New sonographic measures of peripheral nerves: a tool for the diagnosis of peripheral nerve involvement in leprosy

Marco Andrey Cipriani Frade/+, Marcello Henrique Nogueira-Barbosa, Helena Barbosa Lugão, Renata Bazan Furini, Wilson Marques Júnior, Norma Tiraboschi Foss

Divisão de Dermatologia, Divisão de Radiologia, Departamento de Neurologia, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brasil

To evaluate ultrasonographic (US) cross-sectional areas (CSAs) of peripheral nerves, indexes of the differences between CSAs at the same point (ΔCSAs) and between tunnel (T) and pre-tunnel (PT) ulnar CSAs (ΔTPTs) in leprosy patients (LPs) and healthy volunteers (HVs). Seventy-seven LPs and 49 HVs underwent bilateral US at PT and T ulnar points, as well as along the median (M) and common fibular (CF) nerves, to calculate the CSAs, ΔCSAs and ΔTPTs. The CSA values in HVs were lower than those in LPs ($p < 0.0001$) at the PT (5.67/9.78 mm²) and T (6.50/10.94 mm²) points, as well as at the M (5.85/8.48 mm²) and CF (8.17/14.14 mm²) nerves. The optimum CSA- receiver operating characteristic (ROC) points and sensitivities/specificities were, respectively, 6.85 mm² and 68-85% for the PT point, 7.35 mm² and 71-78% for the T point, 6.75 mm² and 62-75% for the M nerve and 9.55 mm² and 81-72% for the CF nerve. The ΔCSAs of the LPs were greater than those of the HVs at the PT point (4.02/0.85; $p = 0.007$), T point (3.71/0.98; $p = 0.0005$) and CF nerve (2.93/1.14; $p = 0.015$), with no difference found for the M nerve (1.41/0.95; $p = 0.17$). The optimum ΔCSA-ROC points, sensitivities, specificities and p-values were, respectively, 1.35, 49%, 80% and 0.003 at the PT point, 1.55, 55-85% and 0.0006 at the T point, 0.70, 58-50% and 0.73 for the M nerve and 1.25, 54-67% and 0.022 for the CF nerve. The ΔTPT in the LPs was greater than that in the HVs (4.43/1.44; $p < 0.0001$). The optimum ΔTPT-ROC point was 2.65 (90% sensitivity/41% specificity, $p < 0.0001$). The ROC analysis of CSAs showed the highest specificity and sensitivity at the PT point and CF nerve, respectively. The PT and T ΔCSAs had high specificities (> 80%) and ΔTPT had the highest specificity (> 90%). New sonographic peripheral nerve measurements (ΔCSAs and ΔTPT) provide an important methodological improvement in the detection of leprosy neuropathy.

Key words: leprosy - peripheral nerves - neuropathy - ultrasonography

Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae* that predominantly affects the skin and peripheral nerves (Britton & Lockwood 2004, Lasry-Levy et al. 2011). Leprosy is the leading infectious cause of disability (Rodrigues & Lockwood 2011). Although the prevalence of leprosy has declined substantially over the past 50 years (Merle et al. 2010), transmission of the disease continues and it remains a relevant public health problem worldwide (WHO 2008).

Many new leprosy cases are detected worldwide each year. A total of 228,474 cases of leprosy were reported in 2010, 95% of which were found in 17 countries that reported more than 1,000 new cases each that year, including India, Brazil and Indonesia (WHO 2011). In contrast to the decreasing overall leprosy prevalence rates in Brazil, the new case detection rates remain high (34,984 new cases detected in 2010) (Rodrigues & Lockwood 2011, WHO 2011). These data indicate the continuing transmission of leprosy.

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+ Corresponding author: mandrey@fmrp.usp.br
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Although making a clinical diagnosis of leprosy is frequently straightforward, there is not a good point-of-care test to confirm the diagnosis. A delay in diagnosis may result in important negative outcomes, such as an increased risk of nerve damage (Rodrigues & Lockwood 2011). Various factors contribute to a delay in diagnosis, but stigma is an important factor in many cultures (Senior 2009).

The mechanisms involved in nerve damage are not clearly understood. There is no specific test to measure the extent of nerve damage or to show evidence of recovery during the treatment of leprosy with multiple drugs (Rodrigues & Lockwood 2011).

