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PREVALENCE OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION AND IMMUNE STATUS IN NEWLY DIAGNOSED ADULT TUBERCULOSIS PATIENTS

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Tuberculosis (TB) is a major public health problem disproportionally affecting the low income countries. It is estimated that one third of the world's population is latently infected with Mycobacterium tuberculosis (MTB).Each year; 8 million cases of active TB with over 2 million deaths are estimated to occur globally. The vast majority of individuals with TB live in Africa, South-East Asia and Western Pacific regions. TB and HIV form a lethal combination, each speeding the other's progress. Globally the number of people living with HIV continues to grow, as does the number of deaths due to acquired immunodeficiency syndrome (AIDS). A total of 39.5 million (34.1million –47.1million) people were living with HIV in 2006 of which about two-thirds live in sub Saharan Africa. Sub-Saharan Africa thus bears the overwhelming burden of the HIV/AIDS epidemic and TB. In conclusion, HIV sero prevalence in TB patients is a sensitive indicator of the spread of HIV into the general population and this information is essential to respond to the increasing commitment to provide comprehensive HIV/AIDS care and support among the high risk groups identified, including antiretroviral therapy (ART) to HIV-positive TB patients. Therefore, the study will give an understanding of the epidemiological relationship between HIV and TB diseases at the community level in Adama town and the surrounding villages.

Key words: Tuberculosis, HIV/AIDS, Immune status, prevalence, pathogenesis.

INTRODUCTION

Bacteria belonging to the Mycobacterium tuberculosis complex cause tuberculosis, one of the oldest diseases known to affect humans. It was classified as a family of Mycobacteriaceae and the order Actinomycetales. Of the pathogenic species belonging to this complex, the most frequent and important agent of human disease is M. tuberculosis itself. The complex includes M. bovis, M. africanum and M. microti. M. tuberculosis is a rod-shaped, non-spore-forming, thin aerobic bacterium measuring about 0.5 um by 3 um and it do not stain readily and are often neutral on Gram's staining. However, once stained, the bacilli cannot be decolorized by acid alcohol, a characteristic justifying their classification as acid-fast bacilli (AFB). Acid fastness is due mainly to the organisms' high content of mycolic acids, long-chain cross-linked fatty acids, and other cell-wall lipids. Transmission usually takes place through the airborne spread of droplet nuclei produced by patients with infectious pulmonary tuberculosis (Raviglione et al., 2001).

HIV (human immunodeficiency virus), a causative agent of AIDS (acquired immunodeficiency syndrome) belongs to the family of human retroviruses (Retroviridae) and the subfamily of lentiviruses. The most common cause of HIV infection throughout the world is HIV-1, which comprises several subtypes with different geographic distributions. HIV-2, another type of HIV, was first identified in 1986 in West African patients and was originally confined to West Africa (Fauci et al., 2001).

Someone can be infected with HIV in several ways. It can be transmitted through unprotected sexual intercourse with an infected partner, injection or transfusion of contaminated blood or blood products , sharing un sterilized injection equipment that has been previously used by someone who is infected; maternofetal transmission (during pregnancy, at birth, and through breastfeeding). Occupational infections of healthcare or laboratory workers may occur; however, it was not frequent. The risk of occupational HIV transmission from contaminated needles to healthcare workers was found to be around 0.3 % in case series performed prior to the availability of potent Anti Retroviral Therapy (Fauci et al., 2001).

EPIDEMIOLOGY OF TUBERCULOSIS AND HIV INFECTION

Tuberculosis (TB) is a major public health problem particularly in low-income countries. Each year, 8 million cases of active TB with over 2 million deaths are estimated to occur globally. For example in 2004, there were 8.9 million new TB cases in the world of which more than 80% of all cases were in the African, South-East Asia and Western Pacific regions (WHO, 2006).The highest number of deaths was in the World Health Organization (WHO) Africa region and the estimated TB incidence was also exceptionally rising in this region. It was thought that high prevalence of human immunodeficiency virus (HIV) infection particularly in sub-Saharan Africa has fuelled the incidence of TB in the African region. The six WHO regions are Africa, America, Eastern Mediterranean, Europe, South East Asia and Western Pacific (WHO, 2006). In Ethiopia, available data suggest that the incidence of TB has risen in recent years, partly because of the impact of the HIV/AIDS epidemic. The country ranks 8th out of the 22 high burden countries in the world based on estimated number of incident cases of all forms of TB in 2004.The country has an estimated TB incidence rate of 353, prevalence of 533 and mortality rate of 79 per 100,000 populations per year (WHO, 2006).

