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Report of TLMTI Symposium

Relapse and Drug Resistance in Leprosy: Present Scenario and Critical Issues

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The above symposium was organized by
The Leprosy Mission Trust India (TLMTI)
on the 29th November, 2017 at Delhi, India

The symposium was organized by The Leprosy Mission Trust India (TLMTI) on the 29th November, 2017 at India Habitat Centre, Lodi Road, New Delhi, India. The meeting was organized for the stakeholders who are engaged in the leprosy elimination programme for an exposure to the recently emerging scenario on relapse and drug resistance in leprosy. A total of sixty three participants including representatives from Government of India, WHO, ILEP, GLRA, LEPRA India, NLR, DFIT, BLP, FMR, NIMHANS, ICMR-NJIL & OMD and ICMR gathered in the symposium. Most of the famous advisors of the country, leprologists and dermatologists of TLM, Safdarjung, Guru Tegh Bahadur hospitals, PGIMER (Chandigarh, India), DLO and SLO of Delhi participated in the symposium. Leprosy researchers and scientists from different organizations across the country also gathered for the deliberations and discussions. The symposium began with a welcome address from the Executive Director, TLM which was followed by inaugural keynote addresses by the experts of the country. Scientific deliberations by the leprologists, dermatologists and laboratory researchers were divided in four main sessions. This symposium had presentations on most current areas of importance such as goals and achievements of NLEP; diagnostics with focus on different forms of disease including neuritic leprosy; newer methods such as imaging for studying CNS involvement; response to therapy; drug resistance in the context of relapses, poor responders, reactions and multibacillary leprosy, transmission, methods and strategies for detection of drug resistance and its surveillance; national and global perspective etc. The Symposium concluded with a plenary session for the road map of a future strategy with recommendations which include molecular detection of drug resistance with focus on relapses, reactions and MB leprosy; confirmation of relevance of novel mutations in animals; networks for drug resistance surveillance and epidemiology of drug resistance in leprosy.

Abbreviations : *WHO - World Health Organization; ILEP - International Federation of Anti-Leprosy Associations; GLRA - German Leprosy Relief Association; LEPRA - British Leprosy Relief Association; NLR - Netherlands Leprosy Relief; DFIT - Damien Foundation India Trust; BLP - Bombay Leprosy Project; FMR - Foundation for Medical Research; NIMHANS - National Institute Mental Health & Neurosciences; NJIL & OMD - National JALMA Institute for Leprosy & Other Mycobacterial Diseases; ICMR - Indian Council of Medical Research; PGIMER - Postgraduate Institute of Medical Education & Research; DLO - District Leprosy Officer; SLO - State Leprosy Officer*

Session I - Inaugural Session

Dr. Mary Verghese, Executive Director, TLMTI, India in her introductory remark presented the ***"Purpose of the Symposium on Relapse and Drug Resistance"***. She mentioned that India is going through a crucial stage of elimination of leprosy. India attained the elimination figure of prevalence less than 1 case per 10,000 population size in December, 2005. However, the number of annual new case detection rate (ANCDR) is maintained almost at the same rate and is varying between 10.35 and 9.71/100,000 population for the last five years. Child case rate did not also decline and the rate varied between 1.0 and 0.89/100,000 during these years. All these figures indicate that transmission of leprosy is still continuing in spite of effective multi-drug therapy (MDT). There may be several reasons for the maintenance of transmission. One of the reasons is due to the occurrence of relapse in leprosy. Although from the records of National Leprosy Eradication Programme (NLEP), India these are not too many, however, in a tertiary hospital these cases are not uncommon to notice. In field situation a relapse case will be identified very late because of integration of the vertical leprosy programme with the general health services and consequently there will be delay in reporting of leprosy case either to the PHC or to the tertiary care hospital. Because of this delay, the relapsed leprosy case will serve as a source of infection to the community. Further, it has been well established that most of the relapses are from highly bacillated multibacillary cases. It has also been shown by several groups that a very small proportion of these cases are resistant to anti-leprosy drugs. The delay in reporting might lead to transmission of a drug resistant *M. leprae* to a naïve population. Hence, there is a need for vigilance for identification and treatment of such cases as early as possible so that transmission of *M. leprae* infection remains on check.

Reaction in leprosy is another issue which has often been confused with relapse. Reactions may often land up with increase in bacillary load and has been shown to appear with high copy numbers of *M. leprae.* Therefore, reactional cases should be also identified as early as possible for quick management and treatment to check transmission of infection in the community.

Dr. Mary mentioned that TLMTI has organized this one-day Symposium for presentations from the authorities of NLEP, World Health Organization (WHO), experienced clinicians who are engaged in the treatment of leprosy and the laboratory researchers who are engaged in research. She mentioned that this platform today will provide enough scope to discuss the issues and set directions and recommendations to benefit the elimination programme of the country.

