MULTIDRUG RESISTANT PULMONARY TUBERCULOSIS A CLINICAL PROFILE OF 28 CASES

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ABSTRACT

The clinical profile of 28 cases of multidrug resistant pulmonary tuberculosis was studied. All cases were sputum culture proved, with individual patterns of drug resistance. All were exhibited appropriate second-line antitubercular treatment. Seven (25%) patients defaulted, 2 (7.1%) had second line drug failure, but one of these was salvaged and cured after surgery, 3 (10.7%) were cured after drug therapy and 16 (57%) patients were still under treatment, 8 (28.5%) have converted at 6 months.

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KEYWORDS: Multidrug resistance; Pulmonary tuberculosis.

Introduction

The occurrence of resistance to more than one first line antitubercular drugs in sputum culture of *Mycobacterium tuberculosis* (MTB) especially rifampicin (R) and isoniazid (H) defines multidrug resistant pulmonary tuberculosis (MDRTB) [1]. Most patients acquire MDRTB as a result of monotherapy. The reasons for monotherapy may be varied however the net result is suboptimal, selecting out naturally present single-drug resistant mutant strains that mutate further into MDR strains [2]. Such patients are difficult to treat and constitute a serious threat to exposed individuals [3]. At present the MDR strains are a small percentage of the total pool of MTB, but their alarming increase raises the possibility of an epidemic, in the not too distant future, for which the world is ill prepared [4]. This study has been carried out with the aim of evaluating the clinical profile of MDRTB patients.

Material and Methods

All patients displaying MDR strains on sputum culture were eligible for entry into the study. Patients were inducted into the study from January 1994 to December 1995. Sputum culture and antibiotic sensitivity testing was performed on all pa-

tients who had clinical, radiological or sputum smear evidence of persistence or relapse of tuberculosis despite historical evidence of at least 6 months of first-line ATT.

Once proved to have MDRTB as defined above, the patients were taken up for study. A detailed history including previous drug therapy and reasons for monotherapy, if any, were probed. A detailed clinical examination was performed. Baseline metabolic parameters including blood sugar levels, liver and kidney functions were carried out. HIV status was assessed by ELISA. Radiography of the chest and sputum smear and culture studies were carried out every 3 months.

The patients were exhibited ATT according to culture studies. All first-line drugs to which the patient's culture showed sensitivity as well as appropriate second-line drugs were added so that the patient received at least 5 drugs initially, with one aminoglycoside included for the first 6 months. Treatment was considered successful and continued if the patient converted at 6 months and planned to be continued for 2 years from the time of conversion.

A culture positive status at 6 months was considered to constitute drug failure and fresh modification with remaining drugs was to be considered.

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Fig. 1: Age range of patients with multidrug resistant tuberculosis

For treatment failure at a later date the same protocol was followed. Surgical options were considered for disease localized to one lobe or lung.

Care was taken that single drug changes or use of 2 drugs from the same group or where cross-resistance had been documented were not exhibited. The patients were motivated, drug reactions monitored and all ATT was made available free of cost. Criteria of cure was a persistent sputum negative status by culture for a period of 2 years after conversion.

Results

During the study period 722 patients were treated for pulmonary tuberculosis, 43 sputum cultures were performed on suspected MDRTB. In all 28 (3.9%) patients were found to have MDRTB. There were 15 (53.5%) males and 13 (46.5%) females. The age range was from 16 to 80 years with 25 (89.2%) between 20 to 60 years (Fig 1). All patients were from the lower income groups. Though only 6 (21.4%) were smokers, chronic bronchitis and obstructive lung disease was found in 13 patients (46.4%). All denied history of alcohol and substance abuse, 3 (10.7%) gave history of drug reactions requiring modification of 1st line ATT. Four (14.2%) patients had non-insulin dependent diabetes mellitus (NIDDM). Only 5 cases (17.8%) had detailed records of previous ATT. The length of first-line ATT at time of diagnosis of MDR ranged from 1 to 8 years with 20 (71.4%) having taken ATT for 1 or 2 years (Fig 2). The reasons for development of MDR were probed. Fourteen (50.0%) patients admitted to non-compliance,