Although nerve damage in leprosy can be consistently demonstrated by electromyography, which may reveal a pattern that is highly suggestive of leprosy, a definite diagnosis is dependent on nerve biopsy findings. Recently, sonography has been described as a useful tool in the diagnosis of leprosy neuropathy. A highly correlated finding is a fusiform thickening of the peripheral nerves that are generally compromised in leprosy patients (LPs), including the ulnar, median (M) and posterior tibial nerves, which can be measured by the corresponding cross-sectional areas (CSAs) of the affected regions (Martinoli et al. 2000, Elias Jr et al. 2009).

In this study, we evaluated the distribution pattern of peripheral nerve damage in LPs by sonography, examining the CSAs of the ulnar [cubital tunnel (T) and pre-tunnel (PT)], M and common fibular (CF) nerves and comparing them with those of healthy volunteers (HVs).

PATIENTS, MATERIALS AND METHODS

Patients - A total of 126 patients and HVs were included and assigned to one of two groups: LPs (n = 77) and HVs (n = 49). All LPs were selected from the Leprosy Outpatient Clinic of the Sanitary Dermatological National Reference Centre, Clinical Hospital, Medical School of Ribeirão Preto, University of São Paulo (HCFMRP-USP). The diagnosis of leprosy was established based on clinical signs and symptoms, skin smears and skin biopsy. The patients were classified as multibacillary or paucibacillary according to the Ridley and Jopling (1966) criteria and the operational classification (WHO 1998). Sonography was performed before the start of multidrug therapy.

The control group was comprised of randomly chosen HVs. They were selected after ruling out diabetes, hypothyroidism, human immunodeficiency virus infection, trauma-related peripheral nerve disease and alcoholism.

Sonography and image analysis - All sonographic examinations were performed by the same specialised radiologist (MHN-B) with a 12-MHz linear transducer, model HDI-11 (Philips Medical Systems, Bothell, Washington, USA). All individuals were examined in a seated position with a 45º flexed elbow as described by Gelberman et al. (1998) and Marques et al. (2003). The ulnar nerves were scanned from the axilla to the hand along the transverse and longitudinal axes. The greatest CSAs of the ulnar nerve were measured above the medial epicondyle between the triceps brachii and biceps brachii muscles (PT area) and at the cubital T (T area). The M nerve was analysed in the forearm and wrist and the CSAs were measured approximately 5 cm proximal to the flexor retinaculum. The CF nerve was analysed at the fibula head with the patient seated and the leg flexed at 90º. The sonographic evaluation was performed during a single examination period and included the bilateral nerves of the upper and lower extremities.

The CSA of the nerve was obtained by freehand delimitation at the inner borders of the echogenic rim of the nerve. The measurements were performed using the electronic cursor at the time of examination and the CSAs were assessed at the level of maximum nerve enlargement.

Nerve assessment - A total of 924 nerve points were examined, including 234 PT and 240 T points along the ulnar nerve, 224 points along the M nerve and 226 points along the CF nerve. The measurements of the right and left standard CSAs of the previously selected PT and T points of the ulnar nerve, the distal third of the forearms for the M nerve and the lateral fibular heads for the CF nerve were performed in the same manner for each volunteer and each LP.

The CSA measurements were used to calculate the following indexes: (i) differential CSA index (ΔCSAs), calculated by the difference between the largest and smallest CSA measurements for each nerve point independent of the side and (ii) differential T-PT index (ΔTPT) of the ulnar nerves, calculated on the same side as the difference between the largest and smallest CSA measurements of PT and T points along the ulnar nerves.

Statistical analysis - The GraphPad Prism software, version 5.01, San Diego, CA, USA, was used to perform paired t tests to analyse the differences in nerve measurements between sides and unpaired t tests were performed to compare the results between groups. The sensitivities and specificities of each parameter were calculated and receiver operating characteristic (ROC) curve analyses were conducted. The best point of the ROC curve was considered as the greatest value obtained of the product between sensitivity and specificity (Hanley & McNeil 1982).