The Inaugural address was delivered by Dr. Anil Kumar, DDG (Leprosy), DGHS, MoHFW, & Head of NLEP on "*Current activities of the National Leprosy Eradication Programme (NLEP)*". He mentioned that after attainment of the goal of elimination figure in December, 2005 the focus was shifted from active case detection to the mode of passive detection of leprosy cases. However, it was realized later that the trend of two important indicators of NLEP, i.e., ANCDR and PR remained static since 2005 and visible deformity rate of 1.87% in 2006 increased to 4.60% in 2016. Considering the abovementioned reasons several innovations were made during 2016 and 2017 by adopting three pronged strategies: (i) Leprosy case detection campaign (LCDC) (specific for high endemic districts); (ii) Focused leprosy campaign (for hot spots of rural and urban regions where grade II disability is

detected); and (iii) Special plan for hard to reach areas. Further, to make a dent on the prevalence of stigma, leprosy awareness campaigns have been organized from 2018 on the Anti-Leprosy Day (30th January). In order to reduce transmission of *M. leprae* infection in the community chemoprophylaxis of contacts with single dose of rifampicin has been initiated in endemic districts wherein LCDC has been implemented. He further mentioned that due to these interventions the grade II disability rate has declined within 2 years' time from 4.6% to 3.87%.

With regard to relapse and drug resistance NLEP has already conducted a workshop and a work plan has been drawn up with a built-in surveillance mechanism to cover the whole country.

Dr. Laura Gillini, Medical Officer, Global Leprosy Programme, World Health Organization deliberated on *"Antimicrobial-Resistance of Leprosy: Global perspective"*

Dr. Gillini mentioned that the establishment of a network for global surveillance of drug resistance in leprosy was primarily to keep a close vigil on the drug resistance scenario at many vulnerable settings. To accomplish this, WHO developed a simple guideline to carry out sentinel surveillance and this initiative was expected to be conducted annually on a routine basis. This initiative will be coordinated by WHO' Global Leprosy Programme with support and collaboration from national programmes and major research institutes around the world.

Among 1862 (1086 relapse and 776 new) cases studied, 127 (6.8%) *M. leprae* strains were found with mutations conferring resistance to rifampicin, dapsone or ofloxacin. Rifampicin resistance was observed in 12 countries, both among relapses (57/1086, 5.2%) and among new cases (16/776, and 2.1%). No case was detected with both rifampicin and ofloxacin resistance. Weaknesses of the sentinel surveillance were mainly, very partial coverage (very limited proportion of cases globally tested), mostly focused on already treated cases (relapses), no clear network design including for quality control purposes, variability of laboratory methods used (which makes standardization and the quality control difficult) and no clear information flow and lack of national registers/repository for drug resistance data.

New definition of relapse given by WHO: Patient who has completed a full course of treatment and who returns with signs and symptoms of the disease that are not deemed due to a reaction.

The key note address on *"Relapses and drug resistance in leprosy: key issues"* was delivered by Dr. V. M. Katoch, NASI-ICMR Chair at RUHS, Jaipur & Former Secretary, Department of Health Research, Govt. of India and former Director General of Indian Council of Medical Research, New Delhi.

Dr. Katoch gave an account of the implementation of MDT and the remarkable achievement that has been made in the leprosy control programme throughout the world.

He mentioned that most of the relapses are due to growth of drug sensitive organisms and have been re-treated with standard MDT regimen. Issues in case of relapses have been linked to inadequacy of treatment for a particular case/ sub-section of cases with a particular regimen and robustness of classification approach and everlasting problem of differentiation of relapses from reactions – mostly an ideological problem and not adequately addressed the issue on a proper scale. Today we have good tools to distinguish relapse from re-infection which is important from therapeutic and public health management angles. It is perhaps the opportune

time to properly analyze these issues dispassionately and provide evidence based guidelines for implementation, if required for research as well.

Regarding the drug resistance in leprosy a number of these cases were earlier ascribed to monotherapy and erratic management, however, quite a few of them are instances of primary resistance to drugs including Rifampicin (RIF) and fluoroquinolones. Report of many such cases specially from TLM network has raised an alarm in India also. At global level, surveillance systems are being put in place. WHO is playing necessary coordination role. India which had earlier started studying the problem in project mode is now embarking upon a well-organized network surveillance programme for detection of drug resistance in leprosy. Besides the robustness of epidemiological approaches, proper understanding of technology used for detection of drug resistance is also important. Mouse foot pad assay is available only in selected centers in India, is applicable to very small proportion of bacillated cases, is time consuming and has issues of cost effectiveness also. Because of these reasons, molecular assays have been explored as these have been shown to be applicable to low bacillated clinical specimens directly including slit smear specimens. Approaches include gene amplification of target regions (drug resistance determining regions) followed by hybridization with specific probes, PCR-SSCP, other mutation detection methods, real time PCR and sequencing. While resistance can be detected fairly well in most of cases of RIF resistance, to a large extent in case of Dapsone, there are problems in case of section of quinolone resistance, clofazimine, minocycline and clarithromycin in case of leprosy. There is still a great need to generate more evidence to correlate many new mutations in cases of RIF and fluoroquinolones with resistance phenotypes.

He also mentioned in detail different drug regimens for the management of drug resistance cases. He further emphasized that different drug combinations being considered today would be tentative at this stage. Proper documentation and periodic analysis of experiences of various regimens will be essential to develop robust guidelines for drug resistant leprosy in future.

