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Review Article

Use of Validated Severity Scales for Measurement of Lepra Reactions

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The need of a validated scale or tool to measure a disease condition, particularity its severity, cannot be over emphasized in clinical research. A validated scale can be used to compare a condition across cultures. Reactions in leprosy continue to be important causes of morbidity both systematic as well as local in the form of pain and disabilities. Measurement of their severity may be helpful in rationalizing their proper management. In this article, the salient features of validated tools to measure type 1 and 2 reactions in leprosy developed during last 7-12 years have been reviewed. The processes of validations are described too. Experience so far with the use of these severity scales to classify and monitor the anti-reaction treatment is limited. There is need to gain more experience in different endemic countries/regions so that duration and doses of anti-reaction agents could be better rationalized. Depending upon the field experience, these severity grading systems may be evolved further.

Key words: Severity scales, Lepra reactions, ENL, Leprosy

Introduction

Leprosy is a chronic debilitating granulomatous disease primarily affecting the peripheral nerves and skin which accounted 211,009 new leprosy cases registered globally in 2017 (WHO 2019). Delay in treatment of leprosy may lead to disabilities categorized as loss of sensation (Grade 1 disability; G1D) and visible deformities (Grade 2 disability; G2D). Fortunately, the G2Ds have decreased in recent years due to transfer of leprosy care in peripheral centers and increase in awareness among people and health care providers (Alberts et al 2011). WHO has emphasized and targeted a G2D rate of less than 1 case per 1 million people in its Global Leprosy Strategy 2016-2020 (WHO 2016). Despite being one of the earliest diseases that had been confirmed to be caused by any kind of etiological agent, it took some time before any chemical therapeutic agent was developed (WHO 2004). After about 30 years from the first drug developed for leprosy, WHO decided for worldwide distribution of free Multi-Drug Therapy (MDT) (WHO 2004). Since 1980s, the multi-drug therapy (MDT) regimens comprising of Rifampicin, Dapsone and Clofazimine has remained first line therapy for leprosy in most

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parts of the endemic world.

Leprosy is also one of the diseases where many researchers and clinicians have devoted their lifetimes for the better understanding of disease mechanisms, and improving the treatment and prevention strategies of the disease and its implications (Meyers 1998). The main concern for the disease is development of neuropathy. The leprosy bacterium adheres to the Schwann cells and gets phagocytosed (Rambukkana et al 1998). By many known as well as unconfirmed mechanisms, including death or demyelination of Schwann cells and intra-nerve pressure (Misch et al 2010), where the nerves become non-functional and cause motor, sensory and autonomic neuropathy in patients. The nerve function impairment (NFI) in leprosy can precipitate during lepra reactions and also on itself (silent neuropathies). These silent neuropathies occur predominantly during the leprosy reactions (type 1 & 2) (van Brakel & Khawas 1994). The management of reactions in leprosy is still a myth as the treatment is symptomatic and the actual pathogeneses of the reactions is still waiting confirmation. The test for effectiveness of different dosages of drugs under use, different approved drugs for used for other diseases and new possible formulations require validated severity score tools. A severity score is a set of validated questions that can be used with basic clinical knowledge to appropriately quantify the severity of illness across various countries. Just recently, a new tool for the severity scoring for type 2 reaction (T2R) in leprosy was validated (Walker et al 2017). The validated tool for severity scoring of type 1 reactions (T1R) was progressively developed, validated and implemented in various leprosy patients across countries. This review aims at the analysis of valid reaction scoring tools already available in the leprosy space to clinicians in endemic settings.

