HIV/TB Co-Infection in Nigerian Children

Ebele F. Ugochukwu

SUMMARY

Tuberculosis (TB) is an important cause of childhood morbidity and mortality. The burden of childhood disease is not as well documented as that of adult disease, partly because of the difficulty of confirming the diagnosis. In Africa children have been estimated to account for 20-40% of TB case load. Children infected with M. tuberculosis have a high risk of progression to disease, the younger children being at highest risk. Infected children represent a reservoir of future adult disease. The incidence of childhood TB has increased in developing countries. This resurgence is partly attributed to the coexisting burden of human immunodeficiency virus (HIV) disease, which is most pronounced in Sub-Saharan Africa, Nigeria ranking third highest prevalence. The pattern of childhood HIV and TB infection mirror these epidemics in the adult population. The number of children co-infected with HIV and TB is rising, and so is the incidence of congenital and neonatal TB. In addition the emergence of multi-drug resistance TB and extensively drug-resistant TB has occurred within the context of a high prevalence of HIV and TB. The diagnosis of TB has always been difficult in children and is compounded by HIV co-infection. The clinical symptoms in both diseases are similar, and the radiological changes may be non-specific. Treatment of both conditions in children is a challenge due to drug interactions and problems with adherence. There are few stable syrup formulations of antituberculous and antiretroviral drugs in children, and hence division of tablets gives rise to unpredictable dosing and emergence of resistance. To reduce the morbidity and mortality of TB and HIV, existing childhood TB programs must be strengthened, and antiretroviral drug therapy and prevention of mother-to-child transmission programs scaled up. HIV prevalence in the adult population must also be reduced. An increased emphasis on childhood TB, with early diagnosis and treatment, must be a priority.

Niger Med J. Vol. 51, No. 3, July – Sept., 2010: 120 – 124.

Keywords: tuberculosis, HIV, children

From: Neonatology/Retrovirology/Infectious Diseases Unit, Dept of Paediatrics, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria.

***Correspondence*: Dr. E. F. Ugochukwu**,
E-mail: efugochukwu@yahoo.co.uk

INTRODUCTION

Paediatric tuberculosis has been relatively neglected, mainly due to challenges in diagnosis and the lower priority traditionally afforded to children by TB control programmes.[1,2] The emphasis placed by DOTS (Directly Observed Therapy, Short course) on detection of smear-positive cases does not address the situation in children, the vast majority of whom have smear-negative disease.[3] TB nevertheless remains an important and potentially preventable cause of childhood illness and death. Young children have a high risk of progression to disease following infection, and are much more likely to develop severe or disseminated TB. Children with latent TB infection become the reservoir of future disease in adulthood, perpetuating the epidemic.

The HIV pandemic, which disproportionately affects young adults, many of whom are co-infected with TB, may also put their children at particular risk of infection.[3] The highest TB incidences and HIV prevalences are recorded in Sub-Saharan Africa, and, as a consequence, children in this region bear the greatest burden of TB/HIV infection.[4] Nigeria ranks 5th among the 22 high TB burden countries which collectively bear 80% of the global burden of TB, and also takes the third position in the global populations of persons living with HIV/AIDS.[5] HIV/AIDS is the major threat to TB control programmes in Africa. As HIV prevalence rises, so does the TB rates. The control of TB, therefore, partly depends upon the control of HIV transmission.[6]

HIV during infancy increases the risk of developing TB. A number of cross-sectional studies which have taken children with TB as their starting population have yielded high rates of association with HIV.[7-11] Similarly, cross-sectional reviews of children with HIV show that a substantial number have TB.[12-16]

Peculiarities of Childhood TB

Pathophysiology and clinical presentation of TB in children differ from what obtains in adults. Following infection children have a higher risk not only of progression to disease,[17,18] but also of extrapulmonary dissemination and death.[2] The risk is greatest in infants and children under 2 years of age, with the lowest risk between the ages of 5 and 10 years.[2,19] While many factors including host genetics, microbial virulence and underlying conditions that impair immune competence (e.g. malnutrition and HIV infection) determine the outcome of infection, it is likely that the high rate of progressive TB seen in young children is largely a reflection on the immaturity of the immune response.[1] Poor cell-mediated immunity allows unrestrained mycobacterial proliferation with progressive parenchymal lung damage and dissemination.[9]

Anatomical differences in children also modify the presentation of TB compared with adults. Complications arising from enlarging lymph nodes and small airways are common in children less than 5 years of age.[20] Most children with TB are not infectious to others. The commonest type of TB in children is smear-negative pulmonary TB.[18] This is because cavitiating TB is infrequent in children. The next commonest type is extrapulmonary TB military TB, TB meningitis, TB lymphadenopathy, TB effusions (pericardial, pleural and peritoneal) and spinal TB. Smear-positive TB is usually diagnosed in children older than 6 years. The prevalence of pulmonary TB is normally low between 5 and 12 years, and then increases in adolescents. In adolescents pulmonary TB is generally like adult pulmonary TB, e.g. often with cavitation.

