Drug-resistant tuberculosis in Turkish children

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The purpose of this study was to determine the prevalence of anti-tuberculosis drug resistance in children followed at Hacettepe University İhsan Doğramacı Children's Hospital. Sixty cases with tuberculosis for whom susceptibility testing was available were searched retrospectively. Teh overall drug resistance was 26.7 percent. Resistance to streptomycin (sm) was the most frequent (18.3%), followed by isoniazid (6.7%), rifampicin (6.5%), and ethambutol (4.2%). Strain resistant to more than one drug was present in two cases (3.3%).

In summary, excluding SM, both single and multidrug resistance were relatively low in our pediatric patients.

Key words: children, tuberculosis, durg resistance.

Since isolation of tubercle bacilli and susceptibility testing take a long time, test results frequently are not available when the patient needs to start on therapy. Also, a subtantial portion of cases of tuberculosis in children are not confirmed by culture, making susceptibility testing impossible[1,2]. Empiric therapy is often necessary. In order to choose an empiric regimen likely to be effective, local patterns of drug resistance must be known. This is especially important in early childhood because the morbidity and mortality of tuberculosis is at its highest during this period[1,2]. Most studies about drug-resistant tuberculosis have been reported in adult patients. Few extensive data are available in children, a problem not only in Turkey, but also in other countries[2,3]. We thus conducted a retrospective study of M. tuberculosis resistance in children followed in our division with culture-positive tuberculosis.

Material and Methods

We included in this study all patients with culture-positive tuberculosis who were followed at Hacettepe University Children's Hospital between 1975 and 1995 and for whom susceptibility testing was performed in Hıfzısıhha Institute, which is a reference laboratory for tuberculosis (TB) studies in Turkey. According to the localization of the disease, most of the specimens investigated were sputum, followed by tissue specimens, cerebrospinal fluid, and peritoneal fluid, respectively.

Both culture and susceptibility testing was performed on Löwenstein-Jensen solid media. Standard proportion method was used for the susceptibility testing. The drug concentrations used were: isoniazid (INH), 0.2 µg/ml; rifampicin (RIF), 40 µg/ml; streptomycin (SM), 4 µg/ml; and ethambutol (EMB), 2 µg/ml. Drug resistance was defined as the presence of at least one percent growth on the drug plate for INH and RIF and 10 percent for SM and EMB when compared with that on the control plate.

Single drug resistance was defined as the presence of resistance to a single drug tested and multidrug resistance as presence of resistance to at least two drugs tested. Drug resistance detected in patients without a history of previous treatment was defined as primary resistance. Resistance in a patient with a history of previous drug treatment was defined as secondary resistance.

Other clinical and demographic information about the patients were obtained from the hospital files. Student's t and chi-square tests were used in the statistical analysis.

Results

Between 1975 and 1995, among the culture-positive patients, 60 cases for whom susceptibility testing was performed in Hıfzısıhha Institute were reported. All isolated strains were M. tuberculosis hominis. Patients were from different regions of the country. Their ages ranged from two months to 15 years (mean 5.2 ± 4.5 years, median 4.0 years). Human immunodeficiency virus serology was not investigated but within the three to 15 year follow-up period (mean 6.05 ± 0.44 years), no patients were diagnosed as acquired immunodeficiency syndrome. Forty-one patients were diagnosed as pulmonary disease and 19 as extrapulmonary tuberculosis. Eight patients with extrapulmonary tuberculosis also had pulmonary involvement. Lymph nodes were the most common extrapulmonary sites (13.3%), followed by tuberculous meningitis (10%), osseous tuberculosis (6.7%), and abdominal tuberculosis (1.8%), respectively.

Overall resistance to at least one antituberculous drug was present in 16 (26.7%) patients (Table I). Strains of M. tuberculosis resistant to a single drug were found in 14 (23.3%) patients. Nine of the single drug-resistant strains were found to be SM-resistant. Multidrug resistance was present in only two (3.3%) cases: one against two drugs and one against three drugs. Strain resistant to more than three drugs was not isolated. The most common drug resistance was found to be SM (18.3%), followed by INH and RIF. No strain was resistant to INH and RIF simultaneously, but resistance to one or the other was present in seven patients. Since there was no history of previous treatment, all resistance was defined as primary resistance.