Session II – Diagnosis and Treatment

"Limitation of cardinal signs in the diagnosis of MB leprosy" **-- V. Ramesh, Safdarjung Hospital, New Delhi**

Over the years the three cardinal signs of leprosy, out of which practically only two were being followed, have certainly helped in the diagnosis of leprosy. This has greatly brought down the leprosy load in terms of the numbers affected and helped in the elimination of the disease. The next step is to eradicate the infection in the population. This involves stopping the transmission of infection so that fresh cases decrease noticeably. However what is happening is that the new case detection rate is not showing such a trend. It is also being seen that the number of multibacillary (MB) patients of leprosy being reported is on the rise, contrary to the dominance of paucibacillary cases during the period prior to elimination. This does not mean that the medical personnel and the programme managers are failing in their job. What is less realized is that the MB patients are not being detected at an early stage. This is because their disease does not exhibit the manifestations that fall into the cardinal signs. Leprosy is a disease with protean manifestations and the time is ripe for looking at the disease beyond what is described as the cardinal signs. MB disease can present in the early stages with less sensory dysfunction or nerve thickening. The

disease can also present as reactions for the first time. Suspicion should be foremost and this is where the role of dermatologists is undeniably needed to train the medical and paramedical personnel. The performance of the simple slit-skin smear examination is an invaluable aid in clinching the diagnosis. At the same time misdiagnosis can also be avoided as many dermatoses can mimic MB leprosy.

The development of drug resistance, a neglected aspect of leprosy treatment, would pose a bigger problem if MB patients are diagnosed late or incompletely treated. Currently most major hospitals and medical colleges have no guidelines for using any facility to diagnose drug resistance. Relapse and re-infection have frequently been incriminated in situations where the lesions reappear following treatment.

Dr. Atchayram Nalini: What are the criteria for smear and biopsy in case of diagnosis of leprosy?

Dr. V. Ramesh: There are no specific criteria. Both can be done depending on the availability of the resource for the purpose of diagnosis.

Dr. Kiran Katoch: One could also perform molecular method of diagnosis with RLEP PCR from skin smear in addition to staining because many of the BI negative cases will be positive for *M. leprae.*

"Pure or Primary Neuritic Leprosy" - Dr. Bhushan Kumar, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh

Leprosy is primarily a disease of the nerves but subsequently involves the skin. Leprosy is a disease of great variability – sometimes with primarily skin involvement and sometimes more nerve involvement and related anesthesia and deformities. In about 4-8% of the cases the clinical presentation is exclusively with nerve involvement in the form of nerve deficit and / or nerve thickening without any cutaneous lesion, with negative skin smears and no other identifiable pathology. This is known as primary neuritic leprosy (PNL). The most common presentation is a mononeuritis (single nerve involvement) followed by mononeuritis multiplex (more than one nerve involved) and polyneuropathy (symmetrical nerve involvement). In addition to anesthesia, nerve thickening and neural pain are the predominant symptoms. In about 15-35% of the patients on close follow up skin lesions are known to develop. If required, a close follow up is essential to revise the diagnosis. Histological alterations have been found in the anesthetic areas supplied by the affected nerve in about 15% cases.

The definite diagnosis of PNL is difficult. Nerve biopsy with the demonstration of AFB is the gold standard but is difficult and sometimes risky. The whole spectrum of leprosy is represented but mostly it is I, BT and BB. Nerve conduction studies show changes in about 40% of the cases who have silent neuropathy. The alterations precede nerve function impairment. High resolution ultrasonography and color doppler evaluate the thickness and vascularity of the nerves better than palpation. Detection of thickness can help in selecting the site for biopsy and increased vascularity indicates reaction. Polymerase chain reaction on nerve tissue can help in the diagnosis in AFB negative material. However, a high degree of clinical suspicion is essential.

Treatment is on the basis of classification – PB when only one nerve is involved and MB when two or more nerves are involved as in WHO regimen for skin lesions. A diagnosis of relapse is difficult but it can be suspected with the development of new signs and symptoms or new findings of AFBs in the nerve or overlying skin. PNL is a definite clinical entity with subtle findings, which is diagnosed by clinical, histo-

pathological, bacteriological, electrophysiological and on ultrasound. Early diagnosis and early institution of therapy is required for better functional recovery. Development of cutaneous lesions in PNL confirms the hypothesis that leprosy is basically neural in inception and all other forms follow.

***Dr. Laura Gillini*:** WHO is organizing a meeting to discuss on neuritis and reaction in leprosy and this will help us to have more understanding about diagnosis and management of PNL.

***Dr. Archana Singhal*:** Ultrasonography (US) of nerve will help in diagnosis PNL. US can also be used to diagnosis neuritis in reactions.

Dr. V. P. Shetty: There is a considerable delay in diagnosis of PNL. Even in patient with single nerve involvement may show a borderline pathology in the nerve. Hence, early diagnosis of such patient is very important.

Dr. V. Ramesh: There is need for revision of cardinal sign in leprosy. Even when one nerve is involved it should be considered as MB.

Dr. Jerry Joshua: For the classification of leprosy should we consider all the palpable nerve or only the nerve trunk involvement?

Dr. Bhushan Kumar: It is the palpable nerve, irrespective of it is a cutaneous or a nerve trunk.

***"Increasing incidence of MDT-MBR unresponsive multibacillary leprosy patients: High time to take cognizance!"* – Dr. Sunil Dogra, PGIMER, Chandigarh**

In the absence of Dr. Dogra, the above talk was presented by Dr. Bhushan Kumar.

