Peripheral neuropathy in leprosy among patients attending the Dermatology Clinic in a Tertiary Care Hospital in Sri Lanka: clinical, ultrasound measures and electrophysiological correlations

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Abstract

Introduction: Leprosy primarily affects the peripheral nerves and subsequently spreads to the skin and its appendages. The aim of this study was to correlate clinical patterns of nerve abnormalities of ulnar and common peroneal nerves of leprosy patients with ultrasonography (USG) and findings of nerve conduction studies (NCS).

Methods: 180 ulnar nerves (UN) and 180 common peroneal nerves (CPN) of 90 patients with leprosy were assessed clinically. Cross sectional area (CSA) of nerves was measured by ultrasonography. Motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) were measured in NCS.

Results: The correlation of clinical palpation and ultrasound measures were significant; r= 0.378 ($p<0.01$) in UN and r= 0.158 ($p<0.01$) in CPN. There was a significant correlation between clinical findings and NCS; MNCV of UN r= -0.44 ($p<0.01$), SNCV of UN r= -0.575 ($p<0.01$) and MNCV of CPN r= -0.254 ($p<0.01$). The correlation of maximum CSA and NCS was statistically significant in UN; MNCV r= -0.276 ($p<0.01$) and SNCV r = -0.412 ($p<0.01$).

Conclusion: In leprosy patients, a significant positive correlation exists between clinical detection, ultrasound measures of nerve enlargement and slowing of MNCV and SNCV of UN and CPNs.

In our study, USG was done using 4 - 11MHz linear transducer, which is available at any low resource setting. Therefore, ultrasonography without high resolution can be used to detect nerve enlargement in leprosy.

Introduction

Leprosy is a chronic granulomatous infection with a long incubation period. It is caused by *Mycobacterium leprae* that predominantly infects the skin and peripheral nerves (Britton *et al*., 2004). It primarily affects the peripheral nerves with secondary skin infection and in highly bacillated state internal organs also. Leprosy gives raise a spectrum of manifestation. Nerve damage is seen throughout the spectrum. It is a mixed nerve involvement affecting sensory, motor and autonomic function of peripheral nerve (Britton *et al*., 2004). Central nervous systems is spared.

It often involves peripheral nerves at certain sites of predilection, specially when it is superficial, and subjected to trained. Nerve damage is mainly due to inflammatory and immunologic response to *Mycobacterium leprae* and to a lesser extent due to infection by the pathogen (Rodrigues *et al* 2011). Peripheral nerve damage which start early in the course of the disease, leads to most of the disabling complications on the long term. Patients with leprosy presents with localised disease or widespread disease at times with complications. Leprosy neuropathy is the commonest treatable neuropathy and the foremost infectious cause of disability (Rodrigues *et al* 2011).

Clinical manifestations of early nerve damage are not detected early for number of reasons. This can be due to lack of symptoms/ signs, difficulty in elicitating nerve involvement at various levels of health care and social stigma. It is not only subjective but also has a great inter-observer variability. In some situations such as in obesity, it is difficult to perform. If early detection of nerve damage can be achieved in a reliable way, early initiation of remedial action will be possible. In pure neural leprosy, skin lesions are absent. To assess the leprous neuropathy, a specific test or investigation has not been found. The diagnosis is based on clinical features and histological examination of nerve biopsy specimens. Even though nerve involvement can be assessed by nerve conduction studies, which may show a pattern suggestive of leprosy, histology of nerve biopsy can only confirm the diagnosis. Nerve biopsy is an invasive procedure and may carry a risk of iatrogenic nerve damage leading to nerve disabilities. Therefore, it is necessary to develop an objective evidence of leprosy nerve involvement in these scenarios.

Ultrasonography of peripheral nerves was first documented in 1988 (Fornage *et al* 1988). High resolution ultrasonography detects anatomical and pathological changes of peripheral nerves which mirrors histopathological features (Jain *et al* 2009). Recently, high resolution ultrasonography has been described as a useful tool in the diagnosis of leprosy

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neuropathy (Elias e*t al* 2009). Ultrasonography of nerves readily visualizes peripheral nerves and is non-invasive.

