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Review Article

Detection and Classification of Leprosy : Future Needs and Strategies

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Abstract

This paper focuses on the obstacles and dilemmas in detection and classification of leprosy cases and suggested strategies for the same. This review attempts to raise some cardinal issues within leprosy diagnosis and the need for capacity building at clinical and field level in light of research conducted. It also recommends strategies to overcome these obstacles.

Key words : Detection, Classification, Diagnosis, Leprosy.

Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* and affects mainly skin, peripheral nerves, eyes and mucosa of the upper respiratory tract. There has been a decline in the global annual case detection rate for leprosy since 2001 (WHO 2006). The global burden of leprosy at the beginning of 2006 was 219,826 cases with only six countries with prevalence rate of greater than 1 per 10000 (Announcement 2006). Though India has been declared as having achieved leprosy elimination in 2005, a large proportion of international figures still come from India (WHO 2006). According to National Leprosy Elimination Program reports. a total of 137685 new leprosy cases were detected in the year 2007-2008 with Uttar Pradesh, Chattisgarh, West Bengal, Bihar and Maharashtra being the states with highest number of new cases. About half of the Indian leprosy cases are multibacillary (47.2%) (NLEP 2008).

New case detection rate is a measure which is said to be unaffected by changing case definitions and duration of treatment 'and hence is often used along with prevalence to review leprosy situation. Despite the drastic decline in prevalence of leprosy in endemic countries over the past decade, the fall in the new case detection rate has remained stable or shown increasing trends (WHO 2004). Numerous reasons including the increased awareness related to leprosy and increase reporting has been cited as reasons for this trend in the new case detection rate. Timely and accurate detection of leprosy is the comer stone of leprosy control, is important in case management, prevention of deformity and transmission of disease. Hence it is imperative to have capacity and clarity regarding diagnosis

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and classification of leprosy cases at the field level.

Use of the cardinal signs is the single most powerful and time-tested tool in the diagnosis *if applied diligently*. Currently timely detection of leprosy cases is largely dependant on efficacy of lEC programmes, public health system and patients health seeking behavior since the guidelines from the World Health Organization under the 'Global Strategy for Further Reducing the Leprosy Burden and Sustaining Leprosy Control Activities' limit the diagnostic and curative services for leprosy to the health facilities and active detection of leprosy cases in the community was no more recommended (Report of International Leprosy Association Technical Forum 2002). One of the concerns is the over simplified approach used to diagnosis and classification of leprosy. Most of the programmes use single cardinal sign presence of anaesthetic skin patch for diagnosis and skin lesion count for classification. Laboratory based time tested tools such as slit skin smears and histopathology are side lined as they are regarded as not very practical or do not add on to the sensitivity of diagnosis (Saunderson and Groenen 2000).

Early detection of leprosy is defined as diagnosis and initiation of treatment before the onset of nerve impairment (WHO 2000). However, the focus has now moved from early detection to timely detection which is neither too early nor too late.

Timely detection and classification of leprosy

Various systems of classification namely the WHO operational classification, the clinical classification and the histopathological classification are in use for classification of leprosy patients. Ridley and Jopling's classification proposed in 1966 classified leprosy patients into five groups TT, BT, BB, BL and LL based on clinical symptoms was amongst the earliest systems with remarkable scientific validity (Ridley and Jopling 1966). In 1982, the World Health Organization proposed the operation classification into multibacillary (MB) and paucibacillary (PB) cases. However, the heterogeneity of these classification systems often lead to ambiguity and misclassification. The paucibacillary category comprises of patients with indeterminate, TT, BT; BB and some early BL cases. Similarly the multibucillary group consists of BT, BB, BL and LL cases. Thus there is ample scope for misclassification of leprosy cases. Two large cohort studies conducted in India noted that about 60% of the new MB cases were smear negative and hence were likely to be overtreated due to the ambiguous classification (van Brakel et al 2008, Khambati et al 2008). Additionally, the focus on the number of skin lesions in the operational Classification robbed the field level staff of the essential clinical skills which help in recognizing the morphology and presentation of skin lesions typical of leprosy. Secondly there is absence of documentation of risk factors that identify the high risk groups for development of reactions, neuritis and deformity. The histopathological classification on the other hand is vulnerable to observer variations. Fine et al in their study in Malawi showed that there was greater agreement regarding classification than regarding diagnosis amongst three histopathologists who examined 100 biopsies (Fine et al 1993). However the operational classification does find its apt use in hyperendemic, resource poor settings where it is imperative to classify the patients into respective treatment groups. Similarly histopathological classification is significant from the epidemiological and

research point of view where there is need for stratification and in depth analysis. Both these systems of classification need to be used by a harmonizing approach rather than looking at them as exclusive (Lockwood et al 2007).

