Title: Tuberculosis in Children aged 0-5years at the University of Port Harcourt Teaching Hospital (UPTH), Nigeria - How common is HIV in children with Tuberculosis.

Abstract

Background

Tuberculosis (TB) is a leading cause of death in young children and the risk of progression from infection to disease is higher in the very young especially among those with Human Immunodeficiency Virus (HIV) infection. This study therefore aimed to examine the method of TB diagnosis and how common HIV infection is among children 0-5years with tuberculosis at the University of Port Harcourt Teaching Hospital (UPTH).

Methods

Information of children aged 0-5years from 1st January, 2011 to 31st December 2014 were retrieved from the TB register of the Directly Observed Treatment Short course (DOTS) clinic of UPTH. This included the age, sex, HIV status, Sputum AFB status, method of diagnosis of tuberculosis and the treatment outcome of the patients.

Results

Three hundred and thirty five children were treated for TB and 179 (53.43%) of them were aged 0-5years. There were 93 (51.96%) males and 86 (48.04%) females, with male: female ratio of 1.08:1. Their mean age was 1.96 ±1.45.. The sputum or gastric lavage of 21 (11.73%) were positive for acid fast bacilli (AFB). The common method of TB diagnosis was clinical/ radiological method and this constituted 158(88.27%) of the patients with TB. Ninety (50.28%) children with TB were less than one year of age and there was no statistical significant relationship between age and method of TB diagnosis (x^2 = 2.78, p= 0.249). More males 93(51.96%) than females 86(48.04%) had TB but more females 13(61.90%) than males 8(38.10%) were AFB positive, however, these were not statistically significant. (x^2 =1.26 p-value=0.262). Seventy two (40.22%) of the children with TB were HIV positive. One hundred and thirty five (75.42%) of the children recovered following treatment while 44(24.58%) were referred to Dots centres closest to the patients. No child died.

Conclusion

The prevalence of TB among under-fives especially among infants is high. Clinical and radiological methods were the common method of TB diagnosis. HIV prevalence among children with TB was lower than expected by the authors, however, the treatment outcome was good. Re-training of clinicians to improve their expertise on clinical diagnosis of TB and a more in depth search of TB in the community among children 0-5years who are HIV sero negative with persistent cough is advocated.

Key words: Tuberculosis, children 0-5years, HIV

Introduction:

Worldwide, tuberculosis (TB) is the ninth leading cause of death, and the leading cause from a single infectious agent (above HIV/AIDS) and millions of people continue to fall sick with the disease each year. [1] In 2017, TB caused an estimated 1.3 million deaths (range, 1.2–1.4 million) among HIV-negative people.[1]

Human immunodeficiency Virus (HIV) disease continues to be a serious health issue worldwide especially in sub-Saharan Africa. There are about 36.9 million people living with HIV around the world. Approximately 1.8 million children worldwide are living with HIV or Acquired immune deficiency syndrome (AIDS) with over 90% of them living in sub-Saharan Africa. [2]

Tuberculosis (TB) and HIV have been closely linked since the emergence of AIDS. It is not surprising to find that many children with tuberculosis are HIV positive, same also hold that many children with HIV infection have tuberculosis especially in areas where tuberculosis is endemic. Worldwide, TB is the most common opportunistic infection affecting HIV-seropositive individuals and it remains the most common cause of death in patients with AIDS. [3, 4] HIV infection has contributed to a significant increase in the worldwide incidence of TB. [3, 4] and the reported sero-prevalence of HIV in children with TB in countries with moderate to high prevalence ranges from 10% to 60%. [5-8]

This HIV/PTB co-infection is multi factorial in aetiology but has been commonly postulated to be due to the fact that HIV infection causes significant immunosuppression causing a flare up of tuberculosis disease which prior to now remained quiescent. By producing a progressive decline in cell-mediated immunity, HIV alters the pathogenesis of TB, greatly increasing the risk of disease from TB in HIV-coinfected individuals and leading to more frequent extra pulmonary

involvement, atypical radiographic manifestations, and paucibacillary disease, which can impede timely diagnosis.

Although HIV-related TB is both treatable and preventable, incidence continues to climb in developing nations where HIV infection and TB are endemic and resources are limited. Interactions between HIV and TB medications, overlapping medication toxicities, and immune reconstitution inflammatory syndrome (IRIS) complicate the cotreatment of HIV and TB.

