

High Prevalence of Resistance to Anti-Leprosy Drugs in Leprosy Cases with Chronic Erythema Nodosum Leprosum: A Matter of Concern

Sir,

The World Health Organization (WHO) Global Leprosy strategy: 2021-2030 “towards zero leprosy” aims for a leprosy-free world with an emphasis on early and adequate treatment.^[1] At the national level, substantial work is done to detect cases early and treat them in time to decrease disease transmission. However, an additional problem emerging is antimicrobial resistance (AMR) to anti-leprosy drugs, especially rifampicin that forms the backbone of WHO multi-drug therapy. WHO recommends testing for AMR in all relapse cases and a sample of new multibacillary (MB) cases.^[2] However, a recent study has suggested modifying these criteria to include those presenting with chronic/recurrent erythema nodosum leprosum (ENL) as well.^[3]

In the present study, leprosy cases where AMR testing was done between August 2020 and June 2021 were retrospectively analyzed. During this period, 44 new leprosy cases were registered and 21 old/new patients presented with ENL. Antimicrobial drug resistance testing was done in patients presenting with relapse, treatment defaulters, and in those with chronic/recurrent ENL to detect resistance to rifampicin, dapsone, and ofloxacin.^[2,4] Slit-skin smear scraping stored in 70% ethanol was used for polymerase chain reaction (PCR)-based gene amplification using primers according to the guidelines of WHO “Global Surveillance of Drug Resistance in Leprosy 2008” for detection of mutations in the *rpoB*, *gyrA*, and *folP* genes in the *Mycobacterium leprae* genome in collaboration with “TLM Community Hospital, The Leprosy Mission Trust India, Nand Nagari, Delhi.”^[2]

AMR testing was done in eight patients over the study period. One had relapsed 2 years after completing a course of WHO-MB therapy. Remaining seven patients had chronic ENL and were dependent on either steroids or thalidomide [Table 1]. During the study period, 11 patients with chronic ENL reported to the institute; however, in four patients, AMR testing could not be performed due to financial constraints. In one sample, PCR was negative for all three genes, possibly due to sampling error. Of the remaining seven, resistance to at least one anti-leprosy drug was detected in six (85.7%). Three patients had resistance to rifampicin (42.8%) and ofloxacin (42.8%) and five had resistance to dapsone (71.4%). The patient presenting with relapse was resistant to all three drugs. Five of the six patients with chronic ENL had resistance to at least one drug, with two being resistant to rifampicin. The site of mutation observed in each case has been depicted in Table 1. Patients with resistance to rifampicin were started on clarithromycin and ofloxacin along with daily clofazimine. Both patients with chronic ENL having rifampicin resistance had a significant reduction in episodes of reactions after starting the modified regimen. The patient who was sensitive to all the three drugs still had chronic ENL that was managed with a combination of oral corticosteroid and thalidomide.

AMR is one of the critical areas of intervention in the Global Leprosy Strategy: 2020-2030 under the subheading of “stop leprosy and its complications.”^[1] The emergence of drug resistance in infectious diseases poses a grave threat, especially when secondary prevention or treatment is the mainstay of therapy. Indian studies from diverse regions report variable rates

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Table 1: Clinical and demographic details of patients tested for antimicrobial drug resistance

Patient	Age/ gender	Resident of	Type of leprosy	AMR testing done on	Disease duration	Deformity	BI/MI at initiation of MDT	Current BI/MI received	MDT packs received	Reason for AMR testing	AMR detected for
1.	25/Male	Uttar Pradesh	Histoid	08.05.2020	3 years	Grade 1	6+/10%	6+/0%	24	Chronic ENL	PCR did not amplify any gene
2	25/Male	Uttarakhand	LL	08.14.2020	4 years	Grade 1	Not known	3+/5%	12 (2017-2018)	Relapse	Rifampicin (Ser434Cys), dapsone (Pro55Leu), ofloxacin (Ala91Val)
3	29/Male	Uttarakhand	LL	08.10.2020	3 years	Grade 1	6+/20%	3+/5%	20	Chronic ENL	Dapsone (Pro55Leu)
4	30/Male	Uttarakhand	LL	10.21.2020	2 years	Grade 2	6+/20%	6+/0%	24	Chronic ENL	Rifampicin (Val424Gly)
5	27/Female	Uttar Pradesh	LL	03.16.2021	1 year	Grade 2	3+/0%	3+/0%	7	Chronic ENL	Rifampicin (Asp441Tyr), dapsone (Pro55Leu)
6	37/Male	Uttarakhand	Histoid	06.12.2021	1.5 years	Grade 1	6+/10%	6+/0%	8	Defaulter, chronic ENL	None
7	53/Male	Uttarakhand	BL	06.30.2021	2 years	Grade 1	4+/0%	4+/0%	24	Chronic ENL	Dapsone (Pro55Leu), ofloxacin (Ala91Val)
8	66/Male	Uttar Pradesh	BL	06.15.2021	2 years	Grade 1	4+/5%	4+/0%	12	Chronic ENL	Dapsone (Pro55Leu), ofloxacin (Ala91Val)

AMR=Antimicrobial resistance, ENL=Erythema nodosum leprosum, PCR=Polymerase chain reaction, BI=Bacteriological index, MI=Morphological index, LL=Lepromatous leprosy, BL=Borderline lepromatous leprosy, MDT=Multi drug therapy

of drug resistance ranging from 0 to 16.4%.^[3,5-7] The first prospective open survey for determining AMR in leprosy was conducted by a WHO surveillance network for 2009-2015.^[8] MB cases from 19 countries were studied for resistance to rifampicin, dapsone, and ofloxacin. Lepra Blue Peter Public Health and Research Centre, Hyderabad; Stanley Brown Laboratory, New Delhi; and National JALMA Institute of Leprosy and Other Mycobacterial Diseases, Agra participated in this surveillance. A total of 352 MB cases were included from India: 254 relapse and 98 new cases. Primary resistance to rifampicin was seen in 8.2% cases and secondary resistance in 3.9% cases. Resistance to dapsone and ofloxacin was reported in 6.4% and 17% cases, respectively. India, Brazil, and Columbia reported more than five cases of rifampicin resistance.^[8] To date, only patients presenting with relapse/treatment discontinuation have been tested for AMR to detect a possible secondary resistance. However, recent literature suggests patients with chronic/recurrent ENL as another subset harboring an underlying drug resistance with the propensity to improve once they are started on second-line anti-leprosy drugs. Resistance to rifampicin and dapsone was reported in 8.3% and 12.5% of patients with recurrent/chronic ENL respectively, in a recent study from a tertiary care institute in North India.^[3] Five of the six cases with chronic ENL in the present study had resistance to one or more drugs, with two having rifampicin resistance. Modification of treatment regimens in both resulted in excellent control of their type 2 reaction. Thus, it appears justified to test patients with recurrent/chronic ENL for AMR as the failure to timely detect drug resistance can delay appropriate therapy, posing a threat to the patient and the community. The primary limitation of the presented study is the small sample size and the inability to include new cases to detect primary drug resistance.

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Conflicts of interest

There are no conflicts of interest.

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