Lepra Reactions: Type 1 and Type 2 Reactions

Leprosy manifests as a spectrum of immunological status of the patients. The most established Ridley-Jopling classification system classifies leprosy into 5 types based on immunological grading (Ridley & Jopling 1966). These are a spectrum rather than independent classes. The WHO has also classified leprosy so that the two leprosy treatment durations can be streamlined on the basis of severity of the disease (WHO 1998). The WHO classification of a leprosy patient may depend up on clinician's description but 3 criteria for the WHO classifications for Multibacillary (MB) were: presence of one or more nerve thickening/impairment, presence of six or more skin lesions and presence of acid-fast *Mycobacterium leprae* bacteria in slit skin smear (WHO 1988). In the current classification, number of skin lesions and nerves involved are utilized to classify the patient into MB or Paucibacillary (PB) types for better treatment purposes (WHO 1994, 1998a). The PB patients with less severe manifestations for these criteria would be administered 6 months of MDT. The MB patients would require 12 months of MDT treatment. Some MB patients with higher load of bacteria (4 or more in any skin site by slit skin smear) may be prescribed 24 months of MB-MDT by some clinicians. The clinicians may also decide to prescribe MB-MDT regimen for PB patients if they suspect the clinical features have propensities of developing into severe forms (Malathi & Thapa 2013). The T1R, also called reversal reactions, manifest as localized inflamed skin lesions with or without NFI. Reversal reactions may develop anytime in patients when they first visit the clinicians, or during MDT and/or after release from treatment (RFT), similar to T2R (Kahawita et al 2008). The T2Rs, also called erythema nodosum leprosum (ENL), are systemic in nature. The signature features for ENL are the subcutaneous painful

erythematous nodules the patient develops in upper and lower limbs, face and some times in the trunk, in addition to fever, malaise, peripheral edema and joint swelling among other symptoms (Walker et al 2015). The patient usually reports that the ENL nodules subsided with anti-allergens or on itself within few days and many cases have been misdiagnosed (Raffe et al 2013). Generally, ENLs may have reoccurred couple of times within a year period. Considering the association of acid-fact bacteria in the reactions types, any positive bacterial index in slit-skin smear is considered as one of the risk factors for T1R (Roche et al 1997), while high bacterial index of 4+ or more is considered as one of the risk factor of T2R (Manandhar et al 1999).

Severity Scale for Leprosy Type 1 Reaction

This scale was developed in 2008 by researchers at the London School of Hygiene and Tropical Medicine (Walker et al 2008). The test was first validated in patients in Bangladesh and Brazil, both countries being endemic for leprosy, the development and validation being reported in the same article (Fig. 1). The scale was developed on the basis of similar scale used in studies in Nepal (Marlowe et al 2004) and India (van Brakel et al 2007). For the development of the scale, 8 experienced leprologists who were not involved in the study were selected and asked about what they thought about T1R and what criteria they thought were the most important for definition of the reaction and the answers returned from 7 leprologists were incorporated. The principal criteria considered were extent and degree of

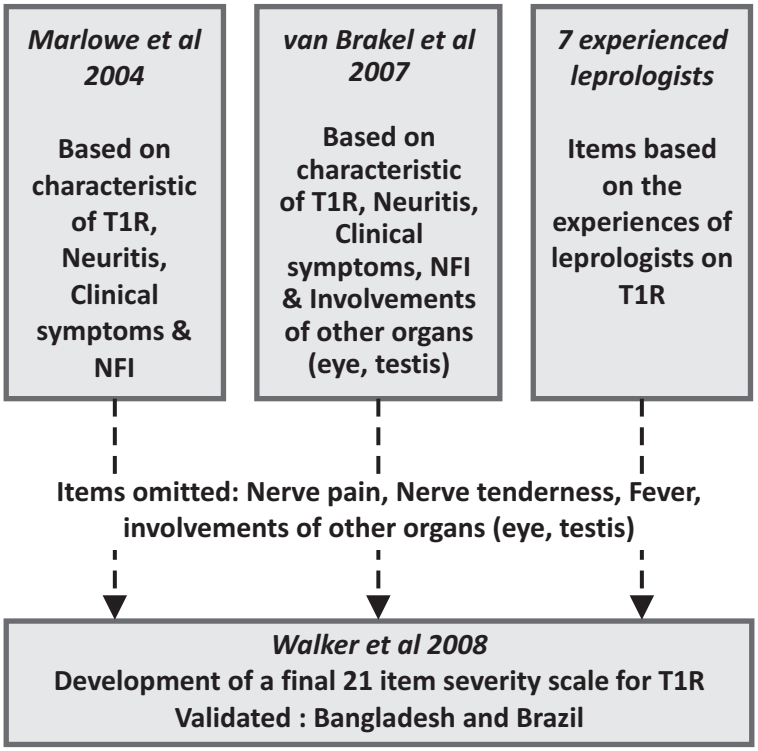

Fig. 1 : Schematic diagram demonstrating the progressive development of T1R severity scale