In an infected child, risk of progression to disease is multifactorial and this includes age, nutritional and immune status, genetic factors, magnitude of initial infection, virulence of the organism, and maturity of immune response.[5]

Studies on the natural history of TB conducted before the chemotherapy era, revealed that age is a strong determinant of which children will progress to disease following infection. Infected infants have a 50% risk of progression to disease and this progressively declines to a 2% risk in children 5-10 years of age. [9-12] Also, young children are more likely to develop severe forms of TB, like military TB and TB meningitis. Despite these facts there is paucity of study in TB in children 0-5years especially in South-South Nigeria. It is therefore pertinent to study TB in the younger child.

This study therefore examined TB in children aged 0-5years, method of TB diagnosis in this age group, age and sex correlates of TB, Treatment outcome and especially, how common HIV infection is among children 0-5years with tuberculosis at the University of Port Harcourt Teaching Hospital (UPTH). It also tries to answer the question “Is HIV the primary risk factor for TB or are there other underlying risk factors to tuberculous infection in young children at the UPTH?”

Methods:

This was a retrospective study carried out over a one Month period from the 1st to 31st October 2018. The National TB register and the Acid Fast Bacilli (AFB) register at the Directly Observed Treatment Short course (DOTs) clinic of the university of Port Harcourt Teaching hospital (UPTH) were the data source. The DOTs clinic follows the National Tuberculosis and Leprosy control programme and the WHO directly observed treatment short course strategy. Relevant information on all children 0-5years with tuberculosis were retrieved. Information retrieved included the age, sex, HIV status, method of diagnosis of tuberculosis and the treatment outcome of the patients. Diagnosis of TB was based on presence of AFB on Zeil Nelson stain of sputum specimen (AFB-positive), clinical and radiological diagnosis. Children diagnosed with TB received Rifampicin, Isoniazid, Ethambutol and Pyrazinamide for 2 months, followed by 4 months of Rifampicin and Isoniazid. Obtained data was entered into an excel data sheet and analysed using SPSS version 20 and presented as descriptive statistics and proportions. Chi-square test was used to show the association between method of TB diagnosis and age, sex and HIV status. The test of statistical significance was at p-value <0.05.

Results:

Three hundred and thirty five children aged 0- 18 years were treated in the DOTS clinic of the University of Port Harcourt Teaching Hospital over a 4 year period from 1st January 2011 to 31st December 2014. Children 0-5years made up 179 (53.43%) of the children treated for TB within the period. There were 93 (51.96%) males and 86 (48.04%) females, with male: female ratio of 1.08:1. Their mean age was 1.96 ±1.45. Ninety (50.28%) were aged 0-1years, 53 (29.61%) were >1 to 3years and 36 (20.11%) were aged >3 to 5years. The sputum or gastric lavage of twenty one children were positive for acid fast bacilli (AFB) giving an AFB-positive prevalence of

11.73%. Table 1. The common method of TB diagnosis was clinical/ radiological method and this constituted 158(88.27%) of the patients with TB. Table 1. More of the children 90(50.28%) with TB were less than one year of age and there was no statistical significant relationship between age and method of TB diagnosis (x2 = 2.78, p= 0.249). Table 1. Table 1 also shows that more males 93(51.96%) than females 86(48.04%) had TB and also that more females 13(61.90%) than males 8(38.10%) were AFB positive, however, these was not statistically significant. (x^2 =1.26 p-value=0.262). Seventy two (40.22%) of the children with TB were HIV positive. Eight (38.10%) out of HIV positive children were AFB positive. There was no statistical significant relationship between TB and HIV sero-positivity. (p-0.832) Table . The mean duration of treatment with anti-TB drugs was 6 months. One hundred and thirty five (75.42%) of the children recovered following treatment while 44(24.58%) were referred to Dots centres closest to the patients. No child died.

Discussion:

This study show that more (56.11%) of the children who were treated for TB, were aged 0-5years This is in tandem with other studies. [12, 13] At this age, due to poor immunity in children, progression from infection to active disease is very high compared to the older children.[13] This age group must be carefully searched out and screened for TB in the community in any case of adult TB. Tuberculosis in children is mainly due to failure of TB control in adults and therefore exists in the shadow of adult TB.

Over 80% of the children were AFB negative with an AFB prevalence rate of 16.3%. The low AFB rate in this study is common in children and have been reported in other studies.[14]This is partly why diagnosis of TB in children is difficult especially in settings where this is the only confirmatory laboratory screening tool for TB. This is worse in the under-fives as many children

with TB have primary TB which is not usually associated with cavitatory lesions. However, this age tend to have more severe forms of the disease like milliary TB and TB meningitis and yet are more difficult to diagnose with available diagnostic tool in resource limited settings. Lack of resources makes accurate diagnosis of TB cases more difficult, and in many countries, TB control programs rely almost exclusively on sputum microscopy for the diagnosis of TB, as part of WHO TB control strategies. This means that TB in children is both undiagnosed and underreported especially in resource limited settings.

