Editorial Commentary

Challenges in Leprosy: Suggestions on the Way Forward

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Leprosy is a chronic mycobacterial disease. It has existed since times immemorial and has been described in all ancient literature worldwide. It has been eliminated as a public health problem (as per WHO definition) at the national level in India in December 2005.[1] There was more than 96% reduction in disease prevalence then. Since then, the NLEP programme has been integrated with the general health services of the country and stigma due to the disease has decreased (which was mainly due to the disabilities), although self-stigma is still prevalent, but declining. New cases are being reported in the programme at nearly a constant rate in the past one and a half decades. Several districts in India still report a substantial incidence of new cases and childhood cases and a high incidence of disabilities in new cases. These all signify continued transmission and late diagnosis of the disease.

The challenges which still remain and are being discussed are: accurate and timely diagnosis, optimal assessment tools to monitor disease activity during and after release from treatment, timely diagnosis and treatment of reactions, disabilities, and lack of effective agents for prophylaxis and prevention of the disease.

Diagnosis: At present the diagnosis of the disease is based mainly on the clinical signs of involvement of skin and nerves and no laboratory diagnostic test is required. The organism is still not cultivable in vitro and light microscopy examination of slit skin smears for acid fast bacilli (AFB) is not required for diagnosis and classification in the programme. This test is otherwise also negative in paucibacillary (PB) as well as in a proportion of multibacillary cases (MB). In addition, due to low sensitivity as well as reproducibility, it has been done away with and diagnosis at present which is solely based on the skin lesions with variable grades of loss and/or diminished sensations, their number, as well as the number of nerve/nerve trunk involvement on palpation. Although careful clinical examination and history taking can no doubt diagnose most cases, diagnostic tests are still required and more so in early lepromatous cases, indeterminate cases, and cases which present for the first time with reactions, etc. Precious time is lost in such cases before diagnosis and initiation of effective treatment which is important for the prevention of disabilities and early interruption of transmission.

Moreover, with dwindling case load, not much emphasis is given to diagnosis and treatment of leprosy in comparison to other more prevalent lifestyle diseases. Fresh medical graduates and students rarely see and discuss the disease and not much emphasis is given to it in the qualifying exams also. As a result, most of the young generation of professionals are not adequately acquainted with the disease. Emphasis needs to be given in medical colleges and professional courses in identifying the clinical signs and symptoms of the disease, including palpation of nerves and their assessment.

Advances in molecular methods and use of Polymerase Chain Reaction (PCR) technology have revolutionized the diagnosis of several diseases including mycobacterial diseases. Several PCR methods have been assessed using *M leprae* specific targets to detect the nucleic acid of the organism/antigen in clinical specimens for definitive diagnosis of the disease.[2-7] Detection of specific repetitive elements in leprosy genome (RLEP) sequence of *M leprae* in skin biopsies, tissues, and skin smears is specific for leprosy, sensitive, and does not cross react with other mycobacterial and bacterial species.[2-5] RLEP is a repetitive DNA sequence of *M leprae*, present as 37 copy numbers and is specific to *M leprae*.[5] The use of RLEP PCR in skin smears and biopsy specimens provides a specific laboratory diagnostic tool and has shown to be positive in more than 70-80% of clinically diagnosed PB cases and

more than 95-99% in MB cases.[2-5] The test is user friendly and PCR machines are available at the district level and in some states also up to the Community Health Centre (CHC) level. The test is sensitive, commercially available, and can be used as an early definitive diagnostic tool directly from smears as well as from fresh and stored biopsy and tissue samples.

