CLINICAL PROFILE OF PAEDIATRIC DRUG RESISTANT TUBERCULOSIS AT A TERTIARY CARE HOSPITAL IN MUMBAI, INDIA- A SANGUINE STUDY

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ABSTRACT

BACKGROUND

Paediatric drug resistant (DR) tuberculosis (TB) continues to be a mammoth challenge and there is limited literature available to shed light on this. To study the clinical profile and outcome of paediatric DRTB in India under the programmatic settings.

MATERIALS AND METHODS

We conducted retrospective observational study to analyse the clinical profile and treatment outcome of DRTB in paediatric population. Data of patients aged below 18 years enrolled at programmatic management of DRTB register, from July-2013 to oct-2014 was reviewed to record demographic details, resistance pattern, management and outcome. Quantitative data was analysed using mean and percentages.

RESULTS

Out of 120 patients, 95% (114) were above 12 years and rest 5% (6) were below 12 years, male to female ratio was 1:2.53. MDR-TB was present in 85% (102), 9.17% (11) had pre-XDR-TB, 5.83% (7) had XDR-TB. Pulmonary-DRTB was seen in 89.17% (105), 10.83% (15) had extrapulmonary-DRTB. Primary-DRTB was observed in 11.67% (14). Complications noted were pneumothorax (5.83%, 7 cases) and haemoptysis (2.5%, 3 cases). Mean duration of culture conversion was 3.33 months. Commonest adverse drug reactions (ADRs) were Psychosis, gastritis (11.67%, 14 cases each). Overall treatment success was 42.5% (51) which was better in MDR-TB (44.11%, 45 cases) than XDR-TB (28.5%, 2 cases) and Pre-XDR-TB (36.36%, 4 cases). Mortality was 21.67% (26) of whom 19.60% (20) had MDR-TB, 42.8% (3) had XDR-TB, 27.27% (3) had pre-XDR-TB and 20% (24) failed to treatment.

CONCLUSION

Optimistic results can be achieved by early diagnosis, meticulous counseling, legitimate follow ups and management of ADRs even under programmatic conditions with varying resources.

KEYWORDS

MDR-TB, XDR-TB, Pre-XDR-TB.

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BACKGROUND

Tuberculosis is an infectious disease prevalent since blue moon which continues to gain momentum owing to the monstrous problem of drug resistance. In India DRTB has been perpetually identified ever since the inception and implementation of the revised national tuberculosis control program (RNTCP). The paediatric population is a scapegoat for acquisition of TB as well as DRTB. Despite of the advances in the diagnostics and the amended therapy protocols TB still continues to prevail as one of the ten major causes of mortality in the paediatric age group.[1] Incidence of Paediatric DR-TB has seldom been estimated precisely although they constitute more than a quarter of the global population.[2] The situation is quite bloodcurdling with the 2016 statistics which estimated 1 million children being afflicted with TB and 250,000 children succumbing to TB.[3] In 2016, World Health Organization (WHO) estimated 600,000 incident cases of MDR-TB globally.[3] Paediatric tuberculosis can act as sentinels of DRTB it is an aftermath of adult TB. Paediatric DRTB is a silent epidemic which is often overlooked and the cases which present to us may just be the tip of an iceberg. Burden of DRTB and its clinical profile in paediatric population is inadequately scrutinized. The diagnosis in this age group may be an uphill task due to various hurdles like difficulty in history taking, complex examination findings and difficulty in procurement of sample for an accurate microbiological diagnosis. The therapy of DR-TB in children can be quite wearisome due to quandaries with the dose adjustment modes of drug dispensation and the therapy related ADRs. The predicament may become more intricate owing to the delicate parental and caregiver

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sentiments connected to their cherub. Management has to be a holistic one taking all these contingencies into consideration. The treatment of paediatric DR-TB has been updated and improvised from time to time under the programmatic management of drug resistant TB (PMDT). However, the field outcome of the same has not adequately studied. The lacunae in the system need to be unzipped with proficient studies and exhaustive literature review. Attaining insights into the sensitive disease will enable us to improve patient management by identifying gaps in existing knowledge. This study was therefore undertaken to infer the clinical profile and outcome of DRTB in paediatric population under the programmatic conditions.

Aims and Objectives

To study the clinical profile and outcome of paediatric DRTB in India under the programmatic settings.