The common method of TB diagnosis was by clinical evaluation and use of chest radiograph. The low diagnostic yield of AFB makes it an unreliable method in children. It therefore requires a high index of suspicion and clinical expertise to make a diagnosis of TB in this age group, meanwhile this is the age group that is froth with severe disease and who are more likely to succumb to the disease if TB is not detected early and treatment commenced. Despite the endemicity of TB in this part of the world, the paucity of physicians with the clinical expertise for its diagnosis makes it more worrisome. Tuberculosis is a significant childhood problem but is neglected because many cases are usually smear negative and therefore not considered a major contribution to its spread. However, children with latent infection become the reservoir for future transmission following disease reactivation in adulthood, fueling future epidemics. TB diagnosis requires clinical expertise and early screening of children who presents with worsening and unrelenting cough lasting for 2 weeks or more with associated fever, weight loss or poor weight gain and a positive history of contact with an adult case of TB. Screening includes; Tuberculin sensitivity Testing (TST)-Mantoux test, chest radiograph, sputum for Acid fast bacilli (AFB) using the Zeil Nelson stain, Sputum culture and more recently, using the polymerase chain reaction tests such as Xpert MTB/RIF screening for mycobacterium TB (MTB) detection and

Rifampicin and Isoniazide (INH) drug resistance. Sputum for AFB using the Zeil Nelson stain for detection of AFB is diagnostic of TB but its yield in children is low due to their paucibacillary nature and difficulties in specimen collection. The more reliable screening tool and the first line WHO screening tool for TB the Xpert MTB/RIF screening which has been recently introduced in the researchers study area, was not rife when the subjects for this study were being screened. This test is an important advance in rapid detection of TB disease and detection of drug resistance. Studies have shown that it is much more sensitive than microscopy, with sensitivity being reported from 75 to 90% on sputum samples and nearly 70% on gastric aspirates, with comparable performance in HIV positive and HIV negative children. [15,16] However, despite its high sensitivity, Xpert MTB/RIF test cannot be used to rule out TB, as substantial proportion of children with negative test had positive MTB cultures. MTB culture remains a necessary diagnostic tool. The current use of only sputum or gastric aspirate for this screening in the researchers study area also limits its usefulness in children considering the rigors and invasive nature of gastric lavage. Making available the use of less or non invasive methods of sample collection, such as naso-pharyngeal aspirates (NPA) and stool samples for a PCR-based diagnostic test is highly advocated. [17, 18]

More than half 90(50.28%) of all under-fives who were treated for TB were infants. This prevalence decreased with increasing age in concordance with other studies.[13, 19] It is not surprising why more infants than other under-fives are diagnosed with TB. Tuberculosis in children usually follow an adult source and since many of these infants are still in close contacts with the adult source- parents, caregivers and relatives, transmission of the disease among them is high. This close contact with the adult source most likely increases their contact with aerosolized tuberculous droplets and coupled with their low immunity increases their susceptibility to the disease. Also, in TB endemic areas such as ours, sociodemographic factors

such as overcrowding and a predominant young population there is increased exposure of children to adults with pulmonary TB.[20, 21]

This study showed that among under-fives, TB was commoner in males, however this was not statistically significant. Mayank et al in India reported a male: female ratio of 1.8:1 among children less than 8years.[19] Also, Blount et al reported a higher male prevalence among males in a Vietnam study. [22] Males may be more predisposed due to a yet unidentified genetic risk or the fact that parents have a better health seeking behaviour for their male children especially in our part of the world. Other studies have also reported a female predominance of TB cases among children but female predominance in these studies were among older children aged 11years and above.[23-26] This age group has been found to have a higher prevalence of TB due to hormonal and reproductive changes in this age group. Generally however, there is no significant difference in sex distribution of TB in young children as was found in this study. The age range of 5-14 year is often called the "favored age," because in all human populations this group has the lowest rate of tuberculosis disease.[27] Among adults however, two thirds of TB cases occur in men and globally, men are significantly more at risk of contracting and dying from TB than women. [27, 28]

