RESEARCH BRIEF

Clinical Profile of Drug Resistant Tuberculosis in Children

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This Cross-sectional observational study was conducted to determine the clinical profile of drug-resistant tuberculosis in children. Patients were classified as monoresistant TB, polyresistant TB, multidrug resistant (MDR)-TB and extensively drug resistant (XDR - TB). We coined a term called as Partial XDR-TB when isolates of *Mycobacterium tuberculosis* were confirmed to be resistant *in vitro* to be MDR along with either a fluoroquinolone or an aminoglycoside resistance (apart from streptomycin). Of 500 children analysed, 34 (6.8%) had drug resistant TB. Mean age of presentation was 6.8±3.2 years (Male: Female ratio 13:21). 18 (52.9%) children had been treated for tuberculosis in the past (1 defaulted), 7 patients had been in contact with an adult suffering from drug resistant TB and 3 patients (10.3%) were HIV co-infected. Fourteen children (41.2 %) had MDR TB, 11 (32.4 %) had Partial XDR, 1 each (2.9 %) had polyresistant TB and XDR TB. Clinical features of DR-TB are similar in all age groups. Past history of TB with treatment with antitubercular agents, and contact with adults suffering with drug-resistant TB are important risk factors in development of drug-resistant -TB in children.

Key words: *Children, Drug resistant tuberculosis, India, Outcome.*

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The current threat to tuberculosis (TB) control is due to the emergence of strains resistant to the two most potent anti-TB drugs *viz*., isoniazid (H) and rifampicin (R) (multidrug resistant-tuberculosis, MDR-TB). The response of patients with MDR-TB to treatment is poor and the mortality rate is usually high [1,2], and situation is further threatened by the emergence and spread of HIV [1]. Information on drug-resistant (DR) TB is limited to a small number of patients or is incomplete, especially in children [1-4]. Thus, this study was done to define the clinical profile of drug resistant TB in children.

METHODS

This cross-sectional observational study was done at our Pediatric TB Clinic over a period of three years from the July 2007 to August 2010 after approval from the institutional ethics committee and informed consent from the parents of children. Five hundred children less than 15 years of age who were diagnosed to have TB were studied. Children were defined to have drug resistant -TB if their drug susceptibility testing (DST) detected resistance to any of the antitubercular drugs, or these children were in contact with an adult suffering from culture proven drug resistance. Specimens used for cultures were sputum/ bronchoalveolar lavage (BAL) in case of pulmonary TB, lymph nodes in case of TB lymphadenopathy, pus in case of bone TB, cerebrospinal fluid (CSF) in case of TB meningitis, pleural fluid in case of pleural effusion, and DST from contacts with DR-TB. Children who were clinically suspected to DR- TB but were not culture proven were excluded from the study. Patients were classified to have monoresistant TB, polyresistant TB, MDR TB and XDR-TB as per WHO classification [3]. Others were classified as contact with DR-TB, and Partial XDR TB if they had MDR TB along with either a fluoroquinolone or an aminoglycoside resistance (apart from streptomycin) [4]. Antitubercular therapy (ATT) susceptibility pattern testing for all 13 drugs including isoniazid(H), rifampicin(R), pyrazinamide(Z), ethambutol(E) and streptomycin(S), amikacin (Amk), kanamycin (Km), fluoroquinolones, capreomycin, Clofazimine (Cfz), ethionamide (Eth), PAS were done for these patients after culture on broth and solid media was positive and appropriate second line drugs were started on them.

A detailed clinical history and physical examination were done in all patients. History of BCG vaccination, past TB or contact with TB (contact with a person who is taking ATT or has taken ATT in past 2 years was elicited. All patients were screened with chest *X*-ray and mantoux test (MT). In case of positive MTB on smear or culture, or a patient who had a positive MT in the past, MT was not done. A positive Mantoux test was considered if it was more than 10 mm with maximum 5 TU units. Latent TB

was defined as an asymptomatic MT positive child in close contact with an adult having open TB in the past 2 years. Radiological evaluation of disease progression in form of Chest *X*-ray, ultrasound of abdomen and neuroimaging (CT scan and MRI) were done and as and when required. Tissue cultures for repeat DST testing were done when feasible. Pre-test HIV counselling was done in all patients as per WHO criteria [5] and HIV-ELISA was done only after consent in these patients. Investigations such as hemogram, liver and renal biochemistry, uric acid, thyroid function tests and ophthalmological examination for colour blindness along with hearing assessment were done at start of therapy as well as bimonthly intervals when these patients were put on second line ATT.

