Persistence of Bacteriological Index After 1 Year of Multidrug Therapy Intake in Hansen's Patients: An Indication to Strengthen the Antimicrobial Surveillance

Dear Editor,

Leprosy has become a treatable disease with the invention of multidrug therapy (MDT). Even after 4 decades of usage of MDT, there is worldwide transmission, with nearly 200,000 new cases reported annually between 2013 and 2019, with only a reduction in case detection during the years of the coronavirus disease epidemic. This could be due to several reasons, such as failure to detect new cases, late detection, inadequate treatment, poor adherence, endemicity, zoonotic leprosy, and resistance to antileprosy drugs, all of which could contribute to continued transmission of disease in the community.[1] Besides early case detection and treatment, effective drug resistance monitoring is crucial to the global leprosy control strategy. Resistance is due to mutations in gene segments encoding drug targets called drug-resistant determining regions (DRDRs).

Rifampicin resistance is due to changes in the β-subunit of RNA polymerase encoded by the rpoB gene. Single-dose rifampicin given prophylactically to contacts of leprosy-detected patients poses a risk for rifampicin resistance, and hence, monitoring it is now essential. Dapsone resistance is usually associated with the mutation of folP1gene. Fluoroquinolone (FQ) resistance is associated with mutations in a region of the gyrA gene, known as the quinolone resistance-determining region. Newer studies have shown a higher frequency of ofloxacin resistance patterns due to rampant use in nonmycobacterial infections.[2] FQ resistance would leave us with fewer alternatives for second-line drugs in the form of quinolones and is a matter of serious concern.

World Health Organization (WHO) recommends molecular methods to locate mutations in the DRDRs of *folP1*, *rpoB*, and *gyrA* genes by using specific primers. Reference techniques include polymerase chain reaction (PCR), Sanger sequencing, a line probe assay, and whole genome sequencing.[3]

As per WHO surveillance (2009–2015), among the 1932 cases, 154 strains were found to have resistance. A total of 352 multibacillary patients were from India. 8.2% and 3.9% of patients had primary and secondary resistance to rifampicin, respectively. 6.4% of cases had dapsone resistance, and 17% had ofloxacin resistance.[3]

The bacteriological index (BI) signifies the density of lepra bacilli, both living and dead, in the smear. A fall is usually seen in the BI by one log after 1 year of MDT intake. The methodology comprises testing the antimicrobial resistance in the patients who had an increased or persistent BI along with persistent skin lesions even after 1 year of treatment with MDT. Slit skin smear samples had been collected from sites with the highest BI in previous examinations. The tissue scrapings were rinsed into a centrifuge tube prefilled with 1 ml of 70% ethanol. Samples were sent to an apex national laboratory for resistance analysis. PCR and Sanger sequencing were used to detect the mutation in the DRDRs of the respective genes. The observations are mentioned in Table 1.

A total of 12 patients diagnosed with multibacillary Hansen's disease were included in the case series. One patient was found resistant to ofloxacin, and another had dapsone resistance. The rest of the patients were found sensitive to all the drugs. Our series's findings warrant exploring other causes for the rise in BI or persistent disease activity. In Hansen's cases, there are several causes of failure in the decline of BI. Nonadherence to drug therapy, relapse of the disease, and high bacillary load at presentation are possible causes of persistent disease activity even at the end of complete MDT therapy. Drug resistance could be one of the contributory factors for the failure of drop in BI even after receiving complete MDT therapy.

The Airaku 3 rifampicin-resistant strain with a wild-type rpoB gene and dapsone-resistant strains with wild-type folP1 genes have unknown mechanisms of resistance that are yet to be explained.[4] A few studies have reported mutations in the *rpoC* and *rpoA* genes associated with *rpoB* mutation, suggesting a compensatory mechanism increasing the transmission of resistant strains.[5] A comparative analysis of the *M. leprae* genome shows the presence of nearly half of the transporters or drug efflux pumps found in *M. tuberculosis*.[6] Hypermutated strains have been found to have spontaneous mutation rates because of altered DNA mismatch repair. They have an increased chance of acquiring drug resistance.[5] The Hansen's Disease Antimicrobial Resistance Profiles (HARP) database is newly invented, and it predicts the missense mutations in the known drug targets and associated genes. It can also predict emerging mutations.[7] The advent of whole genome sequencing is now helping to locate mutations outside the DRDRs.[8]

To conclude, drug resistance analysis in Hansen's patients should be strengthened by using newer techniques to

Table 1: Antimicrobial resistance analysis of the patients

Age/ Sex	Diagnosis	Reaction status	Duration of disease (months)	Treatment duration	Neuritis	Deformity	BI at baseline	BI after 1 year of MDT	Drug resistance analysis
42/F	LL Hansen's disease*	Type 2	18	1 year	Absent	Absent	3+	3+	Sensitive to all drugs
25/M	LL Hansen's disease	Type 2	15	1 year	Present (B/L ulnar nerve)	Absent	5+	6+	Sensitive to all drugs
41/F	BL Hansen's disease†	Type 1	12	1 year	Present (B/L ulnar, CPN*)	Absent	5+	5+	Resistant to ofloxacin
40/M	LL Hansen's disease	Type 2	12	1 year	Absent	Absent	3+	4+	Sensitive to all drugs
29/M	LL Hansen's disease	Type 2	15	1 year	Absent	Absent	3+	3+	Sensitive to all drugs
54/M	LL Hansen's disease	Type 2	12	1 year	Present (B/L ulnar, CPN*)	Absent	4+	5+	Sensitive to all drugs
23/F	Histoid Hansen's disease	_	14	1 year	Absent	Absent	5+	5+	Sensitive to all drugs
37/M	BL Hansen's disease	Type 2	12	1 year	Present (B/L ulnar, RCN#, CPN*)	Absent	3+	4+	Sensitive to all drugs
36/M	LL Hansen's disease	Type 2	18	1 year	Present (B/L ulnar nerve)	Clawing of hand	4+	5+	Sensitive to all drugs
32/M	BL Hansen's disease	Type 2	14	1 year	Absent	Absent	3+	3+	Sensitive to all drugs
43/M	LL Hansen's disease	Type 2	15	1 year	Absent	Absent	4+	4+	Sensitive to all drugs
24/M	LL Hansen's disease	_	12	1 year	Absent	Absent	3+	4+	Resistant to dapsone

*LL: Lepromatous leprosy. †BL: Borderline lepromatous. *CPN: Common peroneal nerve. #RCN: Radial cutaneous nerve

detect the new loci of mutation, the emerging wild variants, and drug efflux transporters to cure and eliminate the disease. Apart from this, screening of all new MB cases to detect primary resistance, screening of close contacts of the resistant case, and adequate treatment of the resistant patients with an alternative regimen are necessary.

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Conflicts of interest

There are no conflicts of interest.

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