Only 72(40.22%) of the children with TB were HIV seropositive in this study. This finding is within the WHO estimate of 10-60% of HIV prevalence among children with TB in countries with moderate to high prevalence of TB. [7] Other studies have shown prevalence ranging from 16-56% of HIV among children with TB. [29-35] However, a retrospective review of TB notifications in the Kilimanjaro region of Kenya showed that of the minority of children who were tested for HIV infection, 82% tested positive. The HIV epidemic is a key factor behind the resurgence in TB incidence worldwide and HIV is the pre-eminent risk factor for the

development of TB. However, Nearly 60% of the children with TB in this study were HIV negative. This means that among under-fives, there are more factors other than HIV that increases TB susceptibility and for effective TB control in children, these must be elucidated and dealt with. Though factors such as poverty, overcrowding, poor living conditions and the nutritional status of the child were not part of this study design, they may be strong and contributory factors to high prevalence of TB in under-fives. These factors cannot be overlooked by any coordinated TB control strategy if a lasting and holistic solution is desired.

About three quarter (75.42%) of these children were treated successfully for TB in this study while the remaining one quarter were referred to the health facilities closest to them for continued treatment. This high successful treatment outcome may be due to early presentation of these children to the DOTs clinic and is similar to findings in a Kampala study where the success rate was 78% in 2011 and this increased to 83% in 2015. [36] Adejumo et al also reported a a similar treatment success rate of 79.2% in TB/HIV-negative children and 73.4% in TB/HIV positive. [37]

As highlighted earlier, the risk of progression of TB to disease in an infected child is multifactorial and includes other factors such as the age of the child, nutritional status, genetic factors, magnitude of initial infection, virulence of the organism, and maturity of immune response.[5] TB control especially among this vulnerable group must therefore involve a holistic approach with strategies to address these factors.

Conclusion:

It is concluded that the prevalence of TB among under-fives especially among infants is high and that the AFB prevalence is low. HIV prevalence among children with TB was lower than expected by the authors, however, the treatment outcome was good. Re-training of clinicians in this region to improve their expertise on clinical diagnosis of TB and a more in depth search of TB in the community among children 0-5years who are HIV sero negative is advocated.

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Table 1: Method of diagnosis of TB and its association between Age distribution and sex

Age group	**Method of diagnosis**		**Total**	**Chi-square (X2) (*p-value*)**
	AFB-Positive	**Clinical diagnosis**		
≤1	8 (38.10)	82 (51.90)	90 (50.28)	2.78 (0.249)
2-3	6 (28.57)	47 (29.75)	53 (29.61)	
4-5	7 (33.33)	29 (18.35)	36 (20.11)	
TOTAL	**21**	**158**	**179**	
SEX				
Male	8 (38.10)	85 (53.80)	93 (51.96)	**1.26 (0.262)**
female	13 (61.90)	73 (46.20)	86 (48.04)	
TOTAL	**21**	**158**	**179**	

No statistical significant association between age, sex and method of TB diagnosis. (p>0.05).

Table 2: Distribution of Age, Sex, AFB status, HIV status, treatment outcome of TB cases in children 0-5years over the 4 years (2011-2014)

Characteristics	2011 (n=48) Freq (%)	2012 (n=56) Freq (%)	2013 (n=35) Freq (%)	2014 (n=40) Freq (%)	2011-2014 (n=179) Freq (%)
Age					
Mean ± SD	2.06 ± 1.60	1.55 ± 1.24	2.26 ± 1.41	2.18 ±1.47	1.96 ± 1.45
Age group					
≤1	28 (58.33)	32 (57.14)	13 (37.14)	17 (42.50)	90 (50.28)
>1-3	7 (14.58)	18 (32.14)	14 (40.0)	14 (35.0)	53 (29.61)
>3-5	13 (27.08)	6 (10.71)	8 (22.86)	9 (22.50)	36 (20.11)
Sex					
Male	30 (62.50)	23 (41.07)	17 (48.57)	23 (57.50)	93 (51.96)
Female	18 (37.50)	33 (58.93)	18 (51.43)	17 (42.50)	86 (48.04)
AFB					
Positive	5 (10.42)	8 (14.29)	4 (11.43)	4 (10.0)	21 (11.73)
Negative	43 (89.58)	48 (85.71)	31 (88.57)	36 (90.0)	158 (88.27)
HIV					
Positive	15 (31.25)	29 (51.79)	16 (45.71)	12 (30.0)	72 (40.22)
Negative	33 (68.75)	27 (48.21)	19 (54.29)	28 (70.0)	107 (59.78)
Treatment Outcome					
Treated	39 (81.25)	42 (75.0)	29 (82.86)	25 (62.50)	135 (75.42)
Referred	9 (18.75)	14 (25.0)	6 (17.14)	15 (37.50)	44 (24.58)
Died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)