WHO-MDT has been used successfully for over four decades and it has played a major role in achieving the epidemiological target of "elimination of leprosy as a public health problem". However, in the past few years, leprologists / dermatologists across India are observing a subset of leprosy patients particularly with multibacillary disease who are suspected to have "clinical resistance" or "non-responsiveness" to fixed duration WHO-MDT multi-bacillary regime (MBR) and for which there are no clear treatment guidelines. The present study was conducted to assess the effectiveness and safety of alternate anti-leprosy therapy (ALT) in MDT-MBR unresponsive leprosy patients. This is a retrospective analysis of patients who were treated with ALT over a period of six years (2010-2015). Data was collected with respect to demographic profile, clinical details, routine investigations along with slit-skin-smear and histopathology. Criteria for inadequate response/ non responsiveness to treatment were: (a) appearance of new lesions with deterioration of the disease after the completion of WHO MDT-MBR (12 months) (b) no decline in the morphological index (MI) at 12 months of treatment. These cases were treated with ALT consisting of minocycline, clofazimine and ofloxacin. A total of 434 leprosy patients were registered at leprosy clinic of this tertiary care hospital during the study period, 63.13% (274) were diagnosed as MB and 36.86% (160) as pauci-bacillary (PB). The prevalence of MDT MBR non responsive patients in this cohort was 8% (35 patients). Mean bacillary index (BI) and morphologic index (MI) at the onset of study (completion 12/24 months of WHO MDT-MBR) was 5.07 and 6.35 respectively. After 6 months of treatment with ALT, MI became negative in all these patients. Patients with recurrent and chronic ENL also responded favourably and were off corticosteroids following ALT. None of the patients developed any serious adverse effects to warrant stoppage of therapy. Alternate drug regimen used in this study is safe and effective in the management of multibacillary leprosy pat-

ients who are clinically or microbiologically non responsive to the current WHO MDT MBR. Further mouse foot pad/molecular studies are of utmost importance to confirm "drug unresponsiveness" or "drug resistance" in such patients.

Dr. Joydeepa Darlong: In case of BI negative patient if there is no change in the patch after treatment should we consider the patient as unresponsive to therapy?

No one responded to this question.

Dr. Loretta Das: It is known that BCG vaccination is helpful in such patient, but why it is not accepted in regular practice?

Dr. Kiran Katoch: Instead of BCG, *M. indicus pranii* (MIP) has been tested and is in regular practice. A total of 4 doses of MIP is given either at 6 or 3-month intervals for immunotherapy.

Dr. Laura Gillini: The role of BCG in prevention of leprosy demands a good quality research to generate evidence. The present quality of evidence of role of BCG in prevention of leprosy is very low.

Dr. Bhushan Kumar: The studies conducted in India suggest that BCG can be used to prevent leprosy among contacts.

"Hansen's disease: Magnetic resonance imaging evidence of central nervous system and plexus involvement" **– Dr. Atchayram Nalini, National Institute Mental Health and Neuroscience, Bangalore**

Hansen's disease (HD) / Leprosy almost always affects the skin and peripheral nerves. We present 7 cases of Leprosy with central nervous system and proximal nerve lesions. All demonstrated *M. leprae* - specific genomic DNA by PCR method. Case 1: A 32-year-old man had relapsing HD for 10 years. During the 3rd relapse he had skin lesions, peripheral / cranial neuropathy. MRI revealed facial nuclei lesions. Case 2: A man - aged - 21 developed pain in right forearm and wrist joint for 12 months, paresthesias and numbness with weakness and wasting of right hand for 4 months. He had BL with AFB. MRI showed signal change from C4-D2. Case 3: A boy aged 17 had acute left foot drop, knee joint pain and absent sensations below knee for 2 months. Skin/sural nerve showed BT with AFB. MRI showed left hemicord linear hyperintensity at conus. Case 4: A 26-year-old man developed painless, bullous skin lesions, loss of touch, pain and temperature sensation over left palm for 6 months, weakness and wasting of left hand for 3 months. MRI showed hyperintensity at C6 and C7. Case 5: A 40-year-old man had RUL impaired sensations up to mid arm, difficulty in gripping objects and urgency and precipitancy of micturition for 3 years. MRI showed a hemi cord enhancing lesion at C4-C5. Nerve showed BT. Case 6: A 26 year old lady developed numbness, inadvertent burns, nodular eruptions of right little finger for 3 years, ring finger for 2.5 years, medial forearm for 1 month, left medial hand and forearm for 2 weeks. Duration of pain in shoulder regions and complain of mild weakness for 1 week. Nerve revealed BT with AFB. MRI showed cord signal at C3. Case 7: A 23-year-old-male had weakness, wasting and impaired sensations in medial 2 fingers and multiple skin lesions for 9 months. Nerve showed BT. MRI showed enhancing lesion at C5-6 level. MIP image of STIR showed symmetrical/asymmetrical thickening of the brachial plexii in all cases. In case 1 brain lesions disappeared with minocycline and clofazimine combination.

Dr. Jerry Joshua: Was there a case with positive slit skin smear with positive MRI findings?

Dr. Atchayram Nalini: Seven of 15 patients had CNS involvement with positive MRI findings.

Dr. V. Ramesh: What prompted you to investigate CNS in leprosy?

Dr. Atchayram Nalini: As there were increased levels of protein in CNS fluid, hence its involvement was suspected.

Dr. Loretta Das: Was there a corresponding lesion in the spinal cord for the clinical symptoms observed?

Dr. Atchayram Nalini: Yes, corresponding lesions were seen for the exaggerated reflex.

Dr. Kiran Katoch: CNS involvement has been reported earlier by us at JALMA but not investigated further.