High resolution ultrasonography is not available in most areas where leprosy is prevalent. It is important to find out whether ultrasonography without high resolution, which is available in any low resourced care can be used to find nerve involvement in leprosy. In Sri Lanka we do not use ultrasound simply because of lack of high resolution ultrasound probes. But still, there is a possibility of detecting early objective evidence of nerve involvement of leprosy with ultrasound probes available in our hospitals and to detect leprosy neuropathy early. This prompts us to focus on this research to evaluate the diagnostic value of ultrasonography to detect leprosy neuropathy early in local hospitals.

Methods

It was a descriptive cross sectional study and done at Colombo North Teaching Hospital, Ragama. A case of a leprosy was defined as a patient who has not completed the course of anti-leprosy treatment and has more than one following characteristic signs: hypopigmented/erythematous skin lesion with definite sensory impairment or loss, peripheral nerve thickening with or without sensory motor dysfunction, positive slit skim smear for acid-fast bacilli or suggestive skin or nerve biopsy. Sever psychiatric illness who cannot give adequate history to come to the diagnosis of leprosy, acutely ill at the time of the survey and uncooperative patients that in whom ultrasound scan cannot be performed were excluded. All patients except 10 patients underwent electrophysiological examination. Five patients refused it due to fear of pain. Others had bilateral leg oedema causing difficult in doing nerve conduction test practically. Calculated sample size of cases was 40. However, it was increased to 90 to increase the accuracy of the study. The number of normal controls was similar to the number of cases.

The data was collected from an interviewer administered questionnaire and personal clinic records. Other co-existing diseases and drugs patient on other than anti-leprosy drugs, which can cause peripheral nerve thickening, were traced from medical records.

UN and CPN were assessed clinically. Neuropathic pain, nerve tenderness, nerve thickening, motor weakness and sensory loss were assessed and graded. The questions were asked to grade neuropathic pain as 0, 1, 2 and 3. Palpation of UN and CPN was done to assess thickness and tenderness. Thickness of the nerves was graded as 0, 1, 2 and 3. Tenderness was graded as 0, 1, 2 and 3. Motor weakness was determined by skeletal muscle testing using the modified Medical Research Council (MRC) scale of 0 - 5. Little finger abduction was tested for abductor digiti minimi muscle to assess UN weakness. dorsiflexion of the foot and big toe was tested for tibialis anterior, peroneus brevis and longus to assess common peroneal nerve. Sensory impairment was assessed using standard Semmes-Weinstein monofilament 0.2g for hand and 2g for foot. UN sensation was tested over the distal phalanx of little finger, head of 5th metacarpal and hypothenar eminence. Common peroneal nerve was tested over the dorsum of the big toe and dorsum of foot.

Electrophysiological tests were done on the same day of clinical assessment. The room temperature was maintained at 26˚C (was confirmed using ambient thermometers). The patients were acclimatized for 15 minutes, before testing. Standard procedures was used for stimulation and recording as described by the accompanying manual of the nerve conduction test machine. Electrophysiological tests of bilateral UN and CPN were done and MNCV and SNCV were recorded.

Ultrasonography of bilateral UN and CPN was done. Maximum CSA, site of maximum involvement of nerve, pattern of nerve thickening and echogenic texture were recorded using multi-frequency 4-11 MHz linear array transducer of Toshiba Xario-200 USG.

Patients who attend the dermatology clinic and do not have leprosy were matched cases for age and sex and were recruited as normal population. Only ultrasonography of UN and CPN was done in normal individuals.

Data was evaluated with Statistical Package for Social Sciences[20]. Suitable statistical methods were used for comparison of variables. The research proposal was approved by the Ethical Review Committee of Faculty of Medicine, University of Kelaniya.

