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Drug Resistant Cases of Tuberculosis in Directly Observed Treatment Short Course

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ABSTRACT

Background: Resistance of Mycobacterium tuberculosis to antituberculous drugs has emerged as a major public health threat. The objective of this study was to determine Multi Drug Resistance cases of tuberculosis in Directly Observed Treatment Short Course program of Nepal.

Methods: The sputum samples collected and culture on Lowenstein Jensen media followed by biochemical test. All the isolates antibiotic sensitivity test performed on medium by proportion method.

Results: Tuberculosis was most commonly found in economically active age group (21-50 years). All the isolates of pulmonary tuberculosis were found to be M. tuberculosis. A Multi-drug resistant case of tuberculosis primary and acquired in Directly Observed Treatment Short Course Program of Nepal was found (3.6%). Out of 460 untreated cases, 9 (1.9%) cases were found to be MDR and among 90 previously treated cases 11 (12.2%) were found to be MDR. Multi drug resistant cases of tuberculosis were found most commonly in productive age group (21-30). The incidence of tuberculosis was found higher in male than in female. But multi drug resistant M. tuberculosis cases equally affected both the gender. Majority of the MDR cases found higher number of M. tuberculosis in their sputum.

Conclusions: The above study showed that drug resistant cases of tuberculosis in DOTS program of Nepal was found higher. To reduce the drug resistance, before starting chemotherapy antibiotic sensitivity test should be performed.

Key words: granuloma, histopathology, leprosy, Ridley-Jopling classification, tuberculoid

INTRODUCTION

Globally, 9.2 million new cases and 1.7 million deaths from Tuberculosis occurred in 2006, of which 0.7 million cases and 0.2 million deaths were in HIV-positive people.[1] The rate of case detection for new smear-positive cases reached 61% in 2006 (compared with the target of at least 70%) and the treatment success rate improved to 84.7% in 2005, just below the target of 85%.[2] Almost one third of disease burden is in South Asian region.[3]

In Nepal, every year 40,000 people develop active Tuberculosis, of whom 20,000 have infectious pulmonary TB. However, the global target of 85% treatment success has already been achieved due to the expansion of DOTS. However, resistance of *Mycobacterium tuberculosis* to antituberculous drugs has emerged as a major public health threat.[3]

The objective of this study was to determine Multi Drug Resistance (MDR) cases of tuberculosis in Directly Observed Treatment Short Course program (DOTS) of Nepal.

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METHODS

A prospective study was carried out in German Nepal Tuberculosis Project Kathmandu, Nepal from January 2006 to December 2007. Ethical approval was taken. Total 550 clinically suspected pulmonary tuberculosis cases were included in this study. The research objective and methods explained to the patients and verbal consent obtained from them before the sputum sample were collected. The cases were selected using random sampling technique. Initially, the sputum samples was collected, stained by Auramine fluorochrome method and observed under fluorescent microscope. For culture sputum sample were decontaminated and centrifugation using 4% NaOH, according to modified Petroff method and inoculated into Lowenstein Jensen medium incubated at 37°C for 6-8 weeks and followed by biochemical tests (Niacin test, Nitrate reduction test). All the isolates antibiotic sensitivity test was performed on Lowenstein Jensen media by proportional method with critical concentration of 0.25µg/ml isoniazid, 2µg/ml ethambutol, 4µg/ml streptomycin and 40µg/ml rifampicin. Approximately 4 mg moist weight of the growth visualized as 2/3 loopful of 3mm internal diameter 24 SWG nichrome wire loop was added to 0.2ml of sterile distilled water in a 7ml bijou bottle containing 2-3 mm glass beads. These bottles were shaken mechanically for 1 minute at a speed which just lifts the beads from the bottom of the bottle, to produce a uniform suspension. Then, 3.8 ml sterile distilled water was added and the bottles were shaken by hand. These suspensions approximately contain 1 mg/ml of the organisms. From these suspensions, 4 serial 10 fold dilutions viz. 1/10, 1/100, 1/1000, 1/10000 was made by adding 0.2 ml to 1.8 ml sterile water. One loopful of 0.01mg/ml and 0.0001 mg/ml bacillary suspension was inoculated on two slants of drug free control Lowenstein Jensen media and one loopful of 0.01mg/ml of bacillary suspension was inoculated each of different drug containing media. Standard drug sensitive strain was inoculated in each new batch of test medium. The tubes were placed at the slanting position in the incubator for 15 minutes and then in up right position. The cap was tightened when the growth appeared on the control medium after 1-2 weeks of incubation and continues the incubation for 4-6 weeks.