inflammation of skin lesions, the presence of peripheral oedema, nerve tenderness and NFI. The final scale was developed removing some of the items from the original scale. These items (nerve pain, nerve tenderness and fever) when removed, resulted in higher overall Crohnbach's alfa (internal consistency) to the scale. While removal of other items; the degree of inflammation of skin lesions, the number of raised inflamed lesions, function of trigeminal nerves, and motor function of the radial nerve, also resulted increase in Crohnbach's alfa, these items were defining features of T1R, and highly considered for retaining. The inter-observer reliability was rated with intra-class correlation coefficient and the correlation proved to be very good. The patients were classified as having mild, moderate and severe T1R. It was observed that the median scores obtained by mild and moderate patients using the final validated scale were disproportionately located with respect to the expected cut-offs, statistically significant grouping of mild, moderate and severe reaction could be made. The recent use of the scale in Ethiopian patients has shown clear difference in scores obtained by mild, moderate and severe patients (Lambert et al 2016). The grading of mild, moderate and severe was done by clinicians blinded to the scores.

The scale was divided into 3 sections.

Section A : This section dealt with 3 cutaneous features which included the degree of inflammation of the lesions, number of raised lesions and the presence of oedema. Each of these items could be scored from 0-3, making a maximum possible score of 9.

Section B : This section dealt with sensory NFI which comprehended bilateral trigeminal (cornea), bilateral ulnar and bilateral median nerves in the palms, and bilateral posterior tibial nerves in the sole. The assessment was done by Sensory Testing (ST) with Semmes Weinstein monofilaments. The monofilaments are standard nylon filaments which impart specific weights when impinged in skin. The skins of palm are sensitive compared to the sole and thus 2 grams and 10 gram filaments were used in palm, and 10 grams and 300 grams filaments were used in sole. Higher points were given when the heavier filaments were not sensed. A total of 24 points could be scored as 3 was the highest score for each of the 4 nerves assessed.

Section C : This section dealt with strength of the muscles innervated by 5 nerves: bilateral facial (eye closure), bilateral ulnar, median and radial in hands, and bilateral lateral popliteal in the foot. Maximum scorable point was 30 as each of the nerves assessed had the 3 highest scorable points. The scoring of the muscle strength is assessed by Voluntary Muscle Testing scale (VMT) with Medical Research Council (MRC) grades. For normal strength, the MRC score of a muscle is 5, for full paralysis of the muscle, the MRC score is 0. The ST-Semmes Weinstein filaments and VMT (MRC grades) are reliable scales in the field of leprosy (Anderson & Croft 1999).

Receiver operator characteristic (ROC) was used to define a number that could be used to differentiate between mild, moderate and severe reactions. Score of 4 or less, 4.5 to 8.5 and the score of 9 or more were categorized as mild, moderate and severe reactions respectively. Analyses based on minimal clinically important difference (Cook 2008) were not assessed.

It was found that the presence of old NFI would overestimate the score and thus impairments older than 6 month could be left unscored. Lambert et al (2016) have opined that scoring system for T1R was not equally weighted where in neurological parameters were more heavily represented.

ENLIST ENL Severity Scale for Type 2 Lepra

Reaction

The project to construct a severity scale for ENL began in 2012 by clinicians and researchers from 7 countries, and the group was referred as the Erythema Nodosum Leprosum International Study Group (ENLIST) (Walker et al 2012). The project initiation was led by the London School of Hygiene and Tropical Medicine and the scale was validated in patients from 6 countries: Bangladesh, Brazil, Ethiopia, India, Nepal and the Philippines (Walker et al 2017). The scale considers the final 10 items which are: 1. VAS (Visual Analog Scale) pain, 2. Fever, 3. Number of ENL lesions, 4. Inflammation of skin lesions (degree), 5. Extent of ENL lesions (body areas involved), 6. Peripheral oedema, 7. Bone Pain, 8. Inflammation of Joints and/or digits during ENL, 9. Lymphadenopathy during ENL, and 10. Nerve tenderness due to ENL.