Results

A total of 90 cases (mean age 45.67 ± 17.59, range 13-77 years, tuberculoid 14.6%, borderline-tuberculoid 49.4%, mid-borderline 4.5%, borderline-lepromatous 15.7%, lepromatous 11.2% and pure-neural 4.5%) were recruited. 51 patients were males and 39 patients were females. Age and gender

matched 90 healthy volunteers (mean age 50.99 ± 15.27, range 14-79 years) were recruited as control. 42 individuals were females while 48 patients were males. There were 23 (25.55%) paucibacillary cases were as 67 (74.44%) patients were multibacillary. 24 (16.85%) patients had type 1 reaction while 09 (10%) patients had type 2 reaction.

12 patients 13.5% complained of numbness or neuropathic pain (Table 1).

Table 1. Frequencies of neuropathic pain

	Right UN		*Left UN*		*Right CPN*		*Left CPN*	
	Number	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*
None	83	93.25	85	95.50	86	96.62	85	95.50
Mild	03	03.37	02	02.24	02	02.24	02	02.24
Moderate	03	03.37	02	02.24	01	01.12	02	02.24
Severe	-	-	-	-	-	-	-	-

20 (22.5%) patients had nerve tenderness (Table 2).

Table 2. Frequencies of nerve tenderness

	Right UN		*Left UN*		*Right CPN*		*Left CPN*	
	Number	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*
None	71	79.77	78	87.64	89	100.00	86	96.62
Mild	10	11.23	08	08.98	-	-	02	02.24
Moderate	07	07.86	03	03.37	-	-	01	01.12
Severe	01	1.12	-	-	-	-	-	-

Nerve thickening was clinically detected in 83 (93.25%) patients (Table 3).

Table 3. Frequencies of nerve thickening

	Right UN		*Left UN*		*Right CPN*		*Left CPN*	
	Number	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*
None	12	13.48	15	16.85	49	55.05	49	55.05
Mild	43	48.31	50	56.17	31	34.83	30	33.07
Moderate	31	34.83	22	24.71	09	10.11	10	11.23
Severe	03	3.37	02	02.24	-	-	-	-

Motor function was not normal in 26 (29.21%) patients (Table 4).

Table 4. Frequencies of motor function

	Right UN		*Left UN*		*Right CPN*		*Left CPN*	
	Number	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*
0	01	01.12	03	03.37	03	03.37	02	02.24
1	-	-	01	01.12	-	-	-	-
2	01	01.12	-	-	-	-	-	-
3	03	03.37	05	05.61	01	01.12	-	-
4	05	05.61	07	07.86	-	-	02	02.24
5	79	88.76	73	82.02	85	95.50	85	95.50

Sensory impairment was seen in 26 (29.21%) patients (Table 5).

Table 5. Frequencies of sensory loss

	Right UN		*Left UN*		*Right CPN*		*Left CPN*	
	Number	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*
Yes	10	11.23	11	12.35	09	10.11	08	8.98
No	79	88.76	78	87.64	80	89.88	81	91.01

Neuropathic pain, nerve tenderness, nerve thickening, motor weakness and sensory loss were reported in 13.5%, 22.5%, 93.3%, 29.2% and 28.1% patients respectively. The overall prevalence of leprosy neuropathy was 94.4%.

80 patients underwent electrophysiological assessment. Table 6 shows results of NCS.

Table 6. Mean of nerve conduction velocities in UN and CPN

	Right UN	*Left UN*	*Right CPN*	*Left CPN*
(Mean) - MNCV	52.75 m/s	52.63 m/s	43.87 m/s	43.90 m/s
(Mean) - SNCV	55.74 m/s	54.13 m/s	-	-

The mean of MNCV of patients was 56.31 ± 6.88 m/s in UN. It was 45.30 ± 7.26 m/s in CPN. The mean SNCV of UN was 61.83 ± 8.66 m/s.

The maximum UN enlargement was at 11.59 ± 6.82 mm proximal to the medial epicondyle. The CSA of UN at the maximum enlargement was 8.22 ± 3.89 mm^2. 48.3%, 30.9%, 20.8% had fusiform, nodular and uniform thickening pattern were detected respectively in UN of leprosy patients.

For convenience in standardizing, we compared mean CSA of UN with controls at the cubital groove. It showed a statically significant greater value of 6.91 ± 3.06 mm^2 as compared with controls 4.98 ± 0.66 mm^2 ($p<0.0001$). The mean CSA of CPN at the fibula neck was statistically significant, 3.72 ± 1.44 mm^2 when compared to controls 2.21 ± 0.25 mm^2 ($p<0.0001$).

