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Original Article

Monitoring the Outcome of Leprosy Using Leprosy Neuropathy Scale: A Preliminary Study

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The disability and progress of leprosy patients is monitored by the WHO disability grading system which has limited sensitivity in leprous neuropathy. This study aims to report the spectrum of leprosy patients at a tertiary care neurology service and compare WHO grading, modified Rankin Scale (mRS) and Leprosy Neuropathy Scale (LNS) in monitoring the treatment outcome. The patients with leprosy diagnosed as per WHO criteria were subjected to medical history and clinical examination. Their disability was graded as per WHO grading scale, modified Rankin scale (mRS) and LNS. These parameters were repeated and compared after six months of multiple drug therapy (MDT). Thirty-eight patients with leprosy, aged 40 (`5-80) years, 33 of whom were males have been evaluated. The duration of symptoms was 24 (91-120) months. Mononeuropathy was present in 14, mononeuropathy multiplex in 24, trophic ulcer in two, claw hand in 11, wrist drop in two, foot drop in four, facial palsy in one, Charcot's joint in one and lepra reaction in seven patients. Their disability as per WHO grade 1 and 2 was in 19 patients each. After 6 months of MDT, WHO grade improved in two patients, mRS revealed improvement in seven and LNS in nine patients. LNS- a clinical scale, seems more effective and easier to use for monitoring the progress/ outcome of neuropathy in leprosy patients and may complement the WHO grading scale.

Keywords : Modified Rankin Scale (mRS); Leprosy Neuropathy Scale (LNS), WHO, MDT, Acid Fast Bacilli. Disability

Introduction

Leprosy is an ancient infectious disease mainly involving the peripheral nerves and skin but also affects mucus membranes, bones, eyes, testes etc resulting in significant disability. On the first of April 2017, the prevalence rate of leprosy in India was 0.66/10,000 whereas the global prevalence of leprosy was 0.25/10,000 population (192,713 cases). At the end of 2017, thus an increase of 20,765 patients was reported over that in 2016 (WHO 2017). Leprosy is prevalent in 17 countries including India and Brazil where more than 1000 new cases are reported annually which accounts for 94% of new cases (Nascimento 2013). Peripheral neuropathy in HD is generally sensory motor mononeuropathy, mononeuropathy multiplex or overlap polyneuropathy often exacerbated by lepra reaction which occur in

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30% to 50% of patients. Lepra reaction affects the skin, nerves and other organ systems (Walker & Lockwood 2007).

In paucibacillary HD, MDT is recommended for 6 months; and in multibacillary for 12 months. For the patients with a single skin patch ROM (Rifampicin, Ofloxacin and Minocycline) is recommended (WHO 2013). The documentation of disability and monitoring of the effect of treatment is done using the WHO grading system and bacteriological studies for acid-fast bacilli (AFB) in slit smear. In pauci-bacillary leprosy, in patients with major nerve and skin involvement AFB cannot be demonstrated. Monitoring the progress of such patients may require detailed clinical evaluation. There is a need for a comprehensive and objective measure to monitor the progress of such (pauci-bacillary) patients. We aim to show that Leprosy neuropathy Scale (LNS) can be a useful clinical tool for day-to-day outpatient based and field-based monitoring systems which may complement the WHO disability scoring system.

Materials and Methods

Between October 2018 and March 2020, patients diagnosed with Hansen's Disease (HD) were included in the study. The SGPGI Ethics Committee approved the project with reference number 2018-44 DM EX, dated 28.1.19. Written consent was obtained from either the patients or their authorized representatives.

Diagnosis of leprosy was determined based on the presence of at least two of the following criteria:

- Maculo- anaesthetic patch.
- Thickened peripheral nerve.
- AFB in slit smear or nerve biopsy consistent with Hansen's Disease (HD).

The criteria for categorization of leprosy patients were as follows:

Tuberculoid (TT) leprosy was diagnosed by solitary papule and plaques which may coalesce with raised borders and an annular appearance. The lesions were frequently atrophic, hypo-pigmented and asymmetrical, with reduced pain touch temperature sensation and anhydrosis.

Borderline tuberculoid (BT): Skin lesions were more numerous and extensive than TT with prominent sharply demarcated borders arranged in an asymmetrical fashion. Sensory and motor nerve involvement was present but less than TT.

Borderline-borderline (BB): There were increase in the number of lesions which were distributed nearly symmetrically and showed clinical features of both TT and LL . Hair growth and sweating were hardly affected. Few or numerous bacteria could be detected.