Ethics - The study protocol was approved by the Ethical Committee of the HCFMRP-USP (3114/2010) and all subjects provided written informed consent. The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

RESULTS

All 126 subjects underwent sonographic evaluation. The clinical data and leprosy classifications, according to the Ridley and Jopling (1966) criteria and the operational classification (WHO 1998), and slit skin smear results are shown in Table I.

The number of nerves, means and standard deviations of the CSAs, ΔCSAs and ΔTPTs in the HVs and LPs, as well as the respective p-values, are shown in Table II. The means of the ulnar, M and CF CSA measurements in the HVs were lower than those in the LPs ($p < 0.0001$).

The distributions of the measurements of each studied nerve are shown in Figs 1, 2. Among the HVs, the CSAs of the right M and CF nerves were greater than those of the left-sided nerves ($p < 0.005$ and $p < 0.0016$, respectively) (Fig. 2A, B). No other significant difference was found between the two sides.

TABLE I

Clinical data of the leprosy patients (LPs) and healthy volunteers (HVs)

Variables	LPs n = 77 n (%)	HVs n = 49 n (%)
Gender		
Male	48 (62.3)	19 (38.8)
Female	27 (37.7)	29 (61.2)
Age		
Mean (range)	46.1 (17-81)	33.1 (12-67)
Clinical classification		
Indeterminate	3 (3.9)	-
Tuberculoid	8 (10.4)	-
Borderline-tuberculoid	31 (40.3)	-
Borderline-borderline	19 (24.7)	-
Borderline-lepromatous	9 (11.7)	-
Lepromatous	7 (9)	-
Operational classification		
Paucibacillary	11 (14.3)	-
Multibacillary	66 (85.7)	-

The LPs had greater ΔCSAs than the HVs at the PT and T points of the ulnar nerve and for the CF nerve (Fig. 3A, Table II). No significant difference was detected for the M nerve.

The mean ± standard deviation of the T CSAs (6.7 ± 2.2 mm^2) was greater than that of the PT CSAs in the HVs (5.88 ± 1.8 mm^2; $p < 0.0001$) and no significant difference was found in LPs between the T-CSAs (10.94 ± 6.35 mm^2) and PT-CSAs (9.78 ± 6.99 mm^2). The ΔTPT values were greater in the LPs than in the HVs. There was no difference in the ΔTPT between the right and left nerves in both groups, as shown in Fig. 3B.

The optimum ROC points of the CSAs, ΔCSAs and ΔTPTs in the HVs and LPs, the respective sensitivities and specificities and the area under the ROC curves (areas, standard errors and p-values) are shown in Table III.

The greatest CSA sensitivity was found for the CF nerve (81%) and the greatest specificity was found for the PT area of the ulnar nerve (85%), with areas under the ROC curve of approximately 0.80 ($p < 0.0001$). Regarding the optimum points of the ΔCSAs, the ulnar nerve measurements had the best specificity for the PT (80%) and T (85%) points, with areas under the ROC curve greater than 0.66 and p-values lower than 0.003. The ΔTPT had the lowest sensitivity and the highest specificity (90%) among all the variables.

DISCUSSION

Leprosy neuropathy is responsible for many of the feared consequences of an *M. leprae* infection, which may progress to severe impairment followed by disabilities and deformities if diagnosis and treatment are delayed. Considering the polymorphic aspect of leprosy neuropathy, diagnosis may be difficult even in countries with high incidence rates. Clinical findings, electrophysiological tests and nerve sonographic characteristics of leprosy neuropathy have been described previously (Grimaud et al. 2000, Martinoli et al. 2000, Marques et al. 2003, Arruda et al. 2004, Elias Jr et al. 2009, Bathala et al. 2012).

Ultrasonography (US) is non-invasive, useful for studying changes at nerve sites and more cost-effective than other imaging procedures, such as magnetic resonance imaging (MRI). Current technological developments leading to improved image quality, reduced US device sizes and reductions in price will make it possible for US to become a tool that can be used in countries in which leprosy is endemic (Jain et al. 2009).

The higher mean CSA values in the T region in LPs compared with HVs (Fig. 3B) suggest that sonographic evaluation of the T region can be a useful tool for detecting neural involvement in leprosy. According to Elias Jr et al. (2009), the best sonographic discriminator for the ulnar nerve in LPs is the CSA of the ulnar nerve measured in the elbow region and not only at the cubital T. Consistent with this suggestion, the T-CSAs in this study had significantly higher values than the PT-CSAs ($p < 0.0001$) in HVs, while these measurements were similar in LPs.