MATERIALS AND METHODS

A retrospective study was conducted at the PMDT site of tertiary care hospital in Mumbai, India after approval from Ethics Committee for Academic Research Projects, Postgraduate Academic Committee, T. N. Medical College and B. Y. L. Nair Hospital, Mumbai. The data of 120 patients aged less than 18 years enrolled in PMDT register from July 2013 to October 2014 was recorded. Patient's demographic details, pretreatment status and type of TB were noted. Diagnosis of DRTB in those patients was made on basis of microbiological tests such as nucleic acid amplification tests, line probe assay and conventional drug susceptibility testing (DST) done on sputum, gastric lavage sample or tissue sample from a Revised National TB Control Programme (RNTCP) accredited laboratory. All patients underwent second-line DST to diagnose additional resistance to Fluoroquinolone (FQ) or Second line Injectables (SLI) at baseline. After thorough pretreatment evaluation these patients had received standard category four regime comprising kanamycin, ethionamide, cycloserine, levofloxacin, ethambutol, and pyrazinamide as per PMDT guidelines. Pre-XDR or XDR-TB had received modified therapy as per DST. Levofloxacin was substituted with Para -Aminosalicylic Acid (PAS) and moxifloxacin while kanamycin was substituted with capreomycin wherever the particular drug was proven to be resistant. Follow-up sputum Acid-Fast Bacilli (AFB) smear and cultures done according to PMDT guidelines at 3, 4, 5, 6, 9, 12, 15, 18, 24 months. A complete follow-up data pertaining to the clinical improvement, microbiological conversion, ADRs on therapy, and treatment outcomes were also recorded. All data obtained were meticulously reviewed to study epidemiology, drug sensitivity pattern on the basis of sputum examinations, frequency of MDR, pre-XDR, XDR-TB, sputum culture conversion, treatment outcome, ADRs. Culture was considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative, in such a case, the specimen collection date of the first negative culture was used as the date of conversion. Treatment outcomes of DRTB were defined in terms of cured, treatment success, treatment failure, died, lost to follow up and not evaluated. Cured is defined as treatment completed as recommended by the national policy without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase. Treatment completed means treatment completed as recommended by the national policy without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase. Treatment failure is defined as treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of either lack of conversion by the end of the intensive phase or bacteriological reversion in the continuation phase after conversion to negative or in case of evidence of additional acquired resistance to FQ or SLI drugs or due to ADRs Died is termed when a patient who dies for any reason during the course of treatment. Lost to follow-up is defined as a patient whose treatment was interrupted for two consecutive months or more. Treatment success is the sum of cured and treatment completed and not evaluated is defined as a patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown). Statistical analysis was done using mean and percentages.

RESULTS

In the study period we came across a total of 750 patients of DRTB of which 120 (16%) belonged to the paediatric age group. These constituted our study group. Out of 120 patients 95% (114) were aged more than 12 years and rest 5% (6) were below 12 years. Male to female ratio was 1:2.53. In terms of the baseline drug susceptibility tests, 105 (87.5%) were MDR-TB, 8 (6.67%) patients were MDR-TB with additional FQ/SLI resistance (pre-XDR) and 7 (5.83%) patients were XDR-TB. The commonest site of predilection was pulmonary which was observed in 105 cases (89.17%) and 15 cases (10.83 %) were extra pulmonary DRTB. HIV was the only associated comorbid condition and was observed in 2 cases (0.17%). Primary DRTB was seen in 14 cases (11.67%) and 106 (88.34%) had received ATT in the past. Mean sputum conversion was noted at 3 months in MDR patients (41), while at 3.5 months in XDR (2) and Pre-XDR (2) (Table 1). Overall 51 (42.5%) patients out of 120 were successfully treated (cured 36 [30%] + treatment completed 15 [12.5%]). Twenty-six (21.67%) died, 24 (20%) failed, 13 (10.83%) lost to follow up, and 6 (5%) were transferred out to other sites (Table 2).Complications noted were pneumothorax in 5.83% (7 cases) and haemoptysis in 2.5% (3 cases). Out of 120 patients 46 patients (38.3%) had ADRs, commonest of which were psychiatric and gastrointestinal (11, 11.67% each) (Figure 1).

Resistance Pattern	Mean Duration of Sputum Conversion in Treatment Success (in Months)
MDR PTB (Pulmonary TB) (n=45)	3
Pre XDR PTB (n=4)	3.5
XDR PTB (n=2)	3.5

Table 1. Mean Duration of Sputum Culture Conversion in Pulmonary DRTB

Status	Overall	MDR (102 Cases)	XDR (7 Cases)	Pre XDR (11 Cases)
Cured	30% (36)	31.37% (32)	28.5% (2)	18.18% (2)
Treatment completed	12.5% (15)	12.74% (13)	-	18.18% (2)
Treatment Failure	20% (24)	20.58% (21)	-	27.27% (3)
Treatment success	42.5% (51)	44.11% (45)	28.5% (2)	36.36% (4)
Lost to follow up	10.83% (13)	11.76% (12)	14.28% (1)	-
Not evaluated	5% (6)	3.9% (4)	14.28% (1)	9% (1)
Dead	21.67% (26)	19.60% (20)	42.8% (3)	27.27% (3)

