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Primary and Acquired Drug Resistance in Childhood Tuberculosis

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ABSTRACT

Background: *Increased rates of multidrug-resistant tuberculosis (MDR-TB) have been reported from developing countries. We evaluated the incidence of drug resistance in children in order to determine the magnitude of the problem, in our region.*

Objective: To determine the resistance pattern of Mycobacterium tuberculosis to four anti-tuberculosis drugs in childhood pulmonary tuberculosis at National Research Institute of Tuberculosis and Lung Disease (NRITLD) which is a referral centre in Tehran. Treatment of the patients was based on the DOTS strategy according to the WHO protocols since 1989.

Materials and Methods*: Retrospective analysis of all cases of pulmonary tuberculosis with positive M. tuberculosis culture who had referred to paediatrics ward from January 1999 to August 2004. M. tuberculosis sensitivity testing was performed by the Lowenstein-Jensen medium for isoniazid (INH), rifampicin (RMP), streptomycin (SM), and ethambutol (EMB).*

Results*: Among 350 children (0-15years) with confirmed tuberculosis, 7 children had resistance to at least one of the four anti-TB drugs. Out of the 7 patients, 6 were Afghan refugees and one patient was Iranian. Among those 85.7% had resistance to RMP, 71.4% to INH, 57.1% to SM, and 28.6% to EMB .In addition, 28.5% of patients had resistance to all four drugs (RMP, INH, SM, EMB), 14.2% to INH, RMP, SM, 28.5% to INH, RMP and 14.2% had resistance to each of SM and RMP.*

In this study 2% of children with TB had resistance out of which primary resistance was detected in 57.1%. Secondary resistance was found in 42.9% of cases who had previous history of anti-TB therapy.

Conclusion: *According to 2% prevalence of drug resistance in children and high resistance to RMP in our study, more aggressive interventions should be considered. Further management and supervision in DOTS implementation is highly recommended to prevent transmission of resistant tuberculosis.* ***(Tanaffos 2004; 3(10): 33-39)***

Key words*: Tuberculosis, Resistance, Children*

INTRODUCTION

Drug-Resistant tuberculosis and particularly Multi- Drug Resistant tuberculosis (MDR-TB is defined as resistance to at least INH and RIF) is an increasing health problem and a serious challenge for TB control programmers (1). The drug resistant mycobacterium tuberculosis strains emerge whenever heavily infected individuals are inadequately treated,

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when treatment has been interrupted or when a single drug has been added to a failing regimen (2).

Children with multi-drug resistant tuberculosis usually have primary resistance and they are infected with strains transmitted from adult MDR-TB. The transmission rate of strains of MDR-TB has been shown to be the same for children as for adults (3).

The frequency of drug resistance, especially MDR TB is found to be generally high in countries categorized by the WHO as having poor control programs (4, 5). Sub-optimal control programs can lead to rapid emergence of drug resistance in both developed and developing countries such as New York City (6) or India (7).

According to the reports from South Africa the incidence of INH resistance was 5.6% and MDR rate was 1% among children below 5 years of age (8). There is few studies of drug resistant TB in children and no data from developing countries could be traced.

Information about the susceptibility patterns of Mycobacterium tuberculosis isolates against anti tuberculosis drugs is an important aspect of tuberculosis control. Surveillance and analysis of local rates of TB drug resistance is helpful in the detection and monitoring of the extent of MDR strains indicating a quality of TB control in the country (9).

The aim of this study is to determine the prevalence of drug resistance among children with tuberculosis who were admitted to NRITLD and to compare the clinical and radiological features of drug resistant and drug susceptible TB among these children.

MATERIAL AND METHODS

Setting

This retrospective study was conducted between January 1999 and August 2004 at NRITLD, a referral center for TB and Lung diseases in Tehran, Iran. DOTS regimen was carried out for all cases since 1989.

Clinical Data

The clinical records of all children with positive cultures for M. tuberculosis were reviewed. A history was obtained from all children regarding previous TB prophylaxis or treatment and whether they were in close contact with adults suffering from pulmonary TB. Site of the tuberculous involvement was recorded. Results of tuberculin skin test (Mantoux test by intra dermal injection; 0.1 ml of 5 tuberculin units) were noted down. An induration of ?15mm after the testing was regarded as significantly positive in accordance with WHO criteria (10). Chest radiographs or CT-scan were assessed and classified.

