

Clinical evolution of neural function in a series of leprosy neuropathy cases after ulnar neurolysis^{☆,☆☆,*}



Dear Editor,

Leprosy is a chronic infectious disease with a disabling potential due to the affinity of the agent, *Mycobacterium leprae*, for peripheral nerves and skin. Of the 208,619 new cases detected worldwide in 2018, a total of 11,323 cases already had apparent deformities, of which 2,109 (18.6%) were from Brazil, a figure that was second only to India, with 3,666 new cases with deformities.¹

Neuropathy in leprosy can occur insidiously, more commonly as multiple mononeuropathy, with the simultaneous involvement of two or more peripheral nerves in different regions of the body, with the ulnar and posterior tibial nerves being the most frequently affected. Neural damage can also often occur during acute episodes of immunological reactions against bacillary antigens that may occur during the course of the disease or even after polychemotherapeutic treatment, in the form of neuritis with edema, vascular obstruction, ischemia, and strangulation in the passage through the osteofibrous channels of the limbs, leading to pain and deficit of function, the main cause of physical disabilities and stigma of the disease.^{2,3}

The basis for neuritis treatment is prednisone, used to control the inflammatory process and pain, preventing permanent neural damage. Neurolysis is surgery for nerve decompression through an incision in the epineurium and opening of the osteofibrous canal to release the nerve, at the level of the elbow and/or wrist.³ It is performed mainly in cases of nerve abscess, neuritis not responsive to clinical treatment for four weeks, recurrent or subentrant episodes of neuritis, chronic neuritis with deficit and pain, and neuritis in patients with comorbidities that contraindicate the use of corticosteroids aiming to decrease the dose and in cases of corticosteroid contraindications.⁴

With the purpose of describing the clinical evolution of neural function and neuritis recurrences of leprosy patients with neuritis submitted to neurolysis, we present a series of 22 cases of ulnar nerve surgery performed in the years 2015 and 2016, at Fundação de Dermatologia Tropical e Venereologia Alfredo da Matta, located in the state of Amazonas, in the city of Manaus, Brazil.

Immediately before the neurolysis and after it (30, 90 days and according to the follow-up), the Simplified Neurological Assessment was carried out according to the protocol of the Ministry of Health of Brazil.⁴ Sensibility evaluation was performed with an esthesiometer or Semmes-Weinstein

monofilament, which consists in a set of six nylon threads of different colors and thicknesses that, pressed against the skin, correspond to different weights (from 0.05 g to 300 g). The 0.05 g (green) and 0.2 g (blue) monofilaments were considered as normal sensibility and above that, as decreased sensibility.⁵ For the assessment of muscle strength, the abductor muscle of the fifth finger was assessed and the Medical Research Council scale was used, which ranks strength from zero (no muscle movement) to five (complete movement against gravity with maximum resistance).⁴ Levels four (full movement against gravity with partial resistance) and five were considered normal.⁵

The time between the first episode of neuritis and the performance of neurolysis was, on average, 25.3 months (SD = 63.3; Min. = 1; Max. = 303), with the procedure being performed after up to six months in 11 (50.0%) patients, which is related to the best results by other authors.⁵ For comparison purposes, the last neurological evaluation was considered in the present study, which ranged from three to 168 months, with 12 (54.5%) patients having more than one year of follow-up.

Of 12 cases that already had altered sensibility before surgery, seven (58.3%) showed improvement and, of the six that had altered muscle strength, five (83.3%) maintained the same level, and only one (16.7%) showed worsening. Fifteen (68.2%) patients did not have any neuritis in the operated nerve; however, three of these patients still had to use prednisone, because they had a leprosy reaction and/or neuritis in other nerves. Two patients had only a single episode of neuritis, which occurred three and four months after surgery. Another five patients (18.2%) had subentrant episodes of neuritis in the operated nerve, for an average of 52.6 months (SD = 63; Min. = 17; Max. = 172) after surgery, without necessarily developing loss of function (Table 1).

This series of cases emphasizes the clinical importance of the results in a routine situation, where the greatest contribution of neurolysis associated with the clinical treatment of leprosy neuritis was the non-recurrence or non-chronicity of the condition. Neurolysis also prevents prolonged corticosteroid therapy and its consequences, in addition to the possible evolution into physical disabilities. There was sensory function gain in most of the assessed cases. However, it is necessary to carry out studies with appropriate methodology to evaluate the effectiveness of neurolysis or its benefits in comparison to clinical treatment alone, even considering the studies that have been published for decades.⁵

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Authors' contributions

Juliana Barroso-Freitas: Design and planning of the study; drafting and editing of the manuscript; collection, analysis, and interpretation of data; critical review of the literature.

Pedro Arthur da Rocha Ribas: Critical review of the literature; collection, analysis, and interpretation of data.

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Table 1 Characteristics of leprosy cases submitted to ulnar neurolysis.