Studies have shown the crucial role of timely detection of leprosy in prevention of disability. While a majority of leprosy patients present with a single skin lesion (70%), about one third of leprosy patients do not have any skin signs signifying leprosy. In view of that scenario, it is imperative to disseminate the knowledge regarding the non-dermatological manifestations of leprosy and methods to identify them at the field level to facilitate early identification. Palpating just 2 nerves (the ulnar and the common peroneal) may permit diagnosis of as many as 90% of patients with any nerve enlargement. Referral of the suspected cases from this estimated 30% case load that does not have anaesthetic patches, to a health professional trained in palpation of peripheral nerves would be helpful in confirmation of leprosy and early initiation of treatment (Sundar Rao 2006). In Bangladesh and Ethiopia cohorts, 96% and 91% patients with multibacillary disease and 86% and 76% with paucibacillary leprosy disease had enlargement of one or more nerves (Groenen et al 2000, Saunderson and Groenon 2000).

The proposal that leprosy might be diagnosed by the presence of an anaesthetic skin lesion alone does not pass critical assessment (Britton and Lockwood 2004). Although 70% of leprosy skin lesions have reduced sensation, the non-anaesthetic 30% lesions occur in patients with multibacillary disease who are infectious and have a higher risk of developing disability than those with paucibacillary disease. Thus, the diagnosis of the latter is crucial. In addition, indeterminate leprosy lesions are not anaesthetic and early macular lepromatous lesions may not have loss of sensation and thus pose dilemma in diagnosis (Job 2007).

The World Health Organization's 'Global Strategy for Further Reducing the Leprosy Burden and Sustaining Leprosy Control Activities' recommends the presence of any one of the following three cardinal signs to be used as the diagnostic criteria for leprosy world wide :

a) Definite loss of sensation in a pale (hypopigmented) or reddish skin patch
b) A thickened or enlarged peripheral nerve, with loss of sensation and/or weakness of the muscles supplied by that nerve
c) The presence of acid fast bacilli in a slit skin smear (WHO 2005).

Reliability of these cardinal signs used for the diagnosis of leprosy has been extensively reviewed (Report of International Leprosy Association Technical Forum 2002). In Ethiopia, use of these 3 criteria for diagnosis of leprosy resulted in sensitivity of 97% with a positive predictive value of 98% for the diagnosis of leprosy. In Bangladesh and Ethiopia cohorts, 96% and 91 % patients with multibacillary disease and 86% and 76% with paucibacillary leprosy disease had enlargement of one or more nerves (van Veen et al 2006).

Skin smears taken to detect intradermal acid fast bacilli have high specificity but low sensitivity because about 70% of all leprosy patients are smear negative. Nevertheless, skin smears are important because they identify the most infectious patients and those at a higher risk of relapse (Lockwood 2002). Histological diagnosis when available is deemed the gold standard for diagnosis of leprosy. One of the major roles of neural histology is to elicit the presence of neural

inflammation which differentiates leprosy from other granulomatous disorders.

Classification of leprosy

One of the major concerns related to classification of leprosy patients is the over simplified approach used to diagnosis and classification. Most of the National Health Programmes in leprosy endemic countries use a single cardinal sign, presence of anaesthetic skin patch for diagnosis and skin lesion count for classification of these patients. Laboratory based time tested tools such as slit skin smears and histopathology are not given importance as they are regarded either as not very practical or do not improve the sensitivity of clinical diagnosis (Saunderson and Groenan 2000).

A study on 77 patients with one to five lesions of leprosy were studied by Rao et al (2006). 4/58 patients (7%) with less than or equal to five skin lesions showed BL leprosy on histopathology classifying patient by body area was also not found to be perfect. In addition 6/59 (10%) with less than 2 body areas showed MB histopathology. Even after combining these 2 parameters there were 4 patients (7%) with histopathology of MB leprosy. This study emphasizes the vainness of simplified classification of leprosy which can lead to under diagnosis and hence encourage transmission in the community from unidentified cases (Srinivas and Rao 2002, Rao et al 2006).

Another issue in classification is the need of a tool for differentiating between post-MDT reactions and relapses which have similar clinical presentation and serious implications (Shetty et a1 2001).