Considering the fact that a given nerve on one side of the body is thicker than the same nerve on the opposite side of the body due to the dominance of one side, we proposed to assess the ΔCSA. The ΔCSA values were significantly lower in HVs compared with LPs. This study sought to evaluate peripheral nerves in the arms and lower limbs to minimise the influence of the dominance of one side or occupational activities in nerve thickness, which is predominantly detectable in the upper extremities. The results confirmed higher ΔCSAs in LPs even in the lower limbs (CF nerves).

Concerning the use of such parameters in other diseases, Klauser et al. (2011) described the use of the ΔCSA parameter as improving the diagnostic accuracy of US for the presence of carpal T syndrome in patients

TABLE II

Number of nerves, means and standard deviation (SD) of cross-sectional areas (CSAs), differential CSA index (ΔCSAs) and differential tunnel (T)-pre-tunnel (PT) index (ΔTPT) in healthy volunteers (HVs) and leprosy patients (LPs) with respective p values

		Groups				
		HVs		LPs		
Nerves	Variable	n	Mean ± SD	n	Mean ± SD	p
Ulnar (PT)	CSAs	92	5.9 ± 1.8	142	9.8 ± 7.0	< 0.0001
Ulnar (T)	(mm^2)	92	6.7 ± 2.2	148	10.9 ± 6.4	< 0.0001
Median		96	5.9 ± 1.5	128	8.5 ± 4.4	< 0.0001
Common fibular		96	8.2 ± 4.4	130	14.1 ± 7.3	<0.0001
Ulnar (PT)	ΔCSAs	46	0.9 ± 0.7	71	4.0 ± 7.8	0.0067
Ulnar (T)	(mm^2)	46	1.0 ± 0.7	74	3.7 ± 5.1	0.0005
Median		48	1.0 ± 0.8	64	1.4 ± 2.2	0.17
Common fibular		48	1.1 ± 1.1	65	2.9 ± 5.0	0.0154
Ulnar (T and PT)	ΔTPT (mm^2)	98	1.4 ± 1.6	146	4.4 ± 6.7	< 0.0001

with bifid M nerves and they demonstrated that a ΔCSA threshold of 2 mm^2 yielded the greatest sensitivity (99%) and specificity (100%) for the diagnosis of carpal T syndrome (Klauser et al. 2009).

In a study by Elias Jr et al. (2009), the sonographic examination of three patients showed ulnar nerve thickening without electrophysiological nerve abnormalities, indicating that an affected peripheral nerve may function normally. If a sonographic finding is highly suggestive of leprosy neuropathy, it may play an important role in detecting neuropathy. There is no report regarding the effectiveness of the ΔCSA and the ΔTPT in leprosy diagnosis.

Leite et al. (2010) showed the extent of nerve damage in LPs using the Semmes Weinstein monofilament test to detect the frequency of nerve impairment of the ulnar, CF and M nerves. In accordance with the Leite et al. (2010) study, our data showed that, compared with other nerves, the ulnar nerve was the most frequently involved.

Based on the optimum point of the ROC curve, the PT ulnar CSA had the highest specificity, while the highest sensitivity was found for the CF nerve CSA. Although the difference between the sides of the nerve CSAs had good specificities for leprosy diagnosis in terms of the PT and T index (ΔCSAs), the most specific index for diagnosing leprosy was the ΔTPT index.

US and MRI are effective in diagnosing nerve damage in leprosy, primarily during leprosy reactions (Martinoli et al. 2000, Jain et al. 2009). In our study, US was performed at the time of leprosy diagnosis and 17 patients (22%) presented with neuritis and/or clinical signs of reversal reactions, which were not always associated with US abnormalities.

Martinoli et al. (2000) examined the injured M, ulnar and posterior tibial nerves in 23 LPs (58 nerves) with sonography and MRI. Based on the sonographic or MRI appearance, a nerve could be classified as normal (group I), enlarged with fascicular abnormalities (group II) or having no fascicular structure (group III). The nerves in group II were thicker than those in group III. The nerve swelling found in group II was gradual and fusiform and typically occurred proximal to osteofibrous Ts. The primary finding was that nerves that showed a reversal reaction toward a more intense immune response had a hypervascular pattern, as demonstrated by Doppler studies (or by a marked T2 intensity and increased gadolinium enhancement on MRI).