Borderline lepromatous (BL): BL revealed multiple, symmetrical, poorly demarcated, hypo-pigmented papules, nodules, and infiltrated plaques. The hair growth and sweating were hardly affected. There was extensive peripheral nerve involvement and numerous AFB were present in clusters.

Lepromatous (LL): In LL, lesions were multiple, symmetrical, red-brown nodular infiltrates in the skin and mucous membranes with predilection for face and earlobes. Loss of eyelashes and eyebrows, destruction of nasal septum and ocular involvement could occur (Fischer 2017).

Evaluation

The patients underwent detailed medical history including pain, paresthesia, weakness, sensory loss, and ulcer. The examination included pedal edema, iritis, lagophthalmos, sensory loss, focal weakness (Medical Research Council - Wright 1912), wrist drop, foot drop, facial weakness and muscle wasting. Tendon reflexes were graded as normal, reduced or absent. Peripheral nerves namely supraorbital, greater auricular, ulnar, dorsal branch of ulnar, radial, dorsal branch of

redial, median, peroneal, posterior tibial and sural nerves were palpated, and categorized as normal, thickened and tender.

Patients' disability was recorded using WHO grading (Brandsma & van Brakel 2003).

Grade 0: No weakness, visible deficiency or damage.

Grade 1. Anesthesia is present, but no deformity or damage

Grade 2. Visible deformity or damage

Eyes

Grade 0: No eye problem due to leprosy or evidence of uveitis

Grade 1: Eye problem due to leprosy present but vision not severely affected (6/60, finger count 6 m, corneal opacity absent).

Grade 2: Severe visual impairment (<6/60) Finger counting at 6 meters, lagophthalmos iridocyclitis, or media-opacity.

Leprosy Neuropathy Scale (LNS)

Evaluation of motor (grip, facial weakness muscle wasting, walking difficulty), sensory (sensory loss, pain, trophic change and ulcer), nerve enlargement of 10 nerves, activities of daily living -no impairment (0), mild impairment (1) and severe impairment (2). The maximum score was 26, and a lower score suggests milder illness (Table 1).

Leprosy neuropathy scale was administered on the first examination and repeated at 3 and 6 months. The patients with pauci-bacillary HD received MDT comprising of rifampicin 600 mg monthly and dapsone 100 mg daily for 6 months and in multi-bacillary disease rifampicin 600 and clofazimine 300mg monthly and dapsone100 mg and clofazimine 50mg daily for 12 months (WHO 2013). Prednisolone was prescribed 20-30mg/ day for one month and tapered as indicated in the patients with lepra reaction. Higher dose of

Table 1 : LNS (Leprosy neuropathic scale).

Motor	**0**	**1**	**2**	**3**
Grip	0= normal	1-Mild weakness	2-Unable to grip	
Walk	0= normal	1-walking without support	2-with support	
Wasting	0-absent	1 -present		
Facial	0-absent	1-present		
ADL	0-NORMAL	1-MILD	2-UNABLE TO DO DAILY ACTIVITY	
SENSORY				
Number of Nerves Enlarged (Max=10)				
Pain	0-ABSENT	1-PRESENT		
Sensory Loss	0-ABSENT	1-PRESENT less than 5 areas/patch	2- more than 5 areas	
Trophic	0-ABSENT	1-SKIN CHANGES	2-SUBCUTANEOUS	3-JOINT/BONE
Ulcer	0-ABSENT		2-PRESENT	
				MAXIMUM-26

prednisone and other immunosuppression like thalidomide were prescribed if indicated.

Statistical Analysis

The normally distributed variables were presented as mean and SD and skewed data as median and range. The improvement using WHO, mRS and LNS were compared using X^2 test and the sensitivity and specificity were evaluated. Paired t-test was used to compare the outcome of patient. Receiver operating characteristic (ROC) curve was analysed. The statistical analysis was done using SPSS version 20 and a P value <0.05 was considered significant.