In very early disease, the clinical symptoms of loss/ diminished sensations are not often clear and the signs are subtle. Histopathology does help but several times the diagnosis cannot be made with certainty. In such cases, in situ hybridization (for gene sequences and antigens) and PCR directly detect the *M leprae* gene sequences/products antigens, which are suitably stained and examined to clinch the diagnosis.[6,7]

Both cutaneous nerves and nerve trunk thickening are observed in leprosy and need to be looked, palpated, and assessed for diagnosis of the disease as well as preventing disabilities. Often, few of the present generation of professionals/dermatologists tend to overlook these and in some cases the diagnosis of the disease is missed and crucial time is lost with resulting nerve function loss and disabilities. Ultrasonography and colour doppler imaging are objective imaging tools for assessing nerve involvement in leprosy and need to be objectively used.[8-10] Ultrasonography is now available at towns, district headquarters, and several state health facilities and can be used for early diagnosis and monitoring the progress of the disease.

WHO recommends notifying as well as estimating grade 2 disabilities due to leprosy. Grade 1 disabilities, type 1 reactions, and early inflammatory signs in nerves and skin lesions are not given their due attention and not reported/ documented. In a large majority of cases, grade 2 disabilities are preceded by signs and symptoms of grade 1 disabilities and type 1 reaction. Timely detection of these and optimal treatment can prevent grade 2 disabilities and need to be taken up urgently by the practitioners and the program to reach the target of no disability due to leprosy.

Monitoring disease: In the NLEP program, usually the program is satisfied if the PB and MB patient respectively, have completed 6 doses of PB regimen in 9 months and 12 doses of MB regimen in 18 months. The patient is then certified to have completed treatment and removed from the active case roll. Further follow-up is not done in the program. If the patient again reports with signs of activity, reaction, and/ or relapse, usually steroids are administered for late reactions and another course of MDT is given for suspected relapse. With advances in immunology as well as molecular biology the disease is better understood and tools are available for better management of cases. PGL 1 and LAM B (antigens specific for *M leprae)* antigens/ antibody responses to specific epitopes can be assessed by ELISA and Lateral Flow Tests,[11,12] which have been found to fall with the decreasing bacterial load and response to therapy. However, they need to be done sequentially during treatment, at completion of treatment, and also after release from treatment (RFT) to be useful for monitoring treatment and response.

Molecular tools are more specific and sensitive and detection of specific RNA of *M leprae* (16sRNA) is linked to live bacilli and therefore active disease.[13] In several cases of reactions this could be demonstrated in tissue biopsies, warranting addition of MDT with steroids.[14] In the environment (surface water, soil, and water collected around dwellings of active cases), it has been detected for longer time durations indicating that the environment could be acting as reservoirs of infection and continued transmission of the disease.[4,13] It is possible that some intermediate hosts like amoeba/hydra exist, which may be acting as reservoirs/intermediate hosts and contribute to continued transmission of the disease. Studies on these aspects are continuing.

Drug resistance: Although drug resistance in leprosy after use of MDT is not as problematic as in tuberculosis, caution and surveillance strategies are required. As *M leprae* is not cultivable and animal models like limited growth in mouse footpad is no longer available (due to high costs, long time interval for reporting of results, as well as dedicated laboratories required for assessment) for routine clinical use; detection of antimicrobial drug resistance for leprosy involves molecular testing for drug resistance. This is recommended and carried out in different countries. Using DNA sequencing and PCR technology, genetic markers for drug resistance in leprosy have been standardized for Dapsone (folP), Ofloxacin (gyrA), and Rifampicin (rpoB) and are used for antimicrobial drug resistance surveillance (AMR) for leprosy.[15-18] This is done

using both skin smears as well in tissues and biopsy specimens. A standardized protocol has been established and is used for AMR activities. This network of laboratories is recognized by Central Leprosy Division of Government of India but needs to be expanded.