Data were analyzed by EPI-Info version 3.3.2 document version 8.08 updated September 2005.

RESULTS

A total 550 pulmonary tuberculosis patients were included in this study. Multi- drug resistant cases of tuberculosis (primary and acquired) in Directly Observed Treatment Short Course (DOTS) Programme was found 3.6% (Figure 1).

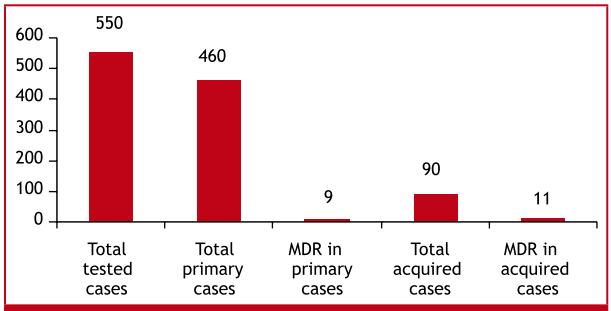

Figure1. Drug resistant cases of *M. tuberculosis* in DOTS programme

Multi drug resistant cases were sensitive to ethambutol 40% and streptomycin 15% (Figure 2).

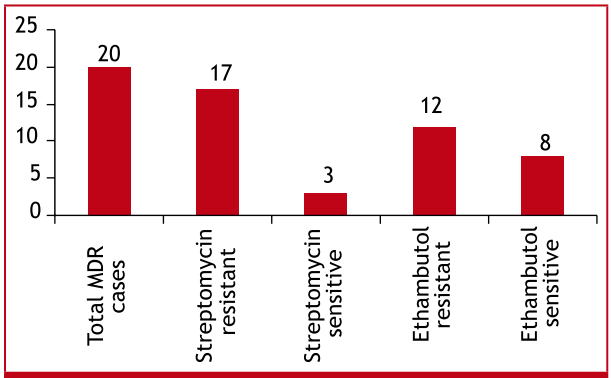

Figure 2. Antibiotic sensitivity pattern of multi drug resistant cases

Majority (60%) of tuberculosis patients sputum found higher number of *M. tuberculosis* (Table 1).

Table 1. Microscopic and culture result interpretation of MDR cases

Microscopic examination	Total cases	New cases	Old cases
1+	9	4	5
2+	5	2	3
3+	6	3	3
Culture			
1+ (20-100 colonies)	8	4	4
2+ (100-200 colonies)	4	2	2
3+ (200-500 colonies) (Almost confluent growth)	8	3	5

The incidence of tuberculosis was found higher in male (64%) than female (34%).

Tuberculosis was most commonly found in economically active (21-50 years old) age group (Figure 3). Multi drug resistant cases of tuberculosis equally affected both the gender. Multi drug resistant cases of tuberculosis were commonly found in 21- 30 years age group (Figure 4).