Clinical and biochemical features associated with drug resistant-TB were analysed. The children were divided into 3 age groups *viz.* <5 years, 5-10 years, and >10 years, and factors associated with drug resistant TB in various age groups both sexes were analyzed. Since patients are on therapy at time of study, their response to treatment has not been assessed in this study. Statistical significance between the mean was calculated by student *t* test and analysis of variance (ANOVA). Proportions were analysed by Fisher Exact test. $P<0.05$ was considered significant.

RESULTS

During the study period, drug-resistant TB was seen in 34 (6.8%) children (***Fig.* 1**). The specimens used was from sputum/BAL in 17 (50%) children, lymph nodes in 8 (23.5%) children, CSF in 2 (5.8%) and pus and pleural fluid in 1 (2.9%) patient each. Five (14.7%) children were defined as DR-TB based on DST report of the contacts. Mean age of presentation of DR-TB was 6.8 ± 3.2 years. Male: Female ratio was 13:21. Common clinical features of DR-TB and their duration are depicted in ***Web Table* I**. Eighteen children (52.9%) had been treated for tuberculosis in the past and took ATT for 10.6 months of which 1 (5.5%) defaulted. The type of TB that they had suffered from in the past were abdominal TB in 3 (16.7%), pulmonary TB in 12 (66.7%), TB lymphadenopathy, TB osteomyelitis and latent TB in 1 (5.6 %) each. Sixteen (47.1%) patients had contact with an adult suffering from TB of which 7 (43.8%) has drug resistant TB. Three patients (10.3%) out of 29 tested were HIV co-infected. Thirty one (91.2%) children had received BCG vaccine and 21 out of 25 patients (61.8%) had a positive mantoux test.

The individual drug resistance in children to different drugs was 100% for isoniazid, 97.1% for rifampicin, 76.5% for streptomycin, 67.6% for ethambutol, 47.2% for ofloxacin, 23.5% for ethionamide, 20.6% for moxifloxacin, and 14.7% for PAS. Repeat TB cultures could only be done in 3 patients of which 2 still grew MTB and one of them showed additional drug resistance to PAS, kanamycin and ethionamide on repeat culture.

Factors associated with DR-TB in different age groups are depicted in ***Table* I**. Nine (69.2 %) boys had contact with an adult suffering from TB as compared to 7 (33.3 %) girls ($P=0.045$). Type of TB did not differ between boys and girls ($P=0.306$). Loss of weight was seen in 18 (85.7%) girls as compared to 6 (46.2 %) boys ($P=0.019$).

DISCUSSION

This is the first study on drug-resistant TB in children from India. Schaaf, *et al*. [6] reported a prevalence of 6.5% of MDR TB in 2003-2005 in children <13 years of age at Children's Hospital in South Africa. Recent estimates on the prevalence of MDR-TB in new smear positive pulmonary TB (PTB) cases in adults in India is <3% and 12 to 17% amongst smear positive previously treated PTB cases [1]. In our study, prevalence of drug resistant TB in children was 6.8%. Though yield of getting a culture proven drug resistant TB is less in children as compared to adults due to inability to get the sputum in children easily, still a prevalence of 6.8% is high and suggests that prevalence in adults may be even higher.

Schaaf, *et al.* [6] in their study from South Africa found that median age of MDR-TB in children was 2.5 years (53.6% boys). In our study, median age of presentation of DR-TB was 7 years and children in the above 5 years constituted maximum number of patients. One of the reasons of presentation of DR-TB in slightly older children as compared to Schaaf, *et al*. may be due to inability to get tissue cultures in younger children [6]. In our study extrapulmonary DR-TB was seen in 64.7% suggesting that tissue culture diagnosis may be difficult in these patients.

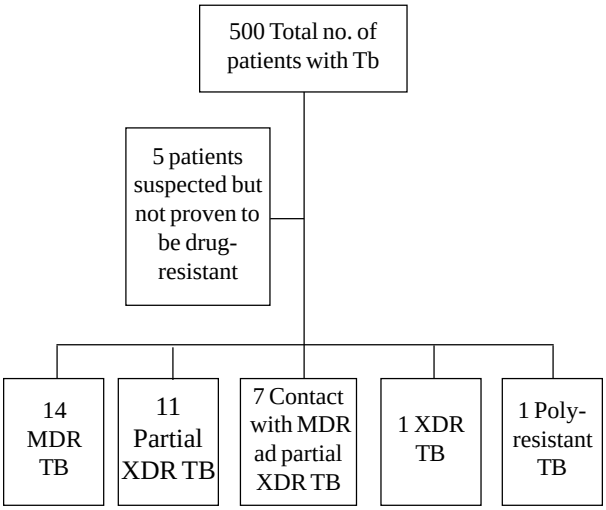

FIG. 1 *Flow diagram of patients in the study*.