This scale was developed in two steps. In the first step, Walker et al (2016) initiated the validation of the scale by referring to three earlier published works: modified Ramu scale (Ramu & Girdhar 1979, Kaur et al 2009), modified van Brakel (van Brakel et al 2007, Feuth et al 2008) and Haslett scale (Haslett et al 2005) and modified their scales (Fig. 2). Those 3 studies developed their own scales and utilized for their specific

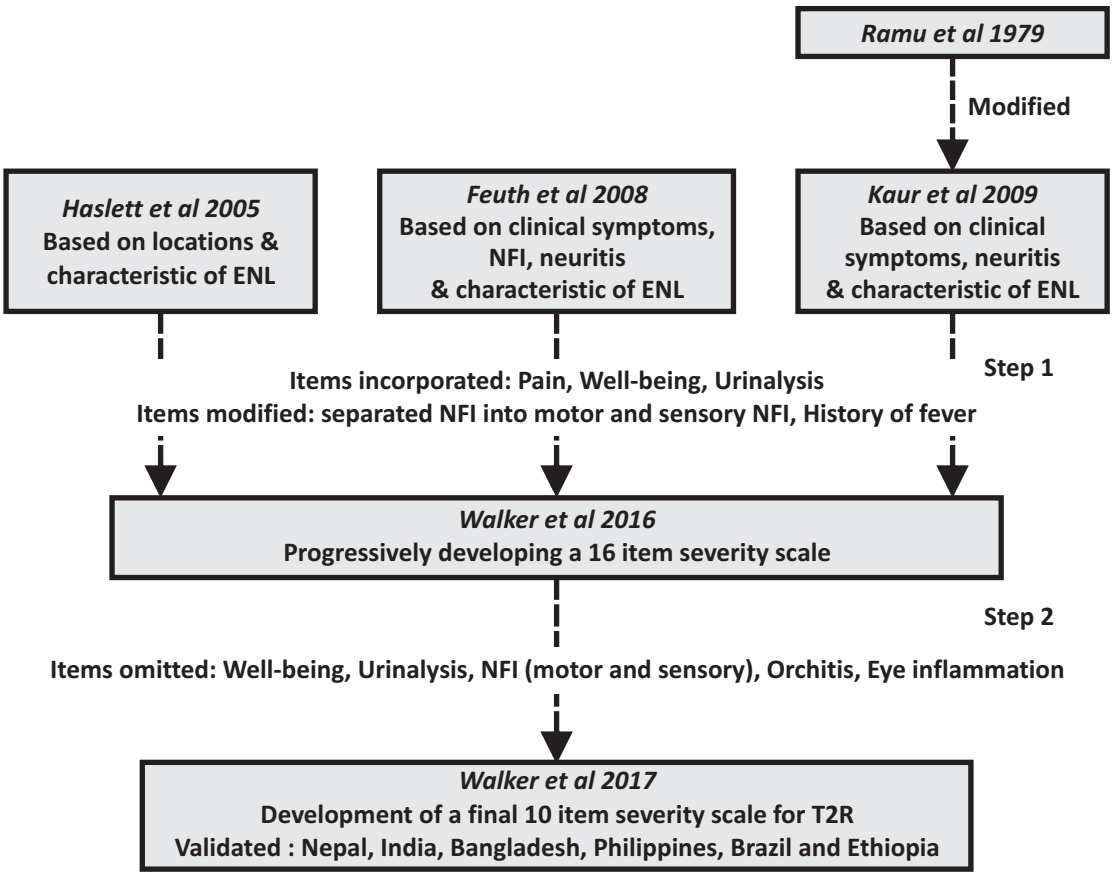

Fig. 2 : Schematic diagram demonstrating the progressive development of T2R severity scale

populations, however, those designated scales were not utilized widely by clinicians and not validated globally.

After discussions about importance of each item in the old scales, a new scale incorporating 16 items was developed. New additional items incorporated were VAS pain, VAS well-being and urine analysis. The VAS pain and VAS well-being scores were used to assess the overall pain and well-being perceived by the patients respectively.