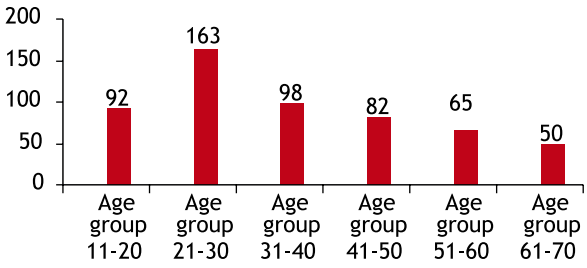

Figure 3. Age wise distribution of patients

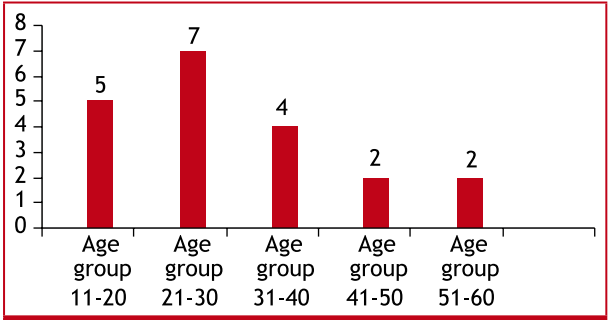

Figure 4. Age wise distribution of multi drug resistant cases

DISCUSSION

With increasing antimicrobial use and misuse over the past several years, resistance to antimicrobial agents has emerged in viruses, bacteria, fungi and protozoa, posing new challenges for both clinical management and control programmes.[4] According to drug susceptibility test out of 550 (both primary and acquired) cases 20 (3.6%) cases were found to be multi drug resistant (resistant to isoniazid and rifampicin). In MDR cases ethambutol was found effective to 8 cases and streptomycin to 3 cases. Multi drug resistant (MDR) cases of tuberculosis were found most commonly in productive young age group (21-40 years age group). Several other workers support our results. A similar study conducted in Nepal, National Tuberculosis Programme (NTP) has carried out repeated surveys on drug resistance. The primary MDR was 1.20% in survey carried out in 1996/97, 3.60% in 1998/99 and 1.30% in 2001/02. NTP surveys have shown around 9 out of 10 chronic TB patients have MDR TB.[6] Similar study conducted in India by TRC and NTI, have found MDR-TB levels is between 0.5% to 3% in new cases and 12% in re-treatment cases.[5] A survey conducted in WHO/IUATLD global project on anti-tuberculosis drug resistance, the third report has data on 77 geographical sites, collected between 1999 and 2002, representing 20% of the global total of new smear positive TB cases. Eight countries did not report any MDR-TB amongst new cases, while the highest incidence of MDR-TB amongst new cases occurred in Kazakhstan and Israel (14%). Significant increases in MDR-TB prevalence were seen in Estonia, Lithuania, Tomsk Oblast (Russian Federation) and Poland and significant decreasing trends in Hong Kong, Thailand and USA. The highest prevalence of MDR-TB among previously treated cases was reported in Oman (58.3%, 7/12) and Kazakhstan (56.4%, 180/319).[6] Thus, genetic resistance occurs in the absence of antimicrobial exposure, but is diluted by the majority of drug-susceptible micro-organisms. The presence of antimicrobials provides the selective pressure for resistant organisms to become predominant, especially in patients with a large load of bacilli e.g. those with extensive cavitary disease.[7, 8]

Drug resistant tuberculosis is a significant threat to tuberculosis control because only a few effective drugs are available against *M. tuberculosis*.[9] In particular, the spread of strains resistant to the two most important drugs, isoniazid and rifampicin could have serious repercussions on the epidemiology and control of tuberculosis. Not only are patients infected with strains resistant to multiple drugs less likely to be cured, but second-or third line treatment is much more toxic and expensive than treatment of patients with susceptible organisms. The emergence of drug resistant *M. tuberculosis* in populations has been associated with a variety of programmatic, health provider and patient-related factors.[10] In many countries, programme factors may include the lack of a standardized therapeutic regimen, or poor implementation compounded by frequent or prolonged shortages of drug supply in area with inadequate resources or political instability. Use of anti-tuberculosis drugs of unproven quality is an additional concern, as is the sale of these medications over the counter and on the black market.

Nearly two thirds (64%) of the patients accounted male as a case of high incidence which is in agreement with (65%) the study conducted by Bam (2003).[11] In almost all areas where the TB is the public health problem, the incidence of TB among women is less than man. This study showed that MDR cases of tuberculosis were equally affected both the gender (50% male and 50% female). Gender is not merely the biological difference but the differences between men and women in their roles, behaviours, expectations and opportunities, within a social cultural and economic context.[12] While drug resistant TB is treatable, it requires extensively chemotherapy (up to two years of treatment) that is often prohibitively expensive (often more than 100 times more expensive than treatment of drug susceptible TB), and is also more toxic to patients.[13] Early diagnosis of the disease and the rapid identification of resistance to primary anti-TB agents are essential for the efficient treatment and control of MDR strains.

The limitation of this study was its small sample size. It represents only 2.75% pulmonary tuberculosis patients

population of Nepal. It is therefore recommended that a large sample size that would cover all rural and urban areas of Nepal to determine prevalence of multi drug resistant should be considered in further investigations.

CONCLUSIONS

Drug resistant cases of tuberculosis in DOTS program was found higher. Hence, it is recommended antibiotic sensitivity test should be performed before starting chemotherapy. Patient should be treated with two or more drugs which are sensitive and ensuring that the treatment is complete, adequate and regular.

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