Impact of HIV on the burden of TB

Childhood TB differs somewhat from the illness in adults, particularly when the child is co-infected with HIV. For instance, the disease may be transmitted congenitally and co-infected mothers are more likely to pass the infection on to their children, who then, may develop active disease while neonates.[16,21] The disease can strike much more quickly: most cases occur within one year of infection and the cases with the most serious complications (such as meningeal TB) have the shortest incubation periods.[22] TB can also infect unusual sites as the middle ear. [23]

HIV infection acquired after TB infection is a significant risk factor for development of active TB mainly due to its effect on the immune system. HIV is associated with decreased chemotaxis, defective granuloma formation and maintenance, impaired antigen processing and presentation as well as generalized loss of CD4+ cells and selective clonal depletion of M-TB specific CD4+ lymphocytes.24 While TB can develop at any CD4+ count, extrapulmonary and disseminated forms of the disease are more common as immunodeficiency increases.[25] Compared to HIV-uninfected children, HIV-infected children demonstrate greater morbidity and mortality from TB, [4,15] as well as increased risk of rapid disease progression,[3,9,25] unsatisfactory treatment responses,[22,26] and TB recurrence.[22,27] In resource-limited settings, mortality rates among HIV-infected children diagnosed with TB range from 20-35%. [23, 27-29]

Impact of TB on HIV infection in children

Dual infection with TB has an important impact on HIV disease. TB accelerates the progression of HIV disease by increasing viral replication, [30] and reducing CD4+ counts further.[26] It is a common cause of acute pneumonia in African HIV-infected children[31,32] and frequently results in chronic lung disease including bronchiectasis.[33] TB is a common cause of death in HIV-infected children.[34]

Diagnosis of TB in the background of HIV infection

The main impediment to the accurate diagnosis of active TB is the paucibacillary nature of the disease in children. 1 Bacteriologic confirmation, the accepted gold standard is, therefore, of limited use in children. In addition to poor bacteriologic yields, the collection of bacteriologic specimens is often problematic (because young children cannot expectorate), necessitating the use of invasive procedures such as gastric aspiration, bronchoalveolar lavage, nasopharyngeal aspiration, lymph node aspiration/biopsy, lung biopsy or mycobacterial blood culture, in the search for Mycobacterium tuberculosis.

Because of the difficulty in obtaining a definitive culture-proven diagnoses of TB disease among children, the diagnosis of TB disease usually involves linking the child to an adult with confirmed pulmonary TB, together with a positive tuberculin skin test (TST) and an abnormal radiograph or physical examination in the child. [2] The diagnostic dilemma is even more pronounced in HIV-infected children. The specificity of symptom-based diagnostic approaches is reduced by the presence of chronic HIV-related symptoms, while the potential window for symptom-based diagnosis is limited by the rapidity with which disease progression may occur.[2] Chest radiograph interpretation is complicated by HIV-related comorbidity and atypical disease presentation.[35] The traditional TST has poor sesnsitivity to detect M. tuberculosis infection in HIV-infected children; 50% or less of HIV-infected children with bacteriologically confirmed TB are TST positive, despite using an induration size of at least 5mm. [23,36]

Treatment challenges

The standard World Health Organization (WHO) recommended anti-TB regimen is a six-month course of rifampicin and isoniazid, with the addition of pyrazinamide, together with ethambutol (or streptomycin) during the first two months of treatment.[37] HIV-positive children with pulmonary TB are classified into WHO Clinical Stage 3 while those with extrapulmonary TB are placed in Stage 4. In HIV-infected children with confirmed or presumptive TB disease, initiation of anti-tuberculosis treatment is the priority. However, the optimal timing for the initiation of antiretroviral therapy during anti-TB treatment is not known. The decision on when to start antiretroviral drugs (ART) after starting anti-tuberculosis drugs (ATT) involves a balance between the child's age, pill burden, potential drug interactions, overlapping toxicities and possible immune reconstitution syndrome versus the risk of further progression of immune suppression with its associated increase in mortality and morbidity. [37]

Pharmacokinetic interactions between ATT (in particular rifampicin) and ART, and similar side-effects profile of many of the drugs pose special challenges. Rifampicin, an inducer of cytochrome P450 CY 3A, decreases the concentration of both the protease inhibitors and non-nucleoside reverse transcriptase inhibitors, leading to sub-therapeutic levels, with an increased risk of inadequate viral suppression and drug resistance.[17] Latest WHO recommendations advice starting ART once ATT is established (after a period of 2-8 weeks) for all WHO clinical stage 4 HIV-infected children and stage 3 children with advanced or severe immunosuppression. For children in WHO clinical stage 3 with mild or no immunosuppression, ART may be deferred until 6 months of ATT are completed. [38]

The large pill burden of two multiple drug regimens increases the risk of adverse events and overlapping toxicities, and

consequently, increases the likelihood of poorer adherence. Poor adherence, in turn, paves the way for development of resistance to the two classes of drugs. Adherence issues may also be pertinent in children with very ill or dead parents, since they are dependent on care-givers to administer their drugs to them. This situation is worsened in the case of orphans taken over by relations who are ignorant of their HIV status, or too old and illiterate to know which drugs and what dosage to administer.