"Criteria for sending biopsy for drug resistance test" **– Dr. Archana Kumar and Rashmi Nayak, Bethesda Leprosy Hospital, TLM, Champa, Chattishgarh**

Current Leprosy control is based on early case detection and treatment by multi-drug regimen recommended by WHO. MDT is highly effective for leprosy treatment and global leprosy prevalence has markedly reduced over two decades. However, chemotherapy and drug-resistance are two sides of same coin. Monotherapy by dapsone or rifampicin alone lasted until multi-drug treatment was applied and many cases resistant to dapsone and rifampicin were reported from various regions of the globe. Besides single drug resistance for dapsone and rifampicin many multi drug resistance cases have been subsequently reported. Spreading of drug resistance bacilli threatened leprosy control and hence surveillance and awareness of level of drug resistance are essential to prevent spreading resistant strains and to keep MDT effective. **Clinically there are no clear guidelines to suspect resistance cases. Therefore in this report, we will discuss the usefulness of set of criteria's used in suspecting cases of drug resistance.** For this in our hospital BLH Champa, we used the following clinical criteria for sending the biopsies for drug resistance study: (i) Initial high bacillary index (≥4+); (ii) Defaulter cases; (iii) Recurrent type 1 lepra reaction after RFT; (iv)Recurrent type 2 lepra reaction; (v) Relapse cases.

Using the above categories a total of 28 cases were enrolled during the period between 2014 and 2016. 46.4% were found to have drug resistance for dapsone or rifampicin or ofloxacin or in combination. We observed that all patients (100%) with re-current type 1 reaction or relapse after RFT were most prone to develop drug resistance followed by patients with recurrent type 2 reaction (75%). Drug resistance in defaulters was only 3%. Forty-five per cent patients showed increase in BI from initial BI.

Dr. Rajkamal Verma: How did you anticipate the symptoms for drug resistance?

Dr. Archana Kumar: We suspected the case from the past history.

Dr. Smita Priyadarshini: What do we do for those non-responders for treatment?

Dr. V. M. Katoch mentioned that no one from this hall can respond to this question confidently. However, there is a need to test new drug regimen (s) for those not responding to treatment.

Dr. Joydeepa Darlong: Test for drug resistance should be considered before continuing MDT for such patients.

Session III – Relapse & Treatment

"Relapse – The TLM Naini experience" **– Dr. Loretta Das, TLM Community Hospital, Naini, Uttar Pradesh**

Relapse is defined as the re-occurrence of disease at any time after completion of a full course of treatment. Relapse is indicated by the appearance of new skin lesions and/or evidence on a

skin smear of an increase in BI of 2 or more units.

Analysis of relapse cases diagnosed at TLM Naini from 2009-2016 has been presented. Analyzed data of 70 cases of relapse diagnosed between 2009 and 2016. Sixty were smear positive relapses (smear ranging from 1+ to 6+). Duration from RFT to relapse was, 4-5 years (10), 5-10 years (16), 11-15years (17), 16-20years (14), >20 years (13). Presentation at relapse with new patches (17), LL features (11), Neuritis (5), Type I reaction (4), Type II reaction (7), Type I and II (1). The remaining 25 presented with 'mixed' symptoms. Drug resistance: 52 cases had successful PCR study done for DR. Five showed resistance to Ofloxacin, 4 to Dapsone and 3 to both Oflaxacin & Dapsone. None was resistant to rifampicin. Patients were put on a 24 month regime of MB MDT or MB MDT + monthly ofloxacin and minocycline. Clinical and bacteriological responses to MB MDT were good.

Our results at 'TLM Naini' are in accordance with current knowledge regarding relapse in leprosy and response to retreatment with MDT. Apart from field studies, it would be useful to have data from large leprosy referral centers in the country.

***Dr. Bhushan Kumar*:** What were the criteria for choosing a relapse case after 3 years of RFT? Whether the cases became BI negative during the previous treatment or at RFT?

***Dr. Loretta Das*:** BI came down in most of the cases and in many cases BI became negative.

Dr. Bhushan Kumar wanted to know the justification for using ofloxacin and minocycline along with MDT in relapse cases because ROM is not a good regimen because of the short half life of ofloxacin and minocycline.

Dr. V. Ramesh mentioned that there should be differentiation of case between "relapse" and "re-infection". IAL text book mentions that if the relapse is within 1 year of RFT then it may be considered as relapse and if it is after 3 years of RFT then it could be considered as a case of re-infection.

Dr. V.V.Pai mentioned that without knowing the strain type of *M. leprae* it will be very difficult to differentiate between relapse and re-infection.

***"Clinical and field experience in dealing with relapses in leprosy"* – Dr. V. V. Pai, Bombay Leprosy Project (BLP), Mumbai**

Multidrug therapy (MDT) for leprosy was introduced by WHO in 1982 in response to the threat to leprosy control posed by Dapsone resistance and thereafter has been the major strategy of NLEP. Relapses in Leprosy pose not only clinical challenges but also epidemiological challenges by adding to transmission of the disease. Post MDT relapse is emerging as one of the impending problem in leprosy. The NLEP and WHO has started collecting information on relapse cases from peripheral centres. impending problem in leprosy. The NLEP and WHO has started collecting information on relapse cases from peripheral centres.