Results

Thirty-eight patients with leprosy whose median age was 40(15- 80) years, 33 of whom were males and duration of illness was a median 24 (1 - 120) months were included. The referral diagnosis was HD in 23 (60. 5%) patients. The other diagnosis included cervical spondylosis, Guillain-Barre syndrome, radiculopathy, non-specific neuropathy in two each; enlarged tendon, Charcot's joint, restless leg syndrome, Carpel tunnel syndrome, stroke, chronic inflammatory demyelinating polyneuropathy, prolapsed intervertebral disc, in one patient each, highlighting misdiagnosis in 39.5% patients. The comorbidities included diabetes mellitus in five, hypothyroidism in two, hyperlipidemia in one and hypertension in three patients. Only motor symptoms were present in five, sensory-motor in 21 and only sensory symptoms in 12 patients; the latter included sensory ataxia in two, restless leg syndrome and cold allodynia in one patient each. Skin lesions were present in 22 (57.8%), only sensory impairment in seven (18.5%) focal weakness in 15 (39.4%) and nerves were thickened in 35 (92.1%) patients. The nerve thickening involved the ulnar nerve in 32, dorsal radial in seven, peroneal in 29, the sural nerve in seven, greater auricular in four, facial weakness in two patients and median nerve in one. Nerve conduction was abnormal in 34 patients four patient had normal nerve conduction study. In six patients there was only nerve involvement

Table 2 : Clinical details of the patients with Hansen's disease (HD) who had Lepra reaction.

S. No	Age /Sex	Referral diagnosis	Onset after MDT (mo)	Duration	Symptoms Sensory/ Motor/ Systemic
1	54/m	GBS	6	3month	Skin lesions, lipomatous lesion, weakness in all limbs
2	18/m	HD	3	4	New skin lesions and edema
3	44/m	GBS	3	2	Oedema, limb weakness, jaundice
4	30	HD	2	1	Ulcer and edema
5	55/m	HD	24	3	Oedema, weakness, pain, new lesions, wasting
6	47/m	HD	2	4	Skin lesions with abscess
7	45/m	HD	3	5	Oedema, wasting, weakness, skin lesions

manifested by sensory and /or motor involvement with nerve thickening but without skin lesion or AFB in slit smear suggesting the possibility of pure neuritic HD.

Based on clinical examination single nerve was involved in 14 patients, multiple nerves in 24 and cranial nerve were involved in one patient. Nerve biopsy was done in one patient showing no evidence of vasculitis or granuloma. Fite Faraco stain was negative for acid fast bacilli as he was on MDT for six months (Reja et al 2013). Slit smear was positive for AFB in two patients. The diagnosis was TT in seven, BT in 23, BB in six, and BL in two patients. Multidrug therapy was started in 29 patients in our care and nine patients were already on MDT prescribed by the referring physician.

Seven (18.4%) patients had type I lepra reactions. The age of the patients with lepra reaction was 18-55 y, all were males. Lepra reaction followed 2-3 months of MDT except in two in whom it occurred after six and 24 months after MDT. Lepra reaction was associated with erythema and enlargement of preexisting skin lesions in five patients, ulcer and nerve abscess in one patient each, edema was present in four patients, pain in two patients, nerve tenderness in two patients, acute generalized weakness in two patients, focal weakness in one. All the patients had good outcome except one who had poor outcome. The clinical features of the patients with lepra reactions are presented in Table 2.

As per WHO grading 19 patients were in Grade 1 and 19 in grade 2. After 6 months of MDT, two patients showed improvement from D2 G to D1 G.

There was no disability in two, trophic ulcer in two, claw hand in six, wrist drop in two, foot drop in four, facial palsy in one, Charcot's joint in one and blindness in one patient. After treatment worsening manifested with neuropathy, a trophic ulcer in one patient after one year of treatment showing an ulcer in the right toe. Response of treatment was resolution in sensory-motor symptoms in 26 but in 10 patients remained unchanged. The change in deformity after treatment is presented in Table 3**.**

As per mRS outcome at six months of treatment was good in seven, poor in 21 by (change from mRS more than 2 to mRS 2 or less) but mRS grading was not reflecting a significant change in outcome (p=0.11). The mean value of LNS was 8.31±4.81 initially, 7.39 ± 4.45 at 3 months and 6.52 ± 4.27 at 6 months. Initially, 22 and 16 patients were in LNS > 6.5 and LNS ≤ 6.5 respectively, however at six months 13 and 25 ~~16~~ patients were in LNS > 6.5 and LNS ≤ 6.5 respectively. There was a significant difference in

Table 3 : Attitudes towards the people affected by leprosy (n=358)

Deformity	Initial	Final
Clawing	11	6
Wrist drop	2	2
Foot drop	8	4
Trophic ulcer	7	2
Lagophthalmos/ VII	1	1
Ear, nose deformity	0	0
Charcot's joint	1	1

Table 4 : Disability after 6 months using WHO grading , modified Rankin scale (mRS) and Leprosy neuropathy scale (LNS).