Table 1 : Studies employing validated severity scale for Lepra T1R, their implications and limitations

Study (Ref: Author, Year)	Study Descriptions	Implications	Limitations
Scollard et al 2011	Country: India Reaction Type: T1R (n=17) Controls: BL/LL (n=20) Study type: Research exploring immunological alterations/system in T1R	Determination of severity levels of T1R	
Walker et al 2011	Country: Nepal Reaction Type: T1R Sample Size: n=42 Study type: clinical trial (RCT)	Measurement of T1R severity scores in comparative (control vs. treatment) groups	Severity levels (mild, moderate and severe) of T1R were not distinguished.
Lambert et al 2016	Country: Ethiopia Reaction Type: T1R Sample Size: n=135 Study type: Validation study	Discernment of whether presence or absence of T1R and determination of T1R severity levels	
Lambert et al 2016a	Country: Ethiopia Reaction Type: T1R Sample Size: n=73 Study type: clinical trial (RCT)	Differentiation of T1R severity scores in control vs. treatment groups	
Lockwood et al 2017	Country: India Reaction Type: T1R Sample Size: n=345 Study type: clinical trial (RCT)	Measurement of clinical severity levels in baseline vs. endpoint and comparative treatment groups	Severity levels (mild, moderate and severe) of T1R were not distinguished
Wagenaar et al 2017	Countries: Nepal, India, Bangladesh and Indonesia Reaction Type: any NFI of < 6 months Sample Size: n=875 Study type: clinical trial (RCT)	Measurement of T1R severity scores in T1R patients on different time points.	Severity levels (mild, moderate and severe) of T1R were not distinguished.

The urine analysis was used to assess the level of urine albumin to determine the renal involvement during ENL. During step 2, the scale was optimized with 10 items and validated in multiple centers across countries by omitting some of the items (Walker et al 2017). To keep all items relating to clinical parameters in the scale, it was decided to remove the VAS well-being item which was the only non-clinical item.

The orchitis item was also removed to maintain a gender-neutral scale. During the analysis for internal consistency, it was decided to remove item describing inflammation of the eyes due to ENL, urinalysis and 2 items related to sensory and motor nerve function as withdrawal of these items resulted an increased in Crohnbach's alfa. Inter-rater reliability was 'good' in T2R compared to 'very good' for T1R severity scale. The 10 item new scale was able to statistically discriminate between patients with active ENL and patients without ENL. However, the scale was unable to properly differentiate patients having “moderate” ENL and those with “severe” ENL. Score of 8 or less denoted mild ENL reactions and score of 9 or more denoted as moderate and/or severe ENL reactions. ENLIST ENL severity score also analyzed for minimal clinically important difference from both patients' and clinicians' perspectives. A score of 9 or more signifies “much better” clinical condition from baseline.

Implications of Validated Severity Scales

Across the leprosy endemic countries, various misdiagnosed case reports of both T1Rs and T2Rs have been regularly reported. Proper utilization of these validated severity scores enable clinicians and para-medical health workers to diagnose and/or refer reaction patients for further treatment. The scales also contribute to the clinicians to better understand the severity stage of reactions in various patients across countries, and whether to determine which kind and what quantity of drug regimen need to be prescribed. In addition, as several drugs used for the management of leprosy reactions are symptomatic, further research activities with clinical drug trials incorporating severity scales are necessary to establish and determine the safety and efficacy of trial drugs. Although severity scales have been implemented, prospectively validated in patients with lepra reactions and utilized in across various countries (Scollard et al 2011, Walker et al 2011, Wagenaar et al 2011, Lambert et al 2016, Lambert et al 2016a, Lockwood et al 2017), further studies are warranted to ascertain its utility in future clinical studies, to prepare the general consensus to report scores, to allow relative comparisons among levels of reactions and further better approach for diagnosis and treatment options of these reactions. Some of the previous studies implementing T1R severity scale are summarized in Table 1 with their important findings and limitation. However, the implementation of T2R severity scale has not been reported yet in any studies after the validation.

Conclusions and Way Forward

As the empirical treatment of both types of leprosy reactions are still symptomatic, intervention and development of therapeutic approaches is urgent which require systematic approach of defining the severities of reactions at initial diagnosis and the recording of the course of reaction during drug administration. Experience so far with the use of these severity scales to classify and monitor the anti-reaction treatment is limited. There is need to gain more experience about their usefulness in the hands of clinicians from different endemic countries/ regions so that duration and doses of anti-reaction agents could be better rationalized. It will not be proper to speculate but more appropriate to generate evidence for their appropriate use. Further

studies and wider experience will also help to improve these severity grading systems.

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