These data show a significant number of relapses reported from endemic states and countries. Relapses could result either due to persistent dormant bacteria or due to inadequate treatment. We present our observations in BLP pertaining to the study of occurrence of relapses and clinical experience at our referral centre. Though the current recommendations for leprosy control programmes include stopping active surveillance in view of low relapse rates, but sporadic relapses reporting voluntarily beyond surveillance periods pose threat of continued transmission. We discuss below our experience related to relapses in leprosy from the following three perspectives: a) Operational studies b) Field based study

c) Clinical studies. In our experience surveillance activity to trace and reassess all MB patients treated with MDT is essential for suspecting and detecting relapses. As per our operational studies undertaken to reassess MB patients treated with MDT/alternative drug regimens, relapses occurred irrespective of the regimens indicating no regimen was free from relapses and it showed higher relapses compared to community-based studies. However, epidemiological inferences could not be drawn based on this data as these were not from specific defined population. It was also noted that almost all relapses occurred after a mean period of 8 to 10 years indicating that the risk of relapses starts after five years. Hence it is necessary to identify relapses early before they transmit infection to a large segment of the urban population. However, it should be noted that although relapses are few in relation to number of leprosy cases completed treatment, it has not been adequately documented at the community level. This phenomenon assumes special dimension in urban areas of large cities such as Mumbai, with high density of population where the source of transmission cannot be determined. In another collaborative field study screening of patients treated from 2005 to 2010 was undertaken by visiting slums in Mumbai engaging community volunteers for new lesions, reactions, relapse and nerve damage. In Mumbai study area eligible RFT population comprised 1170 cases of which 482 (41%) were traced and examined. Proportion of patients (18%) with post RFT events requiring medical attention was fairly large. Occurrence of relapse was seen in 10% of patient's majority being BT-BB leprosy. In another clinical study, patients who have completed treatment and under follow up reporting with new lesions and /or recurrence of lesions attending our Referral center in Mumbai were assessed and investigated to look for relapses and also investigate for drug resistance. During the period from 2013 to 2017, we found fifteen patients (two females, thirteen males) to have new /recurrence lesions with suspected relapses. Lesions developed after stopping treatment with a mean follow up of 10 years. All fifteen patients were assessed clinically and bacteriologically (BI), screened for HIV sero-positivity, blood sugar and Skin biopsy for histopathology and for drug resistance. BI was done in all patients while MI was done in smear positive patients at relapse. Among fifteen patients, thirteen patients had new lesions with sensory loss, two with Type 2 reactions and one with histoid like lesions.

Observations

Among fifteen patients, three relapsed from smear positive to positive, three were initially positive and relapsed with negative B.I, and in six patients relapsed from initially smear negative to negative and one relapsed from negative to positive.

Dr. Laura Gillini suggested performing whole genome sequencing of *M. leprae* strain to determine relapse or re-infection.

Dr. U. Sengupta suggested performing SNP typing and sub-typing of *M. leprae* before performing whole genome sequencing.

"A profile with resistant pattern among relapse patients at The Leprosy Mission Hospital, Purulia" **– Dr. Joydeepa Darlong, TLM Community Hospital, Purulia, West Bengal.**

The single most important tool to measure efficacy of MDT in leprosy is the relapse rate. In the year 2013-14, 919 relapses were reported from India, second only to Brazil who reported 1603 cases. WHO estimates risk of relapse to be

low, hence post-MDT surveillance has been discontinued. Relapsed patients add to the prevalence of leprosy population and undiagnosed cases are a continual source of transmission due to their high BI. The aim of this discussion is to describe the clinical profile of patients diagnosed with relapsed leprosy using WHO guidelines and correlate their bacteriological and histopathological findings. All patients who had successfully completed treatment with WHO MDT in the past, reporting with clinical signs of progression of disease were suspects. WHO guidelines for diagnosing relapse was strictly followed. Two hundred two patients were suspects, 119 (60%) were confirmed cases of relapse. 94 (78.7%) were males. 79(76%) patients were above 40 years of age. The time of relapse after RFT in years was <10 in 28(26%), 11-20 in 49 (41.4%), 20-30 in 34 (27.6%) and >30 in 8 (5.3%). 113 (94%) had solid bacilli reported in the histopathology, 92 (82%) had a granuloma fraction of > 30% and 75 (67%) had BI > 4. Although studies show that relapse rates are very low after WHO MDT, relapses do occur. There is a possibility that more relapses in leprosy may develop if the WHO accepts uniform MDT and the treatment duration is reduced. Clinicians must use their judgment and tailor treatment regimens for individual patients, especially those with high BI. It is imperative that at least bacteriological examination be offered at all peripheral health facilities treating leprosy. Post MDT surveillance must be carried out in those at risk for developing relapse.

Dr. Kiran Katoch suggested the use of MIP (*Mycobacterium indicus pranii*) along with MDT in those patients who are not responding to treatment.

Dr. Loretta Das pointed out that even while screening household contacts slit skin smear should be done to avoid misdiagnosis.