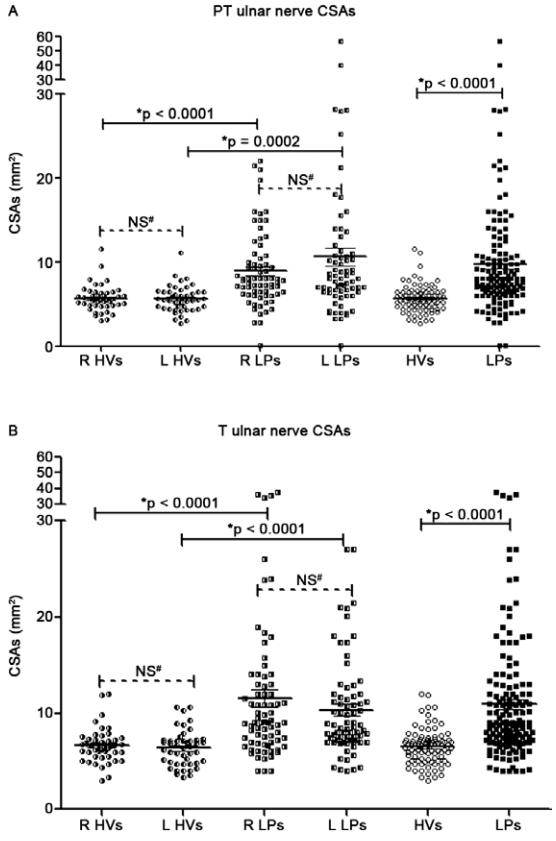

Fig. 1: scattering distribution of cross-sectional areas (CSAs) of right (R) and left (L) ulnar nerves of healthy volunteers (HVs) and leprosy patients (LPs) groups on pre-tunnel (PT) (A) point and tunnel (T) point (B). NS: no significance; p: statistical difference; #: paired t test; *: unpaired t test.

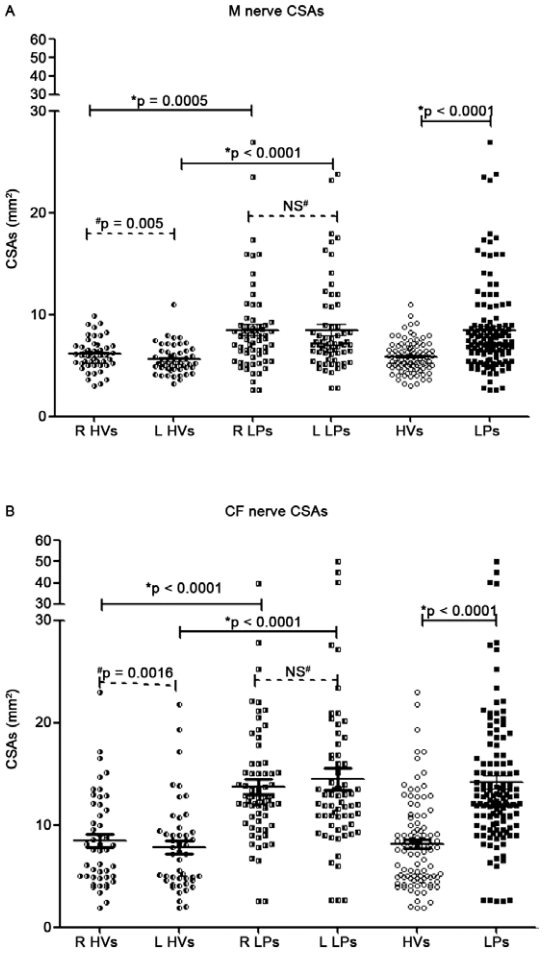

Fig. 2: scattering distribution of cross-sectional areas (CSAs) of right (R) and left (L) nerves of healthy volunteers (HVs) and leprosy patients (LPs) groups: A: median (M) nerve; B: common fibular (CF) nerve; NS: no significance; p: statistical difference; #: paired t test; *: unpaired t test.