More than two decades after the discovery of the first clinical symptoms of the acquired immunodeficiency syndrome (AIDS), the HIV/AIDS epidemic is continuing to expand and globally the number of people living with HIV (PLWHA) continues to grow. An estimated 33.2 million (30.6–36.1 million) people were living with HIV in 2007 (UNAIDS, 2007). The estimated number of new infections in 2007 was 2.5 million of which over two third (68%) occurred in sub-Saharan Africa. Nearly 90% of children infected with HIV live in this region. Overall, Sub-Saharan Africa is home to anestimated 22.5 million adults and children infected with HIV in 2007(UNAIDS, 2007). Ethiopia is among those sub-Saharan African countries most severely affected by the HIV epidemic. The first evidence of positive sera for HIV antibody was obtained in 1984 (Tsega et al.,1988) and the diagnosis of the first AIDS cases in Addis Ababa hospitals, the capital city, was two years later. Since then HIV has continued to spread rapidly in different population groups, mainly through heterosexual contact.

The estimate in 2005 indicated a national HIV prevalence of 3.5% (3% for male and 4% among females). The estimated prevalence in urban areas was 10.5 % (9.1% among males and 11.9% among females) and 1.9% in rural areas (1.7% among males and 2.2% among females). The overall HIV incidence estimate for Ethiopia in 2005 was 0.26 % (0.99% in urban and 0.12% in rural). It was also estimated that 1,320,000 people were living with HIV/AIDS. According to the sentinel surveillance result done on antenatal care clinic attendants of the Adama town, the prevalence of HIV seems gradually decreasing. The respective prevalence rates for the years 2001, 2002, 2003 and 2005 were 18.7%, 16%, 10.8% and 9% (MOH, 2005).

PATHOGENESIS OF MYCOBACTERIUM TUBERCULOSIS

Tuberculosis can involve a delay between infection and clinical disease ranging from several weeks to several decades. Active disease may arise almost immediately after infection in about 5% of exposed individuals. Most of the others infected individuals develop latent infections in which the tubercle bacilli persist in vivo without causing any clinical symptoms (Kaufmann, 2001). The consequences of inhaling or ingesting tubercle bacilli depend on both the virulence of the organism and the resistance of the host. At one extreme, organisms with little virulence for the particular host disappear completely, leaving no anatomic trace behind. At the opposite extreme, the bacilli flourish with in macrophages and disseminate widely, and cause death within a few months (Kaufmann,2002).

MTB infection occurs mainly at the lung through the respiratory route (Neil, 2001). Following its penetration of the mucosal barrier, the bacteria is associated with intraepithelial leukocytes and subsequently conveyed to the draining lymph nodes. Then it spread from the site of initial infection in the lung through the lymphatics or blood to other parts of the body (Mun˜ oz et al., 2003). It is obvious that mycobacterium is an intracellular pathogen in host macrophages and therefore the success of it as a pathogen relies on its ability to survive within this cell. In this type of cells, it resides within early endosome-like phagosomes, which make it persistent to the effect from the cell and even multiply (Pieters, 2001). The mycobacterium containing phagosomes are hampered in maturation and fail to fuse with lysosomes, which enable the cells to kill the bacillus (Fratti et al, 2000). The intralysosomal acidic hydrolases are released from lysosomes to degrade the phagocytized microorganism only upon phagolysosome fusion. This is the reason why prevention of phagolysosomal fusion was one hypothesized mechanism by which the MTB survives inside macrophages (Raja, 2004).

HIV PATHOGENESIS

The pathogenesis of HIV infection is a function of the virus life cycle, the host cellular environment and quantity of viruses in the infected individual. Therefore, disease progression is a direct reflection of virus replication (Wei et al., 1995). In the absence of active viral replication, or when viral replication is low (blood viremia < 100 genome copies per milliliter), HIV infection does not progress to clinical immunodeficiency. Conversely, when viral replication is rapid (viremia > 100,000 genome copies per milliliter), disease progression is correspondingly rapid (Pantaleo et al, 1995). Among HIV-infected patients studied in the pre-HAART era, most progress from infection to