***"Present day challenges in the management of leprosy"* – Dr. Archana Singhal, University College of Medical Sciences, Delhi**

Leprosy is a chronic inflammatory mycobacterial disease chiefly involving skin and peripheral nerves. It is almost world-wide in distribution, with India sharing the major chunk of the disease burden. The goal of elimination of leprosy as a public health problem was reached at the global level in the year 2000 and in India on 31st December, 2005. Thereafter, leprosy services in India have been integrated with General Health-Care System resulting in reduced focus and funds. Sustaining the gains made so far in controlling leprosy is a big challenge and there is no time for complacency. Pockets of high endemicity with prevalence rate of > 1 still exist in many states. Frequent change of places by the leprosy patients result in poor compliance and poor contact/family screening. Our data from a tertiary care centre indicates inadequate epidemiological control and on-going disease transmission. This is evident from the significant number of new, untreated patients, of which majority are multibacillary with *de novo* lepra reactions and deformities. In our experience, the standard WHO guidelines on the use of steroids for management of leprosy reactions seem to be oversimplified and are not effective in a significant proportion of patients. They either need prolonged courses of steroids, or additional/alternative immunosuppressant, drugs not available from the leprosy management. Management of Leprosy cases is singular domain of dermatologists especially in medical colleges. Latter are few in numbers in state endemic for the disease. Problem of drug resistance too, has become a reality. It is essential that dermatologists all over India should continue to play a central role in capacity building and training of undergraduate and post-graduate students,

medical officers, and field workers.

Dr. Laura Gillini mentioned about a new programme to facilitate resources for the leprosy control programme especially in high endemic areas for implementation.

Session IV – Relapse & Resistance

***"Post-RFT events and relapse following MDT are not negligible"*- DR. V. P. Shetty, The Foundation for Medical Research, Mumbai**

Post – MDT deleterious events such as reaction, neuritis, persistence of lesion and relapse have not so far been fully documented or appreciated due to lack of attention to post – MDT surveillance. Timely detection and proper management of post MDT events are important as they impinge on the success of NLCP.

In an ICMR funded study, effort was made to gauge the magnitude of these problems in 6 primary health centers in Panvel block in Raigad district, in patients RFT between April 2005 and March 2010. Of the 620 registered patients 406 (65 %) were examined in 3 annual visits (2012-2015) a total of 76 patients (18.7%) were detected with deleterious events requiring medical attention. The rate of disease relapse after cessation of chemotherapy in this study was 54/406=13.3%, the majority being BT cases receiving 12 months of MB-MDT. We also studied the level of microbial resistance to DDS, RIF and OFX using genotypic and phenotypic assays. Notably resistance to RIF was not observed in any of the 53 relapse and 41 new cases tested, but mono resistance to DDS and OFX were recorded in 4.7% and 2% of relapse cases respectively. While recent revival of active survey and contact examination by the NLCP to detect and treat cases early are indeed a move in right direction, post RFT surveillance should not remain a neglected area. Rate of disease relapse (13.3%) recorded in this study raises concern about the efficacy of the current MDT regime. Efficacy of MDT needs to be monitored with defined treatment end points, should include; a) examination of each patient by an expert at RFT b) slit skin smear examination and c) check for live bacteria and microbial resistance.

V. M. Katoch: This clearly shows that relapse cases do occur and these cases are still responsive to MDT. This might indicate that the reports of rifampicin resistance are from certain regions in India.

***"Drug resistance in leprosy relapse and poor responders: A concise study"* – Dr. U. D. Gupta, Avi Kumar Bansal, Patha Sarathi Mohanty and Farah Naaz, national JALMA Institute for Leprosy and Other Mycobacterial Diseases, Agra, Uttar Pradesh**

Leprosy is a slow chronic infection caused by *M. leprae*, which is a slow- growing intracellular bacillus that infiltrates the skin, the peripheral nerves, the nasal and other mucosa, and the eyes. India achieved leprosy elimination in Dec 2005 but still some endemic pockets exists in the country and still responsible for continue transmission of leprosy. In the present study, we examined the frequency of mutations in the RRDR (Rifampicin Resistant Determining Region) in *rpoB* gene, ORDR (Ofloxacin Resistant Determining Region) in *gyrA* gene and DRDR (Dapsone Resistant Determining Region) in *folP* gene of relapse and poor responder cases of leprosy to elucidate the drug resistant pattern. Slit-skin smears (SSS) samples were taken from patients with leprosy those were failing in treatment after receipt of informed consent. *rpoB*, *gyrA* and *folP* gene region were amplified by WHO recommended primers and sequenced. The mutation rates in *rpoB*, *gyrA* and *folP* were found to be 7 (8%),

8 (9%) and 3 (3%) respectively in 87 samples. None of the patients showed multidrug resistance. Moreover, it was found that many relapse patients with rifampicin resistant mutations had rifampicin monotherapy earlier.

Dr. Kiran Katoch mentioned that follow up of cases of drug resistance should be mandatory.

Dr. Mallika Lavania asked that presentation of rifampicin resistant cases with mutations at 457 and 458 codon positions are not known. She enquired that whether this has been supported by mouse foot pad studies.

Dr. U. D. Gupta mentioned that these have been inoculated in mouse foot pads and results are awaited.

"Molecular Tests for antimicrobial resistance in leprosy – experiences of LEPRA society-BPHRC" – **Dr. Aparna Srikantam, Hyderabad**

LEPRA society - BPHRC is one of the referral laboratories identified by the Central leprosy division, Govt of India. The laboratory located at Hyderabad caters to the needs of leprosy drug resistance tests in its peripheral clinics spread across AP, Telangana and Odisha states of India. During the period, 2013-15, 774 RFT cases from four districts were actively screened for and found 39 relapses, which were subjected for molecular testing for mutations in folP, rpoB and gyrA. 234 new leprosy cases which were diagnosed during that period from the same districts were also studied. It is to be noted that none of the *M. leprae* isolates from these patients showed drug resistance mutations. Though it is expected that leprosy relapses correlates with drug resistance, evidence from our study indicates that there are other factors that need to be looked into.