Grading	Initial(n)	Final(n)	P
WHO 1	19	17	0.80
WHO2	19	19	
mRS ≤ 2	14	21	0.11
mRS > 2	24	17	
LNS > 6.5	22	13	
LNS ≤ 6.5	16	25	0.04

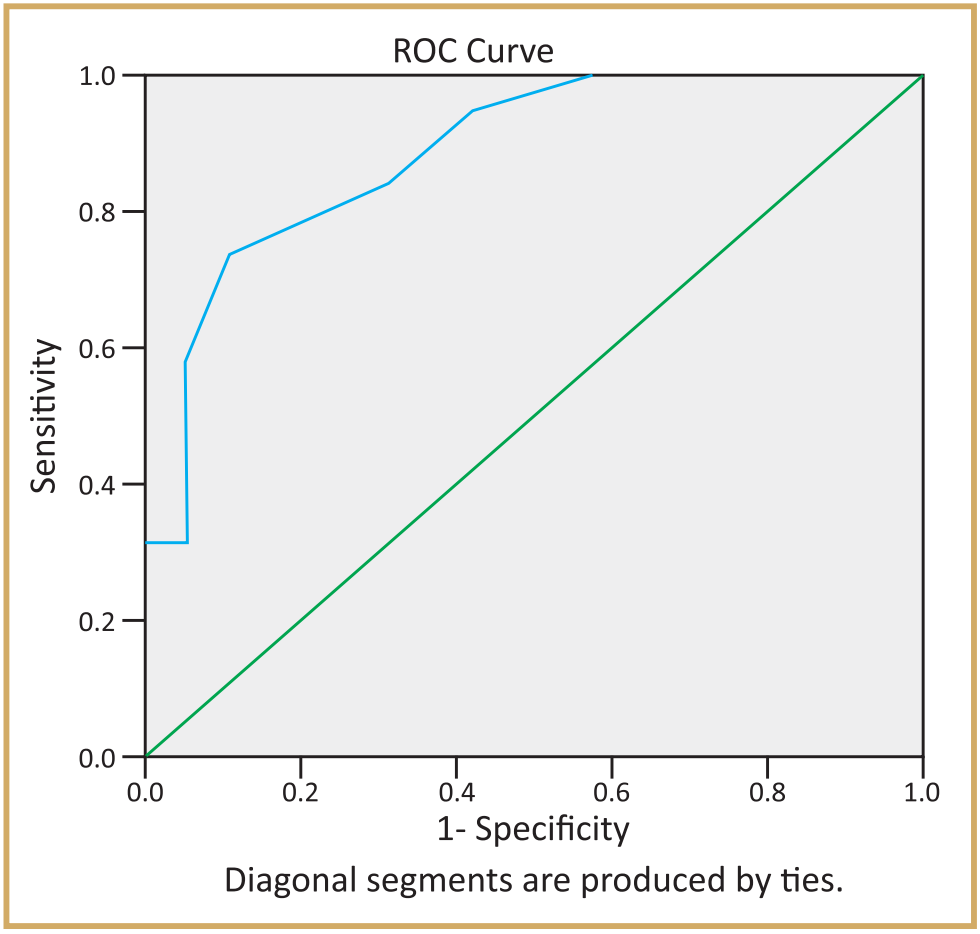

Fig. 1 : ROC curve (Leprosy neuropathy scale at a cut off value 6.5 revealed sensitivity of 84.2% and specificity is 68.8%).

Table 5 : Lepra reaction and the scoring of disability on initial examination and after completion of 6 months of treatment.

Age / Sex	Mononeuritis/ mononeuritis multiplex /poly-neuropathy	Grade TT/BT BB/ BL	mRS Initial /Final	p-value	WHO Initial /Final	p-value	LRS Initial / Final	p-value	Outcome
54/m	Polyneuropathy	BB	5/2		2/2		18/12		improvement
18/m	Mononeuritis multiplex	BB	3/3		2/2		18/15		No improve-ment
44/m	Mononeuritis	BT	4/1		2/2	Not appli-cable	7/4		improvement
30/m	Mononeuritis	BT	3/2	0.06	2/2		11/6	0.001	improvement
55/m	Polyneuropathy	BB	4/4		2/2		20/17		improvement
47/m	Mononeuritis multiplex	BB	3/3		2/2		17/15		improvement
45/m	Polyneuropathy	BB	4/3		2/2		18/15		improvement

six months outcome by LNS (p =0.04) while WHO grading did not reveal significant difference in six months outcome (p=0.80) (Table 4**).**