The correlation of clinical palpation and ultrasound measures were significantly positive; $r(178)= 0.378$ ($p<0.01$) in UN and $r(176)= 0.158$ ($p<0.01$) in CPN. There was a significant negative correlation between clinical palpation and MNCV of UN $r(160)= -0.44$ ($p<0.01$). The correlation of clinical palpation and SNCV of UN was significantly negative $r(160)= -0.575$ ($p<0.01$). The correlation of clinical palpation and MNCV of CPN was $r(160)= -0.254$ ($p<0.01$). The correlation of maximum CSA of UN and MNCV was negative and statistically significant $r(176)= -0.276$ ($p<0.01$). There is a negative correlation was seen in sensory nerve conduction velocity and maximum corss section area of UN $r(160) = -0.412$ ($p<0.01$) and it was statistically significant.

Receiver operating characteristic curve analysis showed that a CSA cut off value of 5.52mm^2 (sensitivity, 0.80; specificity, 0.84) and 2.70mm^2 (sensitivity, 0.80; specificity, 0.91) were the best discriminators for UN and CPN respectively. 90 clinically normal nerves had abnormal ultrasonography findings and 46 nerves with normal ultrasonography findings were considered as thickened clinically. Kappa for clinical palpation and detection of nerve enlargement by ultrasonography was 0.12 for both UN and CPN.

Discussion

Leprous neuropathy can cause devastating complications and deformities which may lead to social stigma. Hence, it is very important to detect leprosy neuropathy at the early stages.

In 94.4% of patients nerve damage was detected clinically. It is higher (61.3%) when compared to a study done in India (Sarker *et al* 2015). Trained and excellent clinical experience may partly explain. This is as majority of leprosy patients are examined by dermatologists. It may most commonly be due to inter personal variability. It also reflects unreliability as clinical examination is subjective. In the above study, the most common feature of peripheral nerve involvement was neuropathic pain (89.4%) whereas our study it was nerve thickness (93.3%), which is a more specific sign.

In our study motor and sensory nerve conduction velocity was significantly slower in patients with leprosy than normal healthy individuals. An Indian study done in 2014, had the same results (Vashisht *et al* 2014). However, the electrophysiological features are not specific to leprosy and can be seen in other inflammatory conditions. The other limitation is that it is a painful procedure and time consuming even with experienced hands.

Several studies explain the usefulness of high resolution ultrasonography in leprosy neuropathy (Jain *et al* 2009). When compared to the studies done in the past, CSA of UN and CPN have higher value (9.8 mm^2) than our study (Elias *et al* 2009). The above mentioned study was done in Brazil and probably due to racial differences in nerve thickness. The other reason is the use of high resolution ultrasonography which is more accurate and give a better outcome.

Review of the literature did not show much evidence of the use of normal ultrasonography in leprous neuropathy. To our knowledge, a study has not been documented in leprous neuropathy using normal ultrasonography. Leprosy is more common among developing countries where there is lack of resources. Hence high resolution ultrasonography is not freely available in such counties. Ultrasonography without high resolution is available in any low resourced setting. Our study identifies certain cut off points in CSA of UN and CPN at certain anatomical sites such as cubital fossa and the neck of the fibula to diagnose leprosy neuropathy. It is the most important finding in our study, as it will help in future to diagnose leprosy neuropathy especially in pure neural leprous cases. It will also minimise the necessity of nerve biopsies hence iatrogenic nerve damage causing deformities.

Conclusion and recommendations

In leprosy patients, a significant positive correlation exists between clinical detection, ultrasound measures of nerve enlargement and slowing of Motor Nerve Conduction Velocity and Sensory Nerve Conduction Velosity of UN and CPN.

Majority of previous studies have been done using high resolution USG. In our study, ultrasonography was done using 4 - 11MHz linear transducer, which is available at any low recourse setting. Therefore, ultrasonography without high resolution can be used to detect nerve enlargement in leprosy.

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