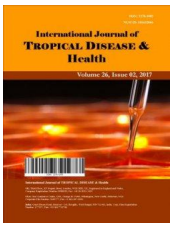

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Multidrug Resistant Tuberculosis in Children in Port Harcourt – A Worrisome Trend

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Authors' contributions

This work was carried out in collaboration among all authors. All the authors were part of data collection and analysis, author LEYI wrote the first draft, author NIP wrote the second draft while all the authors reviewed the final draft. All authors read and approved the final manuscript.

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ABSTRACT

Background: Drug-resistant tuberculosis and multidrug-resistant tuberculosis (MDR-TB) in particular represent a major threat to the fight against tuberculosis globally. MDR-TB presents with similar features and is transmitted in the same way as drug sensitive TB but its progression is rapid and its treatment, associated drug toxicity and monitoring constitute a heavy burden to the patients and the health system. MDR-TB affect people of all age groups but very little is known about the magnitude of this problem in children.
Aims/Objectives: To determine the prevalence of multidrug resistant tuberculosis among children in Port Harcourt.
Materials and Methods: Information on Paediatric tuberculosis was retrieved from the patients' case notes, TB registers at the directly observed treatment short course (DOTs) clinic and the Multidrug resistant tuberculosis (MDR-TB) treatment center of the University of Port Harcourt Teaching Hospital from January 2018 to June 2019. Obtained data was analysed and presented in prose and tables.
Results: There was a total of 1,860 patients records of which 37 were Paediatrics cases giving a prevalence of Paediatric tuberculosis cases of 2.0% Out of these 37cases, four were multidrug

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resistant tuberculosis cases giving a prevalence of MDR-TB cases of 10.8%. There were three males and one female giving a male female ratio of 3: 1. and their ages ranged from 3months to 24months. All belonged to social class 5. Common presentation was chronic cough, prolonged fever, weight loss and lymph node swellings. Three (75%) had no prior treatment for tuberculosis while one (25%) completed 6months of anti TB drugs. All had BCG immunization within one week of delivery. One (25%) child had extra-pulmonary TB while 3(75%) children had pulmonary tuberculosis. Xpert MTB/RIF assay for all (100%) showed MTB detected, RIF resistant detected. Three (75%) of the mothers had MDRTB and the medications for their children was based on the drug sensitivity testing (DST) of their mothers. One (25%) of the children and his mother were HIV positive and the mother had died while still on the intensive phase of second line antiTB drugs. Three (75%) had completed the intensive phase of the conventional therapy with second line antiTB drugs and are closely followed up weekly on the continuation phase while one child is still on admission.

Conclusions: The prevalence of MDR-TB in children in PH is high. All childhood TB (whether drug susceptible or drug resistant) is usually traced to an adult, thus effectively diagnosing and treating all adults as well as a high index of suspicion in presumptive cases is required to curb MDR-TB.

Recommendations: We recommend strict use of the DOTs strategy in TB management to ensure drug adherence. Also, proper contact tracing, investigation and treatment of children of infected parents to reduce cases of MDR-TB is advocated.

Keywords: Prevalence; paediatric; multidrug resistant tuberculosis.

1. INTRODUCTION

One major hindrance to the war against tuberculosis globally is drug resistant tuberculosis. When a strain of mycobacterium tuberculosis is resistant to Isonaizid and rifampicin, infects and causes disease in an individual, it is called MDR-TB. [1] These drugs are the two most potent first-line anti-tuberculosis drugs. In 2011, World Health Organisation (WHO) reported an estimated prevalence of tuberculosis of 12 million with a range of 11-13million. [1] among which sixty-three thousand (5.3%) were estimated to have MDR-TB. [1] Extensively drug resistant TB (XDR-TB) which is MDR-TB with added resistance to at least a fluoroquinolone and one of the injectables such as kanamycin, amikacin or capreomycin) has been detected in 77 nations globally by WHO [1].

MDR-TB can be primary or acquired. It is primary when one is infected from the beginning with a multi-drug resistant mycobacterium strain. In this case a previously untreated person develops a new case of MDR-TB. When an individual with a drug sensitive TB begins to take incorrect or inadequate treatments due to use of the wrong or incomplete (standard treatment requires at least four drugs) medications, not taking medication consistently or for the full treatment period (treatment is required for at least 6 months) he or she can acquire drug resistant TB strain through genetic mutations. This is called acquired drug resistance TB [2].