Diagnosis of single skin lesion paucibacillary cases

Single skin lesion cases (SSL- PB) form a large proportion of new paucibacillary cases. Currently they are considered not of significant consequences. A study by Rao et al showed the high proportion of borderline tuberculoid leprosy in cases with single skin lesion (Rao et al 2006). Similar findings were elicited in a recent study by the Foundation for Medical Research to detect previously undetected cases in the community in Maharashtra 'where out of a total of 48 patients with single skin lesions, 30 were found to have borderline tuberculoid leprosy, one was BB, five were borderline lepromatous where as 11 were indeterminate leprosy cases on histopathological investigation (Shetty et al, submitted for publication). This indicates the high infectiousness of these SSL cases and points to the likely consequences of neglecting such cases on the transmission of leprosy.

Diagnosis of Pure neural leprosy patients

Diagnosis of neural leprosy cases by a single cardinal sign of enlarged nerve with or without nerve function impairment (NFl) is not justifiable. In India and Nepal approximately 5% of patients (van Brakel and Khawas 1994, Mahajan et al 1998) were found have pure neural leprosy with no anaesthetic patches. Enlarged nerve with or with out nerve function impairment (NFl) is the only diagnostic criteria recommended. Though a study by Suneetha et al (1998) revealed that all the pure neural patients had histological confirmed diagnosis of leprosy, there are reports to the contrary. A clinical and histopathological study of thickened nerves in a leprosy endemic region, leprosy was confirmed in only 5/16 (31 %) patients. A retrospective analysis to differentiate clinically between the leprous and non-leprous patients did not reveal any useful information (Srinivas et al 1980).

In our centre in group of 19 referral patients with clinical features of pure neural

leprosy (received between Jan. and Dec. 2007), an involved nerve and overlying skin biopsies were studied in all, to confirm the disease. Leprosy was confirmed in 11 (58%), while in the remaining 8 patients (42%) biopsy of the involved nerve did not confer to leprosy. It was also interesting to note that in the 11 confirmed patients of pure neural leprosy, skin over lying the nerve also showed pathology closely resembling the type seen in the nerve, where as in 8 patients with no evidence of leprosy in the nerve showed only mild nonspecific changes in the skin. These observations strongly suggest that leprosy diagnosis in pure neural patients cannot be relied on clinical signs alone. Secondly the value of a skin biopsy in such patients can be considered (unpublished).

Additionally, the studies conducted by INFIR and FMR in India examined 303 and 400 new MB leprosy patients respectively and found that even in patients with no clinical signs of reaction, nerve tenderness, clinically evident nerve function impairment or symptoms like nerve pain, definite evidence of silent sensory and/or motor neuropathy was present. Thus sensory and motor impairment detected by monofilament testing and voluntary muscle testing represents only the tip of an 'iceberg of neuropathy' in leprosy (van Brakel et al 2008, Khambati et al 2008) .

Lack of efficient surveillance system for relapse and treatment dropouts

With the introduction of new untested short term treatment regimen (WHO 2002), it is imperative to record the number of relapse cases. There is no surveillance system to record the number of relapse cases occurring in the community. In addition there is no recording and tracking system in place to access the number of patients who discontinue their treatment. This is a matter of concern in view of the public health risk posed by the likelihood of infectiousness of the active relapse and treatment fall outs.

Leprosy in nonendemic areas

Amongst new leprosy patients seen during 1995 - 98 at the Hospital for Tropical diseases, London, diagnosis had been delayed in more than 80% of patients. These delays had serious consequences for patients, with over 50% having nerve damage and disability. This was attributed to atypical presentation of the cases (6/28), patient related factors and health system related factors (Lockwood and Reid 2001). Often leprosy was misdiagnosed in these patients as a dermatological, neurological or rheumatic condition and this phenomenon is not uncommon. However the anaesthetic skin lesions seen in leprosy are unique to the condition.

Lack of capacity in diagnosing reactions

It is a known fact that a relapse case in a paucibacillary leprosy patient is difficult to distinguish from a reversal reaction (WHO 1988). Leprosy is a complex immune response mediated mycobacterial infection. It is observed that 30-50% of multibacillary leprosy patients experience acute inflammatory reactions affecting skin and nerves. Reactions in leprosy patients if untreated can have grave biological as well as social implications. In urban Hyderabad district, it was observed that knowledge regarding leprosy was significantly lower amongst other health cadre (nurses, multipurpose workers, auxiliary nurse midwives, pharmacists) compared to medical officers (Rao et al 2007). A study conducted by FMR also revealed that there is a high proportion (35%) of undiagnosed reactions in leprosy patients at the community level (unpublished). This points to the need for capacity building with regards

to diagnosis of type I and II reactions in leprosy patients within the public and private health care systems among all cadres of health personnel.