Optimal treatment regimens: The wide spread use of MDT revolutionized the treatment as well as the perception of leprosy. Drug resistance to Dapsone has decreased and several countries could achieve elimination target, including India. However, a substantial number of patients were not satisfied at the end of 6 months (PB patients) and 12 months treatment (MB patients), respectively. They continued to have reactions before, during, and even after release from treatment. Disabilities continue to occur, lost sensations do not recover, coupled with poor knowledge and empowerment of patients themselves, the affected patients continue to suffer from the complications and disabilities of the disease. Most of the attention has been focussed on the shortening of treatment duration rather than taking care of the above complications and disease sequelae. From 2010-2012 onwards, NLEP has focussed attention on disability prevention, mobilization, and reconstructive surgery (DPMR) activities and patients are examined and encouraged to undergo reconstructive surgery. The NGOs and missionary hospitals lead the way in undertaking these. NLEP also incentivised the process by giving monetary relief to the hospitalized patients during surgery, taking care of the man days lost, and providing incentives to hospitals participating and operating on these patients so that they could build up their resources.[19] Besides, Information, Education, and Communication (IEC) activities were intensified, and patients and patient attendants were taught how to take care of their insensitive hands and feet. They were provided with dressings and splints. After 2015, NLEP[20] in India intensified new case detection campaigns, contact tracing, IEC activities, and focussed leprosy campaigns to detect early cases and treat them. The program has resolved to at least have no disabilities in new leprosy cases. Grade 2 disabilities are notified in the programme but not much emphasis is given on nerve involvement and reporting of grade 1 disabilities as well as reactions. Due attention and emphasis needs to be given to nerve assessment and reactions to take care of the disabilities and prevent their occurrence. Optimum care and assessment of nerve involvement/impairment and partially and inadequately treated reactions (both type 1 and 2) needs to be undertaken as these ultimately lead to grade 2 disabilities and resulting lifelong hardships. Type 1 reactions are usually as a result of changes in cell mediated immunity (CMI) as a response of the host to the invading organism while type 2 (ENL reactions and neuritis) are mainly because of disequilibrium of humoral immunity as a response to the infection.

Anti-mycobacterial drugs: Newer analogues of Rifampicin, Thiomides (Prothionomide and Ethionamide), Clarithromycin, Fluoroquinolones (Ofloxacin and Moxifloxacin), Minocycline etc have been shown to be active against leprosy. Due to their high cost, side effects, and availability they are not used routinely for treatment purposes and are usually reserved for treatment of multi drug resistant leprosy and non-responders.

Clofazimine was first described for tuberculosis, and was found to be equally effective in leprosy also. Besides its antimycobacterial activities, it also has anti-inflammatory activities and helps in treatment of the disease as well as its reactions by modulating the host response. Its usefulness and acceptability in PB disease was demonstrated in a double blind study in comparison to standard PB regimen (6 months of daily Dapsone and 6 monthly Rifampicin).[21] The patients in both the groups were followed up for 2.5 to 3.5 years post treatment. There was statistically significant difference in subsidence of persisting activity,[21,22] late reactions, and relapses in patients on Clofazimine + WHO PB MDT as compared to the PB WHO regimen.[21] This is the new PB regimen endorsed and recommended by WHO in the recent guidelines for diagnosis, treatment, and prevention of leprosy, 2018. It is well tolerated and reduces the severity and incidence of reactions in all types of patients. Thus, we have a common regimen of DDS + CLF + RIF for all types of leprosy with varying duration i.e. six months for PB and one year for MB patients.

Immunotherapy as an adjunct to MDT: Several immunomodulators including Mw, BCG etc have been found to be useful in improving the treatment in leprosy.[24] Among these *Mycobacterium indicus pranii* (MIP; previously known as Mw) is the most promising. Its a rapid growing, saprophytic, non-pathogenic mycobacteria and

shares several antigens with *M leprae*. It is an immunomodulator approved by DCGI for leprosy and is available as heat killed preparation in the market. It has been tried with MDT in both PB and MB patients, with very encouraging results. Several investigators have observed and reported the beneficial effects of MIP when combined with MDT and reported faster smear conversion, decrease in severity and number of reactions,[25-29] faster healing of lesions and also faster loss of viability of bacilli when tested in mouse foot pad as well as by ATP estimation of the bacilli isolated from tissues and biopsies.[26,28] Histologically also there is decrease in granuloma fraction and healing.[26,30,31] No disabilities were observed in post treatment follow-up of about 10 years.[26]