All over the world, many cases of MDR-TB are not picked up and treated because of inadequate laboratory facility to test for drug resistance and restricted access to second-line drugs. The treatment is expensive, lethal and protracted for as long as 12 to 24 months. [1,3,4] Maximum number of MDR-TB ever stated have been in current times. More than 25% of new TB cases in nations like Belarus and Russian Federation are MDR-TB. [1] The condition has become ugly with the finding of total drug resistant TB (TDR-TB) in India [5]. Ten to twenty percent of total TB cases in resource limited countries with infection prevention control constitute childhood TB. This would communicate a worldwide estimate of about 40,000 Paediatric cases of MDR-TB annually [6].

Mechanism by which resistance occurs in patients with TB is multi-factorial and would include spontaneous genetic mutations in genomes of MTB and not from horizontal gene transmission. Bacillary load in the diseased tissue is unswervingly directly proportional to the manifestation of mutations, that is, the higher the bacillary load, the higher the risk of mutation. This type of mutation is more in adult type cavitatory TB with huge number of bacilli. Insufficient drug administration and lack of adherence to prescribed treatment is another

factor responsible for resistance, Transfer of drug resistant bacilli from a close family contact is one of the most important factors in Paediatric DR-TB [7]. Finally, previous treatment with anti-TB drugs is another contributory risk factor in the development of drug resistant TB in children [8].

There is a paucity of data on DR-TB in children, [7,8] this is as a result of small culture yield, and low drug susceptibility testing in children due to the paucibacillary nature of the organism and the problems associated with collecting sufficient samples in Paediatric patients. Also a lot of factors such as the longer duration of treatment(18-24months) high cost of second-line drugs (which are less effective and more lethal) drug regimes, mechanism of degradation and drug preventive treatment in Paediatric patients with MDR-TB are not clear [9]. Thus this study aims to determine the prevalence of MDR-TB in children in Port Harcourt, Nigeria.

2. MATERIALS AND METHODS

2.1 Study Area

The study area were Multidrug resistant tuberculosis (MDR-TB) treatment center, Aluu, Directly observed treatment (DOT) clinic and Department of Paediatrics all of the University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt Nigeria. Diagnosis, Drug sensitivity testing, treatment and follow up of DRTB cases is carried out in these centres according to the National guidelines on TB and leprosy management.

2.2 Study Population/Data Tool

All children diagnosed with tuberculosis by either clinical or bacteriological methods constituted the study population. The data tools were the TB register at the DOT clinic and the patient's case notes at the Department of Paediatrics and MDR-TB treatment centre.

2.2.1 Inclusion criteria

All children aged 0-18years whose information were in the TB register in the DOTS clinic in UPTH and the MDR-TB center.

2.2.2 Exclusion criteria

Patients aged 19 years and above.

2.3 Study Procedure

A retrospective cross-sectional study carried out over 18 Months from January 2018 – June 2019. Relevant information on all children 0-18 years with tuberculosis was retrieved. Information retrieved included the age, sex, HIV status, weight and height, clinical presentation, investigation findings, social class of parents, method of diagnosis of tuberculosis and the treatment outcome of the patients. Bacteriological diagnosis was done using either a positive sputum smear for acid fast bacilli (AFB) by ziel Nelson, or by a positive Xpert MTB/RIF test which also detects Rifampicin resistance. Clinical diagnosis was made in children with presumptive TB diagnosis using suggestive chest radiograph findings and a positive Tuberculin sensitive test (TST). Presumptive TB diagnosis refers to a patient who presented with one or more of the following symptoms: cough for >2 weeks and not responding to adequate dose of first line antibiotics after 7days; unexplained fever for >2 weeks; failure to thrive (FTT) or weight loss.

2.4 Data Analysis

The data obtained was entered into an Excel spreadsheet and was analyzed by calculation of means, percentages and ratios using Epi-info version 7. Results are reported in prose and Tables.