TABLE I FACTORS ASSOCIATED WITH DR-TB IN DIFFERENT AGE GROUPS

Factors	*<5 yrs (n=12) n (%)*	*5-10 yrs (n=18) n (%)*	*> 10 yrs (n=4) n (%)*
Male	7 (58.3)	6 (33.3)	0
Fever	7 (58.3)	15 (83.3)	2 (50)
Cough	5 (41.7)	11 (61.1)	1 (25)
Loss of appetite	7 (58.3)	13 (72.2)	3 (75)
Loss of weight	7 (58.3)	14 (77.8)	3 (75)
Malnourished	7 (58.3)	12 (66.7)	1 (25)
Past history of TB	3 (25)	11(61.1)	4 (100)
History of TB contact	8 (66.7)	7 (38.9)	1 (25)
Type of drug resistance			
Contact with Partial XDR	2 (16.7)	1 (5.6)	0
MDR	2 (16.7)	8 (44.4)	4 (100)
MDR with contact	3 (25)	1 (5.6)	0
XDR	1 (8.3)	0	0
Partial XDR	4 (33.3)	07 (38.9)	0
Polyresistant	0	1 (5.6)	0
Type of current TB			
Pulmonary TB	4 (33.3)	7 (38.9)	1 (25)
Disseminated TB	2 (16.7)	7 (38.9)	1 (25)
TB Lymphadenopathy	2 (16.7)	1 (5.6)	1 (25)
Abdominal TB	0	2 (11.1)	1
(25)Latent TB	1 (8.3)	1 (5.6)	0
TB Osteomyelitis	1 (8.3)	0	0
TBM	1 (8.3)	0	0
TBM with tuberculoma	1 (8.3)	0	0

Also most of the patients had been previously treated for TB or were in contact with an adult suffering from TB suggesting that the resistance in children may due to these factors, and thus an older age of presentation.

In our study, the commonest type of drug resistance was MDR followed by partial XDR. Thus the kind of DR-TB in our geographical area tends to be multidrug resistant TB. This is in contrast to study by Alrajhi, *et al*. [7] who noted polyresistance in 5% of isolates suggesting that type of DR-TB tends to vary from area to area. It is important to identify the trend of resistance pattern in a community to determine the possible antituberculous therapy that may be needed in a child. As per WHO statement [3], a patient can be placed on a likely sensitive regimen based on epidemiological pattern in that geographical area, while DST results are pending, to avoid clinical deterioration and prevent transmission to contacts.

It has been previously reported that HIV co-infection increases the risk of getting drug resistance TB [3]. A study conducted in New York city by Gordin, *et al*. [8] revealed that HIV and TB co-infected patients were significantly more likely to develop resistance to at least one drug (37% *vs*. 19%) and MDR (19% *vs*. 6%) than those without HIV infection. In our study, only 3 patients (10.3%) were HIV co-infected among 29 tested. However, it is not possible to comment on whether DR-TB is low in HIV infected children from this data.

The protective efficacy of BCG for preventing serious forms of TB [9], is clear but its role to prevent drug-resistant TB is not known. Routine BCG vaccination is now recommended for children exposed continually to a patient who has infectious pulmonary TB caused by *M. tuberculosis* strains resistant to isoniazid and rifampin [9]. We cannot comment on efficacy of BCG on DR-TB from our data.

In a study from Saudi Arabia, Alrajhi, *et al.* [7] showed that history of previous ATT was the only risk factor associated with DR-TB with odds ratio 19.9 ($P< 0.001$). We also found previous history of tuberculosis and past history of ATT as an important risk factor for DR-TB in children, similar to most of the published studies in adults [9-11]. Previous studies [12,13] have shown that DR-TB infection rates are more in childhood contacts with resistant index cases compared with drug-susceptible index cases. However, the clinical presentation of DR-TB is similar in children of all ages and does not differ as per the age. This has not been reported previously and could suggest a similar presentation for DR-TB across the pediatric age range.

Our study has a limitation as it has small number of patients, and patients with suspected DR-TB but not culture proven were not included in the study. Thus, we may have missed out on some patients who may have had DR-TB. Moreover, since this is a hospital based study, we may have noted higher prevalence of DR-TB.

Epidemiological surveillance studies in children are required to determine the actual prevalence of drug-resistant TB in children in India. Efforts to isolate TB bacilli from body fluids or tissues should be aggressively pursued so that DR-TB can be identified early and patients can be put on alternative drugs early before significant tissue damage occurs.

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