Numerical order	Sex	Age at diagnosis (years)	Clinical form	Time in months between		Sensibility ^a		Muscle strength ^b		Time with recurrences (months)
				Neuritis and neurolysis	Neurolysis and evaluation	Initial	Final	Initial	Final	
1	M	31	BL	01	03	0.05 g	0.05 g	4	5	–
2	M	22	BL	02	20	0	10 g	4	5	21
3	M	34	LL	02	05	0.05 g	0.2 g	5	5	–
4	M	8	TT	02	44	300 g	10 g	0	0	–
5	M	20	BT	02	08	300 g	0	0	0	–
6	M	26	BL	02	18	0.05 g	300 g	5	4	03 ^c
7	M	13	BT	03	34	300 g	300 g	4	5	–
8	M	35	LL	04	14	0.2 g	0.2 g	5	5	–
9	M	39	LL	04	30	0	4g	3	3	–
10	M	49	LL	05	24	0.2 g	0.2 g	5	5	–
11	M	51	BL	6	03	300 g	0	2	2	–
12	M	24	LL	09	26	300 g	0.2 g	5	5	–
13	M	24	LL	10	02	0.2 g	0.2 g	5	5	–
14	M	11	BL	12	21	0.05 g	0.05 g	5	5	21
15	M	36	BL	16	17	300 g	10 g	3	3	17
16	M	15	LL	17	04	0.05 g	0.05 g	5	5	–
17	F	57	BT	20	08	300 g	0.2 g	4	4	–
18	M	18	BL	20	168	300 g	0	3	1	172
19	M	17	LL	31	10	0.05 g	0.2 g	5	5	32
20	F	12	BT	36	04	300 g	4g	4	5	04 ^c
21	M	19	BL	49	135	0.05 g	0.05 g	5	5	–
22 ^d	M	26	LL	303	03	10 g	10 g	2	2	–

^a Monofilament: 0.05 g (green) and 0.2 g (blue) = normal sensibility; 2.0 g (violet) = decrease in protective sensibility, with decreased discrimination of shape and temperature; 4.0 g (dark red) = decreased protective sensibility; 10.0 g (orange) = can feel deep pressure and pain; 300.0 g (magenta red) = loss of deep pressure feeling, can feel pain; and 0 = does not feel any monofilament or absence of sensibility to pressure or pain.

^b Medical Research Council scale.

^c Month of occurrence of the single episode of neuritis.

^d This patient had a recurrence.

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Conflicts of interest

None declared.

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Comparison of cardiotoxicity between N-methyl-glucamine and miltefosine in the treatment of American cutaneous leishmaniasis^{☆,☆☆}



Dear Editor,

N-Methyl glucamine (NMG) is the first therapeutic option for the treatment of American cutaneous leishmaniasis (ACL), but it has many adverse effects, with one of the most serious and feared complications being sudden death, caused by cardiac electrophysiological alterations in the electrocardiogram (ECG) associated to the QT-interval prolongation corrected by the Bazett's formula (QTc).¹⁻³

The toxicity of antimonials, the occurrence of disease relapses and resistance to these drugs have stimulated the search for other drugs or more effective therapeutic regimens for the treatment of ACL.⁴ This has resulted in the development of miltefosine (hexadecylphosphocholine), which has shown to be effective against several species of *Leishmania* and other protozoa.^{5,6} The drug acts by activating the programmed cell death mechanism, inhibiting the synthesis of phosphatidylcholine, important for cell membrane synthesis and integrity.⁵

This drug has a teratogenic potential, which requires birth control during treatment and up to two months after its completion.⁴

A retrospective cohort study was performed using data from ECG records of patients treated for ACL (20 mg SbV/kg/day for 20 days for cutaneous leishmaniasis and 30 days for mucosal leishmaniasis or miltefosine (1.3 to 2 mg/kg/day - two capsules a day - for 28 days), followed by a weekly ECG in the Dermatology Service between 2008 and 2013.

The inclusion criteria were: patients treated for ACL, aged between 18 and 85 years and the exclusion criteria were: pregnant women, patients with chronic kidney or liver disease, severe heart disease or other diseases, or receiving drugs that could interfere with the ECG. The patients were not taking any other medications at the time and had not been treated for ACL in the past 6 months.

The included patients were divided into two groups: 1 - treated with NMG; 2 - treated with Miltefosine (M).

The relative risk and the percentage of alterations in the ECG during treatment (heart rhythm and rate, P-wave, QRS complex, RR interval, presence or absence of arrhythmias, and QTc interval) were compared in the groups. For the heart rate, the range between 60 bpm and 100 bpm was considered normal, and the limit of 440 milliseconds for QTc for both sexes (Table 1).⁷

The variables were expressed as frequency and the comparison between the groups was done using the Chi-squared test, or Fisher's exact test when more than 20% of the cells showed an expected frequency < 5. A p-value < 0.05 was considered significant. A multivariate model was employed and the relative risk with a 95% confidence interval was calculated to analyze the intensity of the association between each independent variable and the proportion of adverse effects.

The medical records of 111 patients were analyzed and the epidemiological and electrocardiographic data of 53 individuals were recovered, of which 38 were treated with NMG and 15 with M.

The mean age in the NMG group was 48.4 ± 16.29 years, while in the M group it was 58.4 ± 9.16 years, showing a difference between the groups ($p = 0.033$). In the NMG group, 23 individuals (60.5%) and in the M group, 7 individuals (46.7%) were males ($p = 0.37$).

On the seventh day of treatment (D7), 11.4% of the members of the NMG group and 33.3% of the M group had QT-interval prolongation. On the fourteenth day (D14), 26.6% of the NMG group had QT-interval prolongation, but none in the M group had it. The trend continued on the twenty-first day (D21), as 35.3% of the NMG group had an altered QTc, while there were no changes in group M. As for the heart rate, 28.9% of patients in the NMG group and 26.6% of the M group had bradycardia during treatment.

Before treatment, 16 (21%) of the patients in the NMG group and 37.5% of the M group had bradycardia (RR = 0.59; 95% CI 0.17 to 1.99); ($p = 0.44$). The QTc was altered in

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