Table I. Incidence of Anti-Tuberculosis Drug Resistance

	Strains tested	Strains resistant	
Drug	(n)	(n)	(%)
INH	60	4	6.7
RIF	46	3	6.5
SM	60	11	18.3
EMB	44	1	2.3
INH only	60	3	5
RIF only	46	2	4.3
SM only	60	9	15
EMB only	44	–	–
RIF+SM	46	1	22
INH+SM+EMB	44	1	2.3
Overall resistance	60	16	26.7

INH : isoniazid.
RIF : rifampicin.
SM : streptomycin;
EMB : ethambutol.

The number of cases with SM-resistant strains increased from 3/26 (11.5%) to 8/34 (23.5%) (Table II). All four strains resistant to INH were observed in the last ten years (between 1986 and 1995). Neither increase was significantly different (p = 0.23, p = 0.07 respectively). Overall resistance in pulmonary tuberculosis was 21.9 percent, and for extrapulmonary tuberculosis it was 36.8 percent (p = 0.23).

Discussion

The most significant finding in the present study was the high rate of SM resistance, as has been seen in many other reports, including another study from Turkey[3-5]. This is attributed to its being the longest and most frequently used both in TB and other non-TB infections. We excluded SM from intermittent anti-TB therapy in our division after discovering this high resistance rate[6,7]. Indeed, considering our

Table II. Drug Resistance of M. tuberculosis from 1975 to 1995

	Isoniazid			Rifampicin			Streptomycin			Ethambutol		
		Resistant strains			Resistant strains			Resistant strains			Resistant strains	
	Strains Tested	(n)	(5)	Strains Tested	(n)	(%)	Strains Tested	(n)	(%)	Strains Tested	(n)	(%)
1975-1985	26	–	–	14	1	7.1	26	3	11.5	10	–	–
1986-1995	34	4	11.8	32	2	6.3	34	8	23.5	34	1	2.9
Total	60	4	6.6	46	3	6.5	60	11	18.3	44	1	2.3

results, this was an appropriate decision. INH and RIF were the other two drugs with a high resistance rate. On the other hand, resistance to EMB, which is usually employed when the organism is resistant to the more commonly used agents or when there are severe side effects, was low. In this report, EMB had been used in only two cases because of the presence of liver disease.

Two strains showed resistance to more than one drug, but no strain was defined as resistant to both INH and RIF. It is especially important, because these two drugs are the choice in two-drug intermittent regimens in our department. Patients were successfully treated with these regimens and within the three to 15 year follow-up period no relapses were reported.

Resistance rate was unexpectedly higher in patients with extrapulmonary disease (36.8% vs 21.9%). The other report with a similar high drug resistance in extrapulmonary tuberculosis was from Ben-Dov et al.[8]; however, most of their patients had secondary resistance. In our study there was no previous treatment, so all our cases had primary resistance. Because of its high mortality and morbidity when compared to pulmonary disease, we believe that any resistance in extrapulmonary sites is clinically more important.

We observed an insignificant increase in the resistance against SM and INH over the last ten years. Since INH was the drug of choice in the prophylaxis of tuberculosis in our division for many years, more attention should be given to this increase. Rifampicin resistance was not altered during this period.

Few data are currently available about drug-resistant TB in Turkey. In 1992, a study in adult patients revealed that overall drug resistance was 35.5 percent[5]. In the same study, primary and secondary drug resistance were 26.6 and 53.4 percent, respectively. Streptomycin was the drug to which resistance was encountered most frequently, as in our study. Also, in two other studies reported from Turkey, overall and multiple drug resistance were higher[9,10]. The higher drug resistance as compared to our results may be partially due to the high rate of secondary resistance, since there was no secondary drug resistance in our study.

Identification of adult source cases and information about their drug susceptibilities are helpful in the selection of early empirical treatment. In many reports, an excellent correlation of the patient and the adult source was shown[4]. No information about the source case susceptibility pattern was available in our patient files. This is especially important since resistance in our cases, which appeared to be primary, might actually be due to transmission of resistant strains from adult source cases. In sumary, excluding SM, both single and multidrug resistance were relatively low in our pediatric patients. Much attention should be given to adult source case isolation and drug susceptibility pattern. The pattern reported here is important not only for Turkey but also for other developed countries in the selection of empirical regimens for foreign-born patients.

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