digitorum brevis/longus and extensor hallucis longus).[16] Thus, for each nerve we obtained a motor score ranging from 0 (no movement) to 10 (normal function). Any nerve with a motor score less than 10 was considered abnormal. For the tibial nerve, we assessed the abductor hallucis and employed a dichotomic classification: normal vs abnormal strength.

For each specific nerve, we evaluated whether a leprosy reaction was occurring. Leprosy reactions were defined according to Brazilian guidelines for simplified neurologic leprosy evaluation.[15]

Neurophysiological evaluation

We followed the institutional NCS protocol previously reported in detail.[8,17] Five sensory nerves (radial, ulnar: finger V; median: finger II, sural, and superficial peroneal) on both sides were assessed antidromically with a single distal simulation site. Motor NCS of the median, ulnar, peroneal, and tibial nerves in both sides were obtained for all individuals. A-waves were recorded using the stimulating and recording locations for routine motor nerve conduction and F-waves for each specific nerve. Whenever A-waves were identified in a specific nerve, additional testing was performed to further characterize them. Thirty consecutive stimuli were administered, beginning with intensities 20% higher than the supramaximal threshold and then decreasing until the disappearance of A-waves and compound muscle action potentials (CMAPs). We used the following criteria to define A-waves: (1) consistent latency, morphology, and amplitudes; (2) latency variation shorter than 0.5 millisecond; and (3) minimal amplitude of 0.05 millivolt,[3] with persistence >7 of 30. The acquisition settings for A-wave studies were: vertical gain of 5 millivolts for CMAP and 500 microvolts for A-waves; sweep speed of 10 milliseconds and 5 milliseconds for lower and upper limb nerves, respectively; and filter settings of 5 kHz and 20 Hz. A-waves were classified into two subtypes.[3,4] The first is more appropriately named an axonal reflex. It is obtained with submaximal stimulation of motor nerves and disappears with supramaximal stimuli. The second subtype remains despite stimulation, whether sub- or supramaximal.

Statistical analyses

We used descriptive statistics to present clinical, demographic, and neurophysiological data. We then used the Fisher exact test to compare the pattern of nerve conduction abnormalities, sensory deficits, motor strength, and the frequency of neuropathic pain in groups A^+ and A^-. $P < .05$ was considered significant. All analyses were performed with SYSTAT version 13.0 (Systat Software, Inc, San Jose, CA).

1 | RESULTS

Sixty-three patients (47 men and 16 women) had A-waves on NCS and were included in this study. Mean age was 46.5 ± 12.3 years.

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TABLE 1 Clinical and electrophysiological features in nerves with and without A-waves of patients with leprosy

	Nerves with A-waves (n = 83)	Nerves without A-waves (n = 29)	*P* value
Normal conduction (%)	3 (3.6%)	10 (34.5%)	<.001
Leprosy reaction (%)	41 (49.4%)	12 (41.3%)	.520
Neuropathic pain (%)	66 (79.5%)	5 (17.2%)	<.001
Tactile sensory loss (%)	59 (71.1%)	17 (58.6%)	.251
Normal muscle strength (%)	43 (51.8%)	14 (48.2%)	.830

Most subjects had borderline leprosy (borderline tuberculoid: n = 11; borderline borderline: n = 24; borderline lepromatous: n = 13). Four patients had tuberculoid leprosy, seven had lepromatous leprosy, and four had no pathological studies. We identified 83 motor nerves in Group A^+ (8 median, 33 ulnar, 9 peroneal, 33 tibial) and 29 in Group A^- (2 median, 15 ulnar, 1 peroneal, 11 tibial). Four nerves demonstrated the first subtype of A-waves (axonal reflex) and 79 demonstrated the second subtype.

There were fewer patients in Group A^+ with entirely normal NCS parameters (Table 1). The percentages of nerves with predominantly demyelinating vs predominantly axonal findings on NCS did not differ between the two groups ($P = .195$). Most nerves with A-waves had a pure or predominantly demyelinating profile (64%).

NP was significantly more frequent in group A^+ relative to group A^- (Table 1). Within group A^+, frequency of NP was similar in nerves with single and nerves with multiple A waves ($P = 0.93$). There was no significant difference in the presence of leprosy reactions, severity of sensory deficit (based on Semmes-Weinstein testing), or muscle strength (proportion of nerves with normal motor function) between groups A^+ and A^- (Table 1). A-waves were found in nerves with NP experiencing (39 of 66 = 59%) and not experiencing (27 of 66 = 41%) leprosy reactions.

2 | DISCUSSION

In this large cohort of patients with leprosy, we have shown that A-waves are associated with NP, but not with tactile sensory or motor deficits. This association was identified in a wide range of affected nerves in the arms and legs experiencing or not experiencing leprosy reactions.

Considering these findings, one can speculate that A-waves and NP may share a common mechanism in leprosy. The subtype of A-waves called axon reflex is attributed to collateral sprouting in the proximal portions of the nerve. This was very rarely found in our patients. The other subtype of A-waves was the most frequent subtype noted in our cohort. Focal demyelination seems to be an important factor in giving rise to this subtype.[6] Thus, these data suggest that demyelination plays a key role in the generation of A-waves in leprosy. This is in line with the results of NCS in group A^+ (predominantly demyelinating). In this scenario, one may speculate whether demyelination combined with ephaptic conduction could also underlie NP in leprosy. The presence of A-waves may thus characterize a specific mechanism triggering NP, which may be relevant for proper pharmacological choice. Further studies—including correlation with neuropathological data—are needed to confirm this hypothesis.

This study has limitations. No clinical scale to assess NP intensity was used. In addition, we did not perform formal small-fiber assessment. It would be useful to explore correlations between these parameters, neuropathic pain, and A-waves. Furthermore, longitudinal follow-up would be valuable to evaluate how this A-wave vs NP correlation would behave in patients treated with sodium-channel blockers for pain relief.

Our data show that A-waves are associated with NP in leprosy patients, regardless of the nerves affected and of the immune status (in reaction or not). We encourage clinical neurophysiologists caring for leprosy patients, particularly those with pain, to incorporate a comprehensive protocol to assess late responses. Specifically, it would be useful to evaluate the behavior of A-waves in patients under specific treatment for neuropathic pain.

AUTHOR CONTRIBUTIONS

José Antonio Garbino: Conceptualization; data curation; formal analysis; investigation; project administration; writing – review and editing. **Daniel R Kirchner:** Conceptualization; data curation; investigation; writing – review and editing. **Marcondes Cavalcante França Jr:** Conceptualization; formal analysis; funding acquisition; methodology; writing – original draft.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Anonymized data are available from the corresponding author upon reasonable request and after local IRB approval (for data sharing).

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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