The study for borderline leprosy patients was a double blind, placebo controlled, two armed study which included the study arm (MIP with MDT) given 2 doses intradermally on day zero and at end of therapy in borderline tuberculoid (BT) leprosy and 3 doses of MIP (day zero, after 6 months, and at end of therapy i.e.12 months). There was faster decrease in activity in the skin lesions, persistence of activity in few patients at the end of treatment subsided on its own, return of sensation occurred in a statistically significantly larger number of patients on MIP + MDT, no late reactions occurred in this group, and no disabilities were observed in post treatment follow up of around 5 year.[31] The patients in the study became smear negative faster, the incidence and severity of reaction during treatment was less and very few late reactions occurred after release from treatment. Histologically, the granuloma fraction decreased faster and was replaced by non-specific cells. In the MDT + placebo group, the fall in BI was slower and reactions occurred during and after release from treatment in larger number of patients. The granuloma fraction declined slowly and was present in a significantly larger number of patients after completion of treatment.[31] However, there were no disabilities in this group too. The results, therefore, show that MIP immunotherapy acts as an effective adjunct to MDT, is safe, approved and is available in the market, and well tolerated.

Prophylaxis: Leprosy has a long and variable incubation period and is associated with important clinical as well as social consequences. Contacts of multibacillary leprosy patients are 5-7 times more prone to develop leprosy as compared to the general population. The initial strategy is therefore, aimed at protecting them.

Chemoprophylaxis: The possibility of using Dapsone in lower dosages for contacts of active leprosy cases to prevent development of active disease in them existed since the pre-MDT era. After successful use of MDT, the focus has shifted to single dose Rifampicin therapy (SDR) for chemoprophylaxis.[32] Although initial beneficial results have reported in reducing the incidence of leprosy, careful follow-up of the contacts for long duration needs to be done. Moreover, before administration of SDR, tuberculosis has to be ruled out which is some what difficult as most countries that are reporting leprosy cases are also endemic to tuberculosis. It was further also observed that those contacts who had a BCG scar and BCG was given at birth and who were administered SDR were better protected than those without BCG scar.[33] The role of SDR needs to be studied more extensively as single dose of Rifampicin has a half-life of 2-8 hours and what will happen if the contact is later exposed to leprosy or organisms persisting in the body multiply later as Rifampicin will kill only the actively multiplying organisms. Considering these drawbacks, PEP++ (post exposure prophylaxis) has now been advocated.[34] For the PEP++ intervention study, an enhanced regimen comprising three doses of Rifampicin 600 mg (weight adjusted when given to children) plus Moxifloxacin 400 mg given at four-weekly intervals (day 1, day 29 and 57 day) over 8 weeks is proposed (for children and for adults with contraindications for Moxifloxacin, Moxifloxacin is to be replaced by Clarithromycin 300 mg).

Immunoprophylaxis: Although it is known that BCG also protects against leprosy[24], the fact remains that leprosy is still detected in countries where BCG is given. Therefore, other agents besides BCG are required to protect against leprosy in these countries. MIP is administered as a killed vaccine, shares several antigens with *M leprae*, can provoke an immune response, is licensed by DCGI in India as well as FDA, and is available in the market. It also has been tried in contacts of MB cases in large field based studies[35], is safe, and well accepted. It is also one of the vaccines which is promising and recommended for use in leprosy by WHO 2018[23] recently. The protection observed was up to 69% at the end of 6 years but diminished to 30% by end of

10 years.[34] For prophylaxis it is recommended to re vaccinate after 5 years for long time protection. It is an economically viable Indian vaccine, available, and is cost effective; the discounted ICER has been estimated as Rs 73,790 per QALYs gained over a five-year time.

CONCLUSION

Several options are available for early diagnosis of leprosy, nerve involvement and damage; treatment modalities (some recommended to be followed by WHO); taking care of patient satisfaction; and prevention of reactions. These combined with better AMR activities, surveillance of treated patients, and IEC activities are the requirement of the day to meet the challenges of this age-old disease. Nonetheless, more research is also required to unravel the mysteries of this disease.

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