3. RESULTS

There was a total of 1,860 patients treated for TB over this period out of which 37 were Paediatric cases giving a prevalence of Paediatric tuberculosis cases of 2.0%. However, of these 37 cases, four were multidrug resistant tuberculosis cases giving a prevalence of multidrug resistant Paediatric tuberculosis cases of 10.8%. There were three males and one female giving a male female ratio of 3:1. and their ages ranged from 3months to 24months with a mean age of 1.6years ±1.1years. All belonged to social class 5 and lived in very poor living conditions and crowded areas (batchers-name for houses made from Aluminum zinc in Nigeria) Table 1. Three (75%) patients presented with chronic cough, while all (100%) presented with prolonged fever for more than 3weeks, weight loss and lymph node swellings Table 2. Three (75%) had no prior treatment for tuberculosis while one (25%) had a 6months

treatment for TB adenitis and represented 4months later with respiratory symptoms and tested positive to Xpert MTB/RIF and rifampicin resistance. All had BCG immunization within one week of delivery. They were all severely malnourished with a Z-score of < -3. Xpert MTB/RIF assay using gastric aspirate was used for the diagnosis of all (100%) cases. One (25%) child had extra-pulmonary TB while 3(75%) children had pulmonary tuberculosis. All (100%) the children had resistance to rifampicin. Three (75%) of the mothers had MDRTB and the drug regimen medications for their children was based on the drug sensitivity testing (DST) of their mothers. One of the patients however had a change of his drug regimen as he developed hepatotoxicity with rising hepatic enzymes. One (25%) of the children and his mother were HIV positive and the mother had died while still on the intensive phase of second line antiTB drugs. Three (75%) children have completed the intensive phase of the second line antiTB drugs and have been discharged from the multidrug resistant TB center and are being followed up weekly on the continuation phase, but one (25%) child is still currently on admission.

4. DISCUSSION

This study was on the prevalence of paediatric MDR-TB in Port Harcourt, Nigeria. The authors found a prevalence of paediatric MDR-TB of 10.8%. This is similar to the report of Zignol et al [10] who reported 11.1% in Estonia and 10% in Lithuania. However, in South Africa a higher prevalence of 16.4% was reported among 1569 children tested for MDR-TB. [10]. This may be due to better diagnostic tool as sputum culture was part of the diagnostic criteria in this study.

In line with this study, other studies have shown that males are often at a higher risk of Tuberculosis and also more likely to die from TB especially in the older age groups. [11-13] Mayank et al [12] in India reported a male: female ratio of 1.8:1 among children less than 8years. Also, Blount et al reported a higher male prevalence among males in a Vietnam study [13]. However, the genetic risk in males for TB is yet to be elucidated. Also, the fact that health seeking behaviour for male children in this part of the world is better especially among the lower social class may also be contributory.

Mean age of the children with MDR-TB in this study was 1.6 years and this is comparable to the report of Zignol et al who reported age of one year in children with MDR-TB in Turkey, Somalia, Portugal, Lithuania, Estonia, Bangladesh and Armenia. [10] Young age is a risk factor for development of TB disease and MDR-TB as well especially where there is a positive history of contact as was found in 100% of the patients in this study.

The risk factor for drug sensitive TB remains the same for MDR-TB, following infection by mycobacterium tuberculosis complex, disease results when there are risk factors that enhances progression from latent disease to infection and such factors include; young age (under-fives), immunosuppression, Diabetes mellitus, cancers, malnutrition, virulence of the organism, BCG immunization status [14] All patients with MDR-TB in this study were less than five years and severely malnourished while 25% had HIV infection, these factors most likely increased their susceptibility to disease. The source patients for 100% of our cases were their mothers out of

Table 1. Sociodemographic characteristics of the patients

Sociodemographic characteristics	No	%
Gender		
Male	**3**	**75**
Female	**1**	**25**
Age		
<1	1	25
>1	3	75
Social Class		
Upper	0	0
Middle	0	0
Lower	4	100

Table 2. Clinical characteristics of the children

Clinical characteristics	No	%
HIV status		
Negative	3	75
Positive	1	25
Symptoms		
Chronic cough	3	75
Weight loss	4	100
Prolonged fever	4	100
Generalised lymph node swelling	4	100
Chest radiograghs		
Perihilar opacities	4	100
Parenchymal nodular opacities	4	100
Mantoux		
Negative	4	100
Positive	0	0
Type of MDR-TD		
Primary	3	75
Acquired	1	25
Xpert MTB/RIF		
MTB detected/RIF resistant detected	4	100
MTB detected/RIF resistant not detected	0	0
Source case		
Mother	2	50
Father and Mother	1	25
Unknown	1	25

whom 75% had MDR-TB and so transmitted a primary drug resistant TB while one (25%) mother had drug sensitive TB with her child developing an acquired resistance from initial treatment of TB adenitis.