To find out appropriate cut -off of LNS with strategy to get at least 50% sensitivity and 50 % specificity. A cut-off 5.5 in LNS, revealed the maximum sensitivity of 94.7% and specificity of 57.9%. At 8.5 the sensitivity was 57.9 % and the specificity of 94.7 %. At cut-off value 6.5 a a sensitivity of 84.2 % and specificity of 68.8% was noted/ Area under ROC CURVE showing diagnostic accuracy of LNS for discrimination of mild and severe WHO disability grading is presented in Fig. 1**.**

Discussion

The present study of HD reveals male preponderance, type I lepra reaction in 22% of patients and reveals usefulness of LNS in monitoring effect of treatment. In the present study, male preponderance (87%) was in agreement with a study on 2000 patients in which, 71.6% were males (Liu et al 2018). Men have been reported to suffer from multibacillary HD (Varkevisser et al 2009), whereas females have higher disability and had greater delay in their treatment, possibly due to socioeconomic reasons (Richardus et al 1999).

In the present study, most patients had paucibacillary (30) and 9 were already on MDT which could have resulted in a lower frequency of AFB in the present study. In a study from South India, from dermatology service out of 50 patients with HD, the clinical spectrum was BT 54%, BL18%, LL18%, BL2% and BB2% (Raghavendra et al 2017). In a study on 200 patients, 67% were multibacillary and 33% paucibacillary (Rathod et al 2020), somewhat similar results were reported in other studies as well (Richardus et al 1996 & 1999, Raghavendra et al 2017, Rathod et al 2020).

The frequency of trophic ulcers has been reported to be 21.7% - 29.3%. and the other deformities included claw hand, foot drop, lagophthalmos, earlobe deformity, facial palsy and nasal deformity (Rathod et al 2020, Nayak et al 2017). The hand deformities were present in 44.4%, foot deformity in 33.26% and face deformity in 15.74%) (Rathod et al 2020). In the present study

claw hand was present in 11(28.9%), wrist drop in 5.2% trophic ulcers in 18.4%, joint deformity, facial weakness and blindness in 2.6% each. The difference in the presentation and deformity highlights the referral pattern of patients. Ours is a tertiary care neurology service could account for the difference in presentation and disability of HD patients.

In type I lepra reaction, the preexisting skin lesions become inflamed, edematous with weakness, pain and sensory loss. Corticosteroids are the mainstay of treatment of Lepra reaction. Type I Lepra reaction may develop gradually and may last several weeks. In the present study, Lepra reaction lasted 1-4 months.

In the present study, the disability grade was G1D and G2D in 19 (50%) patients each. Using this disability grade the improvement could be documented in two patients only although subjective improvement occurred in sensory symptoms in 10 patients, sensorimotor in 13 patients, motor in 2 patients, and autonomic function in 1 patient. Improvement was documented more frequently with LNS which was more sensitive and responsive to the treatment related changes. Using mRS, improvement was noted in seven patients whereas LNS revealed improvement in nine patients (using 6.5 as cut off**).** In seven patients having lepra reaction, initial and final mRS. WHO grading and LNS were used to monitor the outcome employing paired t-test, it was found LNS was more significantly related to outcome compared to WHO scale (p=0.001) and mRS (p=0.06) (Table 5).

Most of the drug trials in HD are done on multi-bacillary HD and these rely on bacteriological and histopathological endpoints which are less applicable in patients with leprous neuropathy and paucibacillary patients. We feel that LNS may be useful for documenting the changes because it includes, sensory, motor and ADL related changes in the patient.

Leprosy neuropathy scale may be complementary to WHO grading system because the latter is simple for field studies and many of leprosy control programs are based on WHO grading system. According to global leprosy strategy by 2020 the targets are 0 grade 2 deformity in pediatric patients, reduction of leprosy cases with G2D to less than 1 per million population and zero countries with legislation allowing discrimination on the basis of leprosy (WHO 2020). whereas LNS is also a clinical scale does not require laboratory support and can give more detailed information about peripheral nerve dysfunction.

This study has limitations, including a small sample size and a referral bias towards a tertiary care center where severely affected patients with neurological manifestations are referred. Therefore, the findings of this study cannot be generalized to leprosy in general. Nevertheless, this study sheds light on the range of HD in a Neurology service and highlights the potential value of LNS in monitoring patients with HD. It's important to note that these preliminary results need to be confirmed in a larger study.

Conclusion

The LNS scale appears to be easy to use and an efficient tool for monitoring neuropathic symptoms in leprosy. It could potentially complement the WHO grading scale. However, the initial findings of the study require further validation in a larger and more comprehensive study.

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