Definition of primary and acquired resistance in M. tuberculosis isolates

Primary resistance was defined as the presence of resistance to one or more anti-tuberculosis drugs in strains obtained from patients who had never received treatment. Acquired resistance was defined as resistance to one or more anti tuberculosis drugs in strains recovered from patients who had received previous anti tuberculosis treatment (11). MDR TB was defined as a child under the age of 15 years with findings of tuberculosis by radiography and 1) a household contact with MDR TB, or 2) a culture demonstrating M.tuberculosis with resistance to at least INH and RMP by the proportion technique or Bactec (12).

Drug susceptibility testing

Sputum or gastric washing of all children with positive cultures were sent to the NRITLD laboratory for sensitivity testing to INH, RMP, SM, and EMB. Cultures were performed routinely on Lowenstein-Jensen medium. Laboratory procedures for determining drug resistance were as follows: Specimens were digested and decontaminated by N-Acetyl-L-Cystein NaOH method, as described by Kent and Kubica (13), with a final NaOH

concentration of 1%. After decontamination, smear was prepared from the sediments for Zeihl-Neelsen acid fast staining. Then 0.2 ml of the processed was inoculated onto each of four L.J slants (prepared in NRITLD laboratory). All inoculated media were incubated at 37°C. The inoculated solid L.J media was inspected weekly for 8 weeks. All positive results were verified by Zeihl-Neelsen staining. Colonies from surface of L.J medium, were transferred into sterile test tube containing 6-8 glass beads and 3.0ml of middle brooke 7H9 Broth. The suspension was adjusted to 1 McFarland standard. Thereafter, the dilutions of 1/10,1/1000,1/100000 were prepared and inoculated into drug containing media and controls. The concentration of drugs in each experiment were as follows; 0.2 µg/ml for isoniazid, 40 µg/ml for rifampin, 2 µg/ml for ethambutol and 4 µg/ml for streptomycin (14).

RESULTS

During a five-year period from January 1999 to August 2004, 350 children with TB were admitted in NRITLD. Among those seven children with drug resistance were obtained including 5(71.4%) boys and 2(28.6%) girls with a median age of 14.5 years (range 14-15 years). HIV test was performed for all seven cases and the result was negative. All of the children had pulmonary tuberculosis and no evidence of extra pulmonary involvement was found. The majority of cases were from Afghan immigrants; the prevalence of resistance in this group was 6 cases (85.7%) in comparison with one Iranian child who was confirmed as a MDR-TB.

Clinical data

We reviewed the records of all seven children. Among them the most common symptom was productive cough seen in 6 children (85.7%). Other symptoms were fever in 5 children (71.4%), hemoptysis in 3 (42.9%) children, dyspnea and night chills in 2 (28.6%) and weight loss in 1 child (14.3%).

Radiographic data

The radiographic changes in 7 cases were reviewed. Radiographic results were available in 6 patients (85.7%). Among the 6 patients the most common finding was infiltration in lung parenchyma which was observed in 4 cases (57.1%), along with calcification, cavitation, hilar adenopathy, pneumothorax, fibrosis and reticulonodular changes which were seen each in one case (14.3%).

Susceptibility results

In all of the cases susceptibility results were compared. Out of 7 cases, 6 (85.75%) had resistance to RMP, 5 (71.4%) to INH, 4 (57.1%) to SM and 2 (28.6%) to EMB. In addition, 2 cases (28.5%) had resistance to all four drugs (RMP, INH, SM, EMB), 1(14.2%) to INH, RMP, SMP, and 2 (28.5%) to INH, RMP (Table 1).

Table 1. Susceptibility pattern among seven children with drug resistance

Drugs (Resistant)	Number of cases (%)
RMP	6 (85.7%)
INH	5 (71.4%)
SM	4 (57.1%)
EMB	2 (28.5%)
INH,RMP,EMB,SM	2 (28.5%)
INH,RMP	2 (28.5%)
INH,RMP.SM	1 (14.2%)
Only to SM	1 (14.2%)
Only to RMP	1 (14.2%)

Primary and acquired resistance

Among seven children 6 patients (85.7%) had history of household contact. Only one afghan boy

(14.3%) with resistance to INH and RMP didn't have any close contact with other TB patients. The most common contact was with their mother and uncle. Two cases (28.6%) were in close contact with their brother and father (14.3%).