All patients with MDR-TB in this study were found to belong to a low social class with poor living conditions. This is not surprising as TB has been described as a disease of poverty. Individuals from low social class tend to reside in densely populated areas where human traffic and contact is high and this increases TB transmission. However, TB is sometimes also found in person from high social class, so a high index of suspicion is required in all patients presenting with features in keeping with presumptive diagnosis of TB [15].

Chronic cough was found in 75% of this study and in all patients with Pulmonary TB and this is similar to findings in other studies in children with pulmonary TB [15-17]. This cough is initially unproductive but with progressive inflammation and tissue necrosis becomes wet and productive of sputum.

Seventy five percent of the patients had primary MDR-TB, meaning they were infected with resistant strain from the beginning. This gives a bird's eye view of TB treatment in adults as childhood TB only exists as a shadow of adult TB. Studies show that Resistant strains of TB are already present in the population and that primary MDR-TB is responsible for up to 75% of cases as was found in this study [18] The DOTs system was an off shoot to the fact that adherence to TB medications was poor leading to emergence of drug resistant TB strain. Observing patients take their medications on daily basis for the duration of TB treatment especially in the intensive phase was to curb this issue of non-adherence, however, this has become practically difficult even with home visitors and so many patients tend to skip, discontinue, their medications once they observe significant clinical improvements.

The children in this study were all resistant to Rifampicin. Rifampicin has been thought of as the mainstay of tuberculosis treatment, so resistance to it is considered as a pointer to MDR-TB in more than 90% of cases. [19]

Mutations in a definite 81-base pair section of the rpoB gene is accountable for 97% of the rifampicin-resistant strains [19-21]. The *rpoB* gene encodes the beta subunit of the mycobacteria's RNA polymerase. In non-resistant TB, rifampin binds the beta subunit of RNA polymerase and disrupt transcription elongation. Mutation in the *rpoB* gene changes the sequence of amino acids and eventual conformation of the beta subunit. In this case rifampin can no longer bind or prevent transcription, and the mycobacteria becomes resistant. Presently NAATs for Rifampicin-resistant TB strengthen only this 81-base pair area to recognize the changes specifically at codons 531 and 536 [19-21] Xpert MTB/RIF assay was used for detection of Rifampicin resistance in all (100%) cases in this study. Three marketable assays presently in use are Xpert MTB/RIF assay (Cepheid, Inc. Sunnyale, CA), the INNO-LiPA Rif.TB(Innogenetics, Zwijindrecht, Belgium), that enables concurrent recognition of MTB and rifampicin resistance, and the Genotype MTBDR plus (Hain LifeScience, Nehren, Germany) which detects majority of HR resistance mutations [21] Xpert MTB/RIF assay has been said to facilitate the diagnosis of drug resistance in children [22,23].

All patients in this study received six different drugs. This is in keeping with WHO guideline which requires patients with resistance to rifampicin to receive isoniazid, ethambutol and a fluoroquinolone for at least 12-18 months with the addition of pyrazinamide for at least 2 months) [24].

While outcome to MDR-TB is poor ranging from 48-61% in some studies [25-27], our patients have shown a very good outcome so far as 75% of them have completed 4-6months of intensive phase and are at different stages of the continuation phase, while one (25%) is in the intensive phase and is still on admission. One of the patients however had a change of medications as he developed hepatotoxicity with rising hepatic enzymes. Final outcome of these patients is however yet to be assessed.

5. CONCLUSIONS

There is a high prevalence of MDR-TB in Port Harcourt, Nigeria. Since all childhood TB (whether drug susceptible or drug resistant) can be traced to an adult, effectively diagnosing and treating all adults as well as a high index of suspicion in presumptive cases is required to check this rising trend.

6. RECOMMENDATIONS

We recommend proper treatment of every diagnosed case of adult TB by strictly using the DOTs strategy to ensure drug adherence. Since all the children in this study had infected mothers, we further recommend proper contact tracing, investigation and treatment of children of infected parents to reduce cases of MDR-TB.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethical approval for the study was obtained from the Research and Ethics committee of the University of Port Harcourt Teaching Hospital.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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