Dr. Archana Singhal enquired that as Dr. Aparna did not find any mutation against any of the drugs of MDT, whether she counterchecked her data.

Dr. Aparna Srikantam mentioned that the tests were repeated twice for all samples.

"Trend in drug resistance pattern from the relapsed leprosy patients from The Leprosy Mission (TLM) hospitals in India" **– Dr. Mallika Lavania, Stanley Brown Laboratory, TLM, Delhi**

In spite of more than 3 decades of multidrug therapy (MDT), leprosy remains a major public health issue in several endemic countries including India. Emergence of drug resistance in *M. leprae* is a cause of concern and poses a threat to the leprosy control programme, which might ultimately dampen the achievement of the elimination programme of the country. Between 2009 and 2016, slit-skin smears samples were collected from 239 relapse and 11 new leprosy cases from hospitals of The Leprosy Mission across India. DNAs were extracted from these samples and were analyzed for PCR targeting genes *rpoB, folP* and *gyrA* associated with drugs (Rifampicin, Dapsone and Ofloxacin) in *M. leprae. Thai-53* (Wild-type) and *Zensho 4 (*MDR) strains were used as reference strains. Fifteen strains showed representative mutations in at least 2 drug resistant genes. Two strains showed mutation in all 3 genes responsible for resistance. Seven strains showed mutation in genes responsible for rifampicin and dapsone and 7 strains showed mutation in genes responsible for resistance to dapsone and ofloxacin and one with rifampicin and ofloxacin. The study showed emergence of MDR strains of *M. leprae* in MDT treated leprosy patients from endemic regions of India. Further surveillance and necessary actions are needed to ensure successful control of the disease that has reached a stage of elimination.

Dr. V.M. Katoch mentioned that accurate clinical data should be maintained for all MDR cases for proper maintenance of records. These patients should be traced for their past treatment history. Clinicians should be able to keep a track of such cases with utmost interest for the benefit of the leprosy control programme. It should have an epidemiological back up.

Dr. V.V. Pai enquired about the cases with mutation to dapsone, rifampicin and ofloxacin and expressed concern.

Dr. V. M. Katoch mentioned that these molecular findings of mutation detection may not always correlate 100% with clinical situations due to polymorphism. However, this is definitely of importance to further work with good clinical and treatment records.

Concluding Session – Future Strategy

Dr. Anil Kumar, DDG (Leprosy) while elaborating on the future strategy of the Government of India emphasized that during this stage of elimination if drug resistance to rifampicin crops up then it will be very difficult to control the spread of leprosy and its elimination. Hence, steps have to be taken to keep the country under surveillance. NLEP has already planned designed a strategy and planning has been made and the country has been divided in several zones. Referral laboratories conducting the molecular testing have been identified. Procedures for training of technicians for collection of skin smears and their staining from village to district levels have been chalked out. Several regional laboratories for molecular testing have been established and several more will be developed in future so that molecular testing could be performed at more places in addition to the referral centres. He also mentioned that as soon as a resistant case is identified it has to be reported to the Central Leprosy Division so that action could be taken immediately.

The Way Forward : Panel Discussion

Dr. U. Sengupta suggested that in addition to inclusion of relapse cases reactional cases also should be included for screening drug resistance because several cases from TLM hospital at Champa, Chattisgarh with increase in BI were found to be resistant to rifampicin.

Dr. V. M. Katoch suggested that patients with higher BI after full course of MDT should fall into a cohort study with molecular typing of *M. leprae* and a regular follow up with molecular investigation during relapse will provide actual information. Defaulters to full course of MDT should form a different group and should be investigated for MDR before and after completion of MDT. He also mentioned about developing guidelines for management of defaulters based on present records.

Dr. Kiran Katoch mentioned that while screening for MDR one should have different categories of patients who are to be grouped separately like defaulter group, relapse group and reactional group. One may follow the basic guidelines for classification and after two years as per epidemiological criteria of patient one can frame the actual scenario.

Dr. Marry Verghese suggested that there should be more involvement of dermatologists, neurologists and medical colleges. Her emphasis was on the role of tertiary hospitals in disease identification and categorization of patients.

Dr. Anil Kumar shared his views and mentioned that the programme is failing due to the defaulter patients and doctors who are treating patients in private. It is true that leprosy cases have decreased where MDT had been implemented

regularly however it was reverse where MDT administration was not monitored regularly. There should be a liaison between public health personnel and the researchers and clinicians.

Recommendations :

After a thorough discussion the following recommendations have been made:

1. Every relapse case has to be identified and samples have to be processed for molecular mutations for resistance specially MDR.
2. Every new MB case has to be investigated for molecular mutations for resistance specially MDR.
3. All cases of reactions should be investigated for mutations known to be associated with resistance specially MDR using molecular methods.
4. All cases who defaulted from the full course of MDT should be investigated for drug resistance specially MDR.
5. A robust surveillance mechanism has to be created through establishment of a well connected network system for implementation of the above (1-4) throughout the country.
6. Relevance of new / unconventional mutations may be established by mouse foot pad experiments.
7. Transmission dynamics of resistance should be investigated appropriately by epidemiological parameters.

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