Table 2. Treatment Outcome

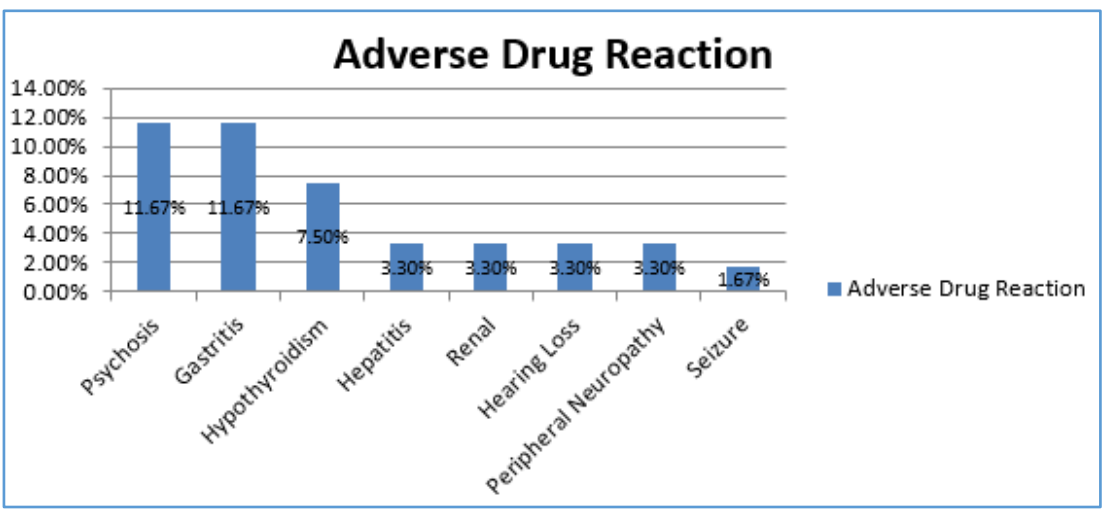

Figure 1. Adverse Drug Reactions Related to DRTB Treatment

DISCUSSION

Tuberculosis has been an obdurate menace which continues to perplex physicians owing to its leviathan spectrum of presentations, ubiquity for organ involvement and calamitous consequences of delayed diagnosis and therapy. The perilousness of the disease worsens with the snowballing of DRTB. The disease shows equipoise in its age distribution however it has a penchant for children. This could be attributable to their fragile immunity, poor avail of protective measures and perpetual exposure to the infectious agent. The impact of DRTB in them becomes consequential from various perspectives like medical, social, economic, epidemiological and psychological. Formulation and implementation of PMDT guidelines has been a landmark achievement to battle this plague. But there is dearth of literature pertaining to their performance in field. This warrants for wider and worthier studies to contemplate this complex issue. We hereby conducted our study with an intention of attaining a better comprehension of the profile and treatment outcome of paediatric DRTB under the PMDT setup.

As per our study, paediatric population made up 16% of the total DRTB cases. Out of the 120 cases, 95% belonged to adolescent group and rest 5% was aged less than 12 years (median age was 16 years). Schaaf , et al reported a prevalence of 6.5% of MDR-TB in children aged less than 13 years (median age was 2.5 years) in 2003-2005 at children hospital, South Africa,[4] whereas Ira shah et al reported a prevalence of 6.8% of drug resistant TB in children (median age was 7 years) in 2007-2010.[5] Difficulty in procuring extra pulmonary sample for the diagnosis of DRTB in younger children might be a probable explanation for presentation of DR-TB in slightly older children in our study .There were more females (71.67%) than males (28.3%) in our study which is comparable with a study by Schaaf et al in which 63.6% were females and 36.4% were males.[4] This female preponderance may be secondary to their predominant role in household chores, which invariably renders them exposed to the index cases. Neglect of girl child leading to poor nutritional status and consequently poor immunity could also be contributory. Various comorbidities in DRTB inflame the severity of disease. Data on DR-TB-HIV co-infection is variable. Sameer Adwani et al reported 4% association of HIV with DRTB in adults and Mukadi YD, et al reported 19% HIV co-infection with TB in paediatric population.[6,7] A study conducted in New York City by Gordin et al reported

increased likelihood of developing MDR TB in HIV- TB co-infected patients.[8] In our study, only 2 patients (1.67%) were HIV co-infected, hence it is difficult to comment the impact of HIV-DRTB co-infection.

The knowledge of trend of resistance pattern in a community enables physicians to design appropriate treatment regimen and to monitor the efficacy of treatment programme. The commonest type of drug resistance was MDR followed by pre-XDR and then XDR in our study, thus the kind of DRTB in our geographical area tends to be MDR-TB. Studies by Schaaf et al and Dipti Agarwal et al also revealed similar results.[4,9] In contrast study by Alrajhiet al observed MDR in 5% cases only.[10] Availability of baseline second line DST for FQ and SLI was a very noteworthy element of our study which facilitated germane treatment modification at the commencement of therapy. This had paramount positive effect on the treatment outcomes.