TABLE III

Receiver operating characteristic (ROC) optimum point of cross-sectional areas (CSAs), differential CSA index (ΔCSAs) and differential tunnel (T)-pre-tunnel (PT) index (ΔTPT) in healthy volunteers (HVs) and leprosy patients (LPs), respective sensitivity and specificity and analysis of area under the ROC curve

Nerves	Variable	HVs (n)	LPs (n)	ROC optimum point (mm^2)	Sensitivity (%)	Specificity (%)	Area under the ROC curve		
							Area	SE	p
Ulnar (PT)	CSAs	92	142	6.85	68	85	0.79	0.03	< 0.0001
Ulnar (T)		92	148	7.35	71	78	0.80	0.03	< 0.0001
Median		96	128	6.75	62	75	0.73	0.03	< 0.0001
Common fibular		96	130	9.55	81	72	0.80	0.03	<0.0001
Ulnar (PT)	ΔCSAs	46	71	1.35	49	80	0.66	0.05	0.003
Ulnar (T)		46	74	1.55	55	85	0.69	0.05	0.0006
Median		48	64	0.70	58	50	0.52	0.06	0.73
Common fibular		48	65	1.25	54	67	0.63	0.05	0.022
Ulnar (T and PT)	ΔTPT	98	146	2.65	41	90	0.66	0.04	< 0.0001

SE: standard error.

Jain et al. (2009), using high-resolution sonography, clearly showed that the kappa value between clinical palpation and the assessment of nerve size by sonography is low. They concluded that clinical examination of enlarged nerves is subjective and inaccurate, whereas sonography provides an objective measure of the nerve dimensions and reveals structural changes over a longer length of the nerve. Our patients and HVs were systematically examined using a linear array US transducer, with the predominant aim of calculating the CSAs of the nerves.

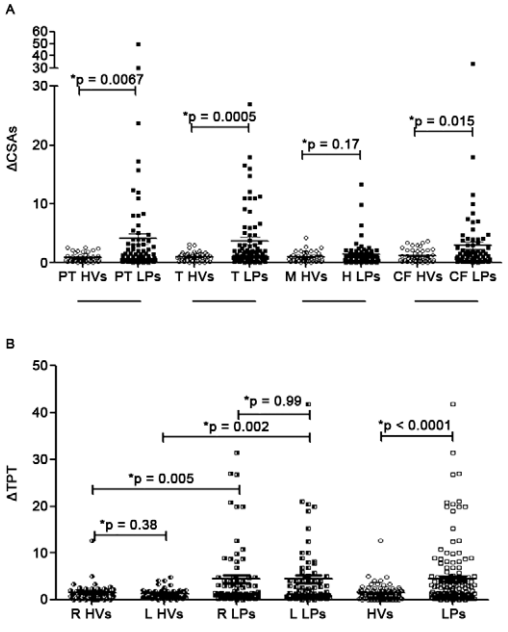

Fig. 3: scattering distribution of cross-sectional areas index (ΔCSAs) of neural points (A) and tunnel (T)-pre-tunnel (PT) index (ΔTPT) (B) in healthy volunteers (HVs) and leprosy patients (LPs) groups. CF: common fibular nerve; L: left nerve; M: median nerve; p: statistical difference; R: right nerve; #: paired t test; *: unpaired t test.

The results showed that the use of sonography, a non-invasive method, to calculate the CSAs of peripheral nerves is an important tool with which to detect large areas of nerve damage in LPs. The ROC analysis of CSAs showed the best specificity and sensitivity at the PT point of the ulnar and CF nerves, respectively. Among the new measurements of peripheral nerves, the ΔCSAs of the PT and T points of the ulnar nerve showed high specificity (> 80%) and the ΔTPTs showed the highest specificity (> 90%).

Sonographic evaluation yields sonographic measurements of peripheral nerves (the CSAs of the PT and T ulnar points as well as of the M and CF nerves) and can be used to obtain indexes of the differences between ΔCSAs and between ΔTPT. These new sonographic measures (ΔCSA and ΔTPT) provide an important methodological improvement in diagnosing neuropathy and may be useful tools for the detection of the peripheral nerve enlargement in LPs.

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