Use of recent technologies in leprosy diagnostics

Development of newer techniques and improvement and refinement of old techniques for diagnosis of leprosy are now being undertaken. Demonstration or localization of *M.leprae* and its antigens in the lesions further increases the specificity as well as sensitivity of diagnosis. Use of Cuper May's fluorescent method (Nayak et al 2003), immunoperoxidase technique with anti BCG polyclonal antibodies (Schetinni et al 2001), demonstration of PGL-1 antigen (Weng 2000). Tissue level localization of antigens of *M.leprae* using more specialized polymerase chain reaction (PCR) and RTPCR, technique have markedly increased the sensitivity (Katoch et al 2007). PCR methodology is now being developed to detect presence of a small number of *M.leprae* its DNA/RNA in the skin smears (Jadhav et al 2005). They can serve as an important/sensitive tool in timely diagnosis and classification.

Development of improved diagnostic tool that are able to detect *M.leprae* infection before clinical manifestations arise and distinguish *M.leprae* infection from infection with other mycobacteria, is an important area where a considerable progress has been made.

In the search of *M.leprae* specific antigens, Araoz et al (2006) used bioinformatics and comparative genomics to identify potentially antigenic proteins for diagnostic purpose. This approach defined 3 classes of proteins

(1) Those restricted to *M.leprae* (class I)

(2) Those present in *M.leprae* with orthologues in other organisms (class II)

(3) Exported or surface-exposed proteins (class III).

Twelve genes (2 class I, 4 class II and 6 class III) proteins were cloned in *E. coli* and their protein products were purified. The immunogenicity of each recombinant protein was then investigated in leprosy patient by measuring the reactivity of circulating antibody and TFN –gamma response in T-cell re-stimulation assays.

One of the lessons learnt from studies is that to in order to design a diagnostic test that is both sensitive and specific for leprosy it is likely that multiple antigens or peptides will have to be incorporated as a mixture or as a polyprotein because it has been shown that the use of multiple antigens increases the frequency of responses in infected individuals (Spencer et al 2005). It should be possible to combine a number of these peptides to formulate a highly sensitive and specific cell–mediated test that will allow timely and rapid diagnosis of leprosy.

IDEAL (initiative for diagnostic and epidemiological assays for leprosy) a consortium established following a WHO/TDR sponsored workshop in Amsterdam in Oct 2003, is working on strategies for development of new diagnostic and epidemiological assays, based technical advances. At the moment the network consists of nearly 30 partners from all continents. IDEAL is concentrating on different recombinant proteins including some fusion proteins employing IFN-gamma assay to develop candidate proteins with promising discriminatory power and specificity and to obtain new specific *M.leprae* antigens to improve the serological diagnosis of leprosy (Aseffa et al 2004).

Future needs and strategies

It is evident that India still has a large number of leprosy cases with about

0.1 million cases detected in the past year. Many diagnostic Issues hinder the correct and timely diagnosis and classification of leprosy. Delayed and missed diagnosis of infectious patients of leprosy and lack of tests to measure asymptomatic *M.leprae* infection in contacts also hamper the assessment of transmission of *M.leprae* infection An important goal would be the development of improved diagnostic tools for instant diagnosis in atypical cases and to detect *M.leprae* infection before clinical manifestation (Sekar 2007). There is also need for development of laboratory tools to evaluate response to treatment and identify patients at high risk of developing lepra reactions and nerve damage. It is also imperative to have more social science studies to understand the help seeking behavior of leprosy patients as that has direct relevance to early diagnosis in terms of provision.

At the field level, we need to redefine the set of diagnostic skills required by health workers in identifying leprosy patients and in particular pure neural leprosy along with identification of reactions and relapses.

Conclusion

Use of cardinal signs is the single most powerful, cost effective and time tested tool for diagnosis and will remain as such in future. Slit skin smear should be made an integral part of leprosy program. With supervision and periodic cross checking it was possible to produce high quality and dependable skin smear reports. Histopathological findings which are not considered relevant for diagnosis and treatment purpose should be given a status in the diagnosis, characterization, and assessment of severity of the disease.

Ongoing efforts to improve the sensitivity and specificity of potentially important tools must continue, must be encouraged and field-tested.

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