Patients with DRTB are classified as having acquired DRTB or primary DRTB on the basis of a history of previous TB treatment. It is assumed that primary drug resistance is due to transmission of drug-resistant strains. History of TB treatment in the past has been identified as a risk factor associated with DRTB in several studies.[5,10] The main mode of acquiring DRTB in children is primary transmission of the resistant bacilli as observed by Newton SM, et al.[11] Drug resistance is rarely acquired in the paediatric population due to the paucibacillary nature of the disease. Overall incidence of Primary DRTB is 4.1%.[1] We observed primary DRTB in 11.67%.

Our study population had more pulmonary TB (PTB) (89.17%) than extra-pulmonary TB (10.83%). Another Indian study by Sanjay Jain also reports higher pulmonary cases.[12] Obtaining sputum sample or gastric lavage for AFB culture and drug sensitivity test is easier than procuring sample from extra pulmonary site, which may explain the higher prevalence of pulmonary DRTB. Also, the sensitivity of molecular test like gene expert in detecting drug resistance is more for sputum than for other samples.[13] Pulmonary complications of TB include haemoptysis, pneumothorax, bronchiectasis, extensive pulmonary destruction, acute respiratory distress. Pneumothorax is a well-known complication of active TB. Previous studies on TB in adult population have shown a 0.6 to 1.4% possibility of this complication occurring.[14,15] We observed pneumothorax in 5.83% cases. Haemoptysis is another life-threatening complication of TB. Shouyong Tan et al observed haemoptysis in 32.8% of PTB in adult population.[16] In our study 2.5% had haemoptysis. Studies quoting incidence of these complications in paediatric DRTB patients are lacking.

In our study mean duration of sputum culture conversion was 3 months in MDR -PTB and 3.5 months in Pre-XDR-PTB and XDR-PTB (Table 1). Studies revealing mean duration of sputum conversion in DRTB in paediatric population are scarce. As per study by Kurbatova EV et al, median duration of sputum conversion in MDR-TB is 3 months and Holtz TH et al mention in their study that 77% converted in a median time of 2 months.[17,18] Sputum culture conversion is a useful and an appropriate interim indicator of treatment outcome in patients with DRTB and it is observed that treatment outcome was worse for patients who failed to convert their sputum culture within 2 months.[18]

Treatment of DRTB is known to be associated with ADRs. Early identification of these reactions is essential to avoid serious complications. We observed adverse ADRs in 38.3% (46) of which psychosis (11.67%) and gastritis (11.67%) were the commonest (Figure 1). Ettehad D et al in their meta-analysis estimated 39.1% (28.7-49.4) ADRs.[19] In their study the most common ADRs were nausea and vomiting and other serious adverse events were hearing loss, psychiatric effects, and hypothyroidism.

Treatment outcome results serve as a proxy of the efficacy TB treatment provided by a health care system. Treatment outcome should be monitored routinely which facilitates health care system to recognize and amend system failures. A systematic review by Ettehad D, et al described the outcomes of 318 children with MDR-TB.[19] As per this review, the pooled estimate for treatment success was 81.7% with a mortality of 5.9% and default of 6.2%. Study by James A Seddon et al reflected a cure rate of 24.2%.[20] In our study 30% patients were cured and treatment success rate was 42.7%. Treatment success was better in MDR-TB (44.11%) than XDR-TB (36.36%) or Pre-XDR-TB (28.5%) (Table 2). Mortality was slightly higher in our study (21.67%) when compared with previous studies.[19-20] This may be because our study included XDR and Pre-XDR patients in contrast to other studies which focused mainly MDR-TB. WHO DR-TB data reports treatment success in 52%, 17% mortality and treatment failure in 9%.[1] The treatment success rate in XDR-TB patients was only 26% as per WHO DR-TB data.[1]

CONCLUSION

Our study shows that optimistic outcomes can be obtained in children as compared to adult DRTB patients with scrupulous and holistic patient management. However our study also had certain limitations.It was a retrospective record review of routinely collected surveillance data, and is therefore subject to errors associated with such data. We reported on a relatively short follow-up time. Longer follow-up would be required to assess long term treatment outcomes. Principally we conclude that treatment of DRTB in children although seemingly a herculean task is surmountable even in resource limited settings. Capitalization of WHO accredited rapid tests for diagnosis, gladiatorial pretherapy counselling, modification of treatment regimen at start of therapy as per DST, meticulous supervision of therapy, due follow ups and addressal of ADRs are the cornerstones of success.

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