Fig. 2: Duration of ATT at time of diagnosis of drug resistance

ance, 8 (28.5%) cases had relapse, 5 had treatment failure (17.8%), and 1 had primary drug resistance (3.6%). Among the non-complaint group 6 (21.4%) patients modified drug therapy on their own. 3 (10.7%) frequently changed doctors, 3 (10.7%) had drug reactions and took prolonged monotherapy whereas 2 (7.2%) took treatment from District Tuberculosis Centre (DTC) where there was frequent change in drug therapy. The radiographic patterns seen were cavities in 11 (39.2%), soft lesions in 5 (17.8%), destroyed lobe in 3 (10.7%) destroyed lung in 8 (28.5%) and hydropneumothorax in 1 (3.6%). Among the patients with destroyed lung it was found that 7 had left-sided lung destruction. No correlation between length of ATT and destroyed lung could be established. All patients were HIV negative. Fourteen (50%) patients had two-drug resistance, 7 (25%) had three-drug resistance, 5 (17.8%) were resistant to 4 drugs, while 2 (7.2%) were resistant to 5 or more drugs.

The extent of drug resistance is shown in Fig 3. Maximum resistance was found to H in 26 (92.8%) and R in 27 (96.4%). Resistance to pyrazinamide, clofazamine, roxithromycin and azithromycin was not tested. Resistance to cycloserine, kanamycin, amikacin was not seen. Three (10.7%) cases were declared cured after drug therapy, 2 (7.2%) had second-line failure, out of these one w been salvaged with pneumonectomy and thoracoplasty (Fig 4). One patient was placed on repeat modified second-line ATT. Seven (25%) patients defaulted, all during the 1st 6 months of starting 2nd line ATT. The remaining

Fig. 3: Extent of drug resistance

16 (57%) were in various stages of treatment and (28.5%) have converted at 6 months of starting second-line ATT. Drug reactions or intolerance requiring change in drug therapy was not seen in any patient while on second-line ATT.

Discussion

Our study shows higher incidence of multi-drug resistance than reported earlier by others [5]. Though the maximum resistance seen was to H and R, a worrying trend is the resistance to second-line drugs that have come into recent use, i.e. ciprofloxacin and ofloxacin, reflecting premature monotherapy by physicians. The major reason for development of drug resistance remain noncompliance, and even where the label of relapse or treatment failure is applied there must be phases of monotherapy for MDR to emerge [6]. We could document only one case where the individual had been infected by a known case of MDR.

Our study showed a higher prevalence of chronic bronchitis and obstructive lung disease in MDR patients as compared to the general population. Chronic tuberculosis predisposes the individual to develop obstructive lung disease independent of smoking, this has been documented by others [7]. The prevalence of NIDDM was also found to be higher than that in the general population reflecting a role of the immune system in clearance of infection [8]. The commoner occurrence of destroyed lung on the left side has been commented on by other workers, and thought to be caused by the poorer drainage created by the hori-

Fig. 4: Radiograph of a MDRTB case salvaged with pneumonectomy and thoracoplasty.

zontal left bronchus [9]. Lung destruction was seen even in those patients who had disease for relatively short periods of time perhaps reflecting excessive hypersensitivity. Twenty five per cent of the patients defaulted in the first 6 months of second-line therapy. We speculate that there are personality types who practice noncomplaint behaviour, they must be identified for sanitorial or directly observed therapy. So far we have managed to cure 4 (10%) of the remaining patients. The cure rate reported from the best centres is 30-50 per cent with a relapse rate of 20 per cent.

Several guidelines emerge from our study. First, the emergence of MDR must be prevented at all costs by preventing monotherapy. This requires physician education, efficient patient management and prescription of fixed drug combinations. Second, the management of MDRTB is complex, difficult, and expensive requiring the availability of sputum culture and antibiotic sensitivity. Lastly, all patients who remain sputum smear positive despite 3 months of adequate first-line therapy, as well as relapse cases must be referred for culture studies and thereafter managed by experts.

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