Table 2. Drug resistance in each of the primary and secondary group

Drug	Primary 4 Cases (57.1%)	Secondary 3 Cases (42.9%)
RMP	3 (77%)	3 (100%)
INH	3 (77%)	2 (66%)
SM	2 (50%)	2 (66%)
EMB	1 (25%)	1 (33%)

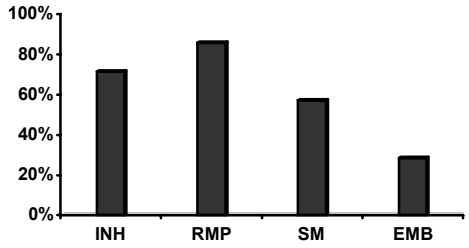

Figure 1. Prevalence of resistance to drugs.

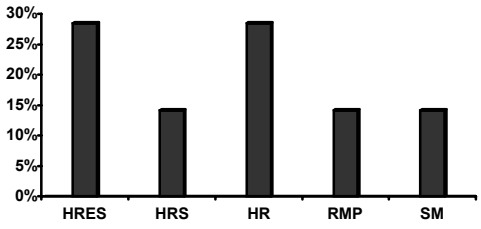

Figure 2. Pattern of resistance to drugs.

DISCUSSION

Surveillance of anti-tuberculosis drug resistance in a community provides a measure of the success of the NTP and gives an indication of suitable drug regimens for future use (15). Primary or initial resistance patterns reflect transmission of drug resistant strains, but as tuberculosis in children is a mark of recent TB transmission in a community, the frequency of drug resistance in children, particularly those<5 years of age, reflects a precise evaluation of the current situation (1, 15)

The most comprehensive study to date, by Steiner et al.., was conducted over a 24 year period(1961-1984) in King country Hospital center, New York.(16,17). Out of 374 children screened for primary drug resistance 16.3% had resistance to one or more anti tuberculosis drugs. INH was relatively stable at 10%, but RMP resistance which was introduced during this period, was on the increase (16).

In another study which was conducted by Schaaf HS et al in the year 2000, out of 306 children with positive culture for M.tuberculosis, 6.9% were resistant to isoniazid and 3.2% had MDR (8). A research was carried out on 11480 children with TB in the United States during 1993-2001. In this research among those children with positive BK culture, drug resistance to isoniazid and rifampin was 7.3% and 1.6% respectively (18).

In third world and developing countries a comprehensive study regarding the prevalence of drug resistance in children does not exist. Although some literatures showing the status of drug resistance among the adult population are present. In the year 2001, a study was conducted by Al-Marri in Qatar. In this investigation out of 406 cases of positive culture for M.tuberculosis, at least 15% of the cases had resistance to one of the 4 anti TB drugs. Out of this, 95% had primary and 5% had secondary resistance. Also, maximum resistance was observed in case of isoniazid which was 15% (19).

In this research out of 350 children, 7 cases had resistance to at least one of the four anti TB drugs.

The prevalence of resistance is 2% which is lower than similar data and studies.

The low prevalence rate mentioned above could

be explained by the absence of culture and antibiogram in children with TB and also the presence of a weak screening system in case of contacts of smear positive adults (specially contacts of MDR patients). Since a comprehensive and thorough study has not been performed in regard to drug resistance in children in Iran, thus accurate data and figures do not exist. As mentioned in this text out of 7 patients that had drug resistance, 6 were Afghan. This high number could be explained by the low socio-economical status, malnutrition, delay in diagnosis and irregular use of anti TB medications, which act as predisposing factors in this group of patients.

Meanwhile, in 4 of the children (57%) primary and in 3(43%) secondary resistance was detected which could be explained by the fact that resistance is more common in children (3).

As reported in several studies, rate of resistance to RMP is very low (3,20,21). However, in our study resistance to RMP both in primary and secondary resistances was high. According to our results 6 patients (85%) had resistance to RMP; 3 (42%) from each of primary and secondary resistance groups. Also, in regard to INH resistance, 3 (75%) from primary and 2 (66%) from secondary resistance groups showed resistance. At the same time resistance to EMB and SM in both groups were nearly similar.

Based on the above statistics, it seems that resistance to RMP was higher in our study as compared to others. Different circumstances such as genetic factors and or the composition of anti TB drugs present in Iran are responsible for the difference observed.

The aim of this research was to determine the pattern of drug resistance in children suffering from TB at National Research Institute of TB and Lung Disease. The result was a 2% drug resistance which was lower than other similar studies carried out in the region. It seems that by implementing DOTS strategy in the country since 1989 and carefully supervising the TB treatment the prevalence rate of drug resistance in children has lowered.

It is recommended that more detailed studies with culture and antibiogram should be conducted in children with TB specially in those who have clinical and or radiological evidences of drug resistance, in order to control the spread of drug resistance in the society.

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