Most of the ART come as syrups (dosed per m2 body surface area) which must be accurately titrated for adequate dosing, and which may also result in administration of large volumes of medications to older children. The ATT come in tablets which when divided to enable administration in younger children, result in unpredictable dosing. For ease of administration these tablets are compounded into unstable syrups with less than two weeks shelf life at a time.

Fixed dose combination tablets of ATT contribute to increased adherence to treatment regimens, but the significant differences in absorption, distribution and excretion of pharmacological agents in children of various ages might require dose-adjustments. Existing fixed dose combinations contain 4-6mg of isoniazid per kilogram, but published pharmacokinetic studies in children support a standard dose of 10mg/kg or even 20mg/kg isoniazid as younger children acetylate the drug more quickly. [39] Pyrazinamide, similarly has a lower half-life in children 40 who also have lower peak serum levels of ethambutol than adults.[41] The ATT are supposed to be administered under direct supervision of health-care personnel. This is however not the case in many centres. The drugs, when available, are dispensed on bimonthly or monthly appointments and entries made in retrospect on the patients' treatment card as they come on follow-up visits. Poor finances, fear of stigmatization, frequent drug stock-outs, and unfriendly health care personnel militate against the effective implementation of the DOTS strategy. In addition, demand for financial remuneration from the patients by the facility staff has also been inimical.[42]

Another problem encountered with the simultaneous administration of ART and ATT is immune reconstitution inflammatory syndrome (IRIS). IRIS in HIV-infected individuals is an adverse consequence of the restoration of pathogen-specific immune responses during the initial months of highly active antiretroviral therapy (HAART) and is generally presented as worsening of the TB symptomatology. [43]

Multidrug Resistant TB (MDR-TB)

The emergence and spread of resistant TB poses a serious threat to TB control. There is a global increase in rates of single MDR (resistance to both isoniazid and rifampicin) including XDR (also resistance to fluoroquinolones and at least one second- line injectable agent such as amikacin, kanamycin and/ or capreomycin). Drug resistance originates mainly in adult patients with high bacillary loads who receive inadequate ATT or are poorly compliant with treatment. Acquisition rarely occurs in children due to the paucibacillary nature of their disease; overall children may also be subject to less selection pressure from ATT therapy. Thus most resistance in children is due to primary transmission of a resistant organism, and MDR-/XDR-TB rates in children reflect community transmission rates.1

Acquired resistance is well described in HIV co-infected adults previously treated for TB, possibly due to malabsorption of ATT. 44 Although MDR-TB has been reported in Nigeria among the adult population 45 there is a paucity of publications concerning MDR-TB in Nigerian children. However, in South Africa the presence of acquired resistance in a paediatric population has been reported. 46 Children with TB/HIV co-infection should be monitored.

Control and Prevention

Collaboration between TB and HIV/AIDS programmes provide the needed support to health care providers in delivering the full range of HIV and TB prevention and care interventions. To counteract the impact of HIV on TB, other interventions are required apart from effective TB case-finding and cure. These interventions include:

- Measures to decrease HIV transmission [promotion of condoms, treatment of sexually transmitted infections, voluntary counseling and HIV testing, reduction in the number of sexual partners, prevention of mother-to-child transmission , HIV screening of blood for transfusion, and application of universal HIV precautions by health workers];
- Antiretroviral therapy [to improve or maintain immune function in people living with HIV infection];
- Care for people living with HIV infection [treatment of HIV-related diseases, prevention of HIV-related infections, TB prevention, palliative care and nutritional support].

All HIV-infected children should be screened for TB and all children with TB should be offered HIV testing and counseling in high prevalence settings like ours. Irrespective of age, all HIV-infected children who are household contacts of infectious TB cases should be evaluated for TB disease and treated or given prophylaxis.[37] The HIV pandemic has implications for BCG vaccination. The immune response to BCG vaccination may be reduced in HIV-infected individuals and the conversion to a positive TST after BCG is less frequent in HIV-infected individuals.[37]

Newer methods of diagnosis are aimed either at detecting the organism or a specific host immune response.[2,47,48] Methods for organism detection have focused on collection of better samples, improved culture techniques, molecular methods or antigen detection.[47,49,50] Recent advances include the use of sputum induction for obtaining a more reliable specimen [51,52] faster and more sensitive culture methods,[49,53] and rapid detection and drug resistance based on nucleic acid amplification.[47,49,50,54] Improved methods for detecting a specific host response have largely focused on the use of gamma interferon release assays.[1, 47, 49] In Ibadan, Nigeria 5% of a cohort of children attending the university immunization clinic shed tubercle bacilli in stool, paving the way for a less invasive method of isolating mycobacteria in infected children.[55] Better diagnostics are not the only challenge, however. Other priorities include the need for better, particularly shorter treatment regimens; improved case management, contact tracing and delivery of chemoprophylaxis in low resource settings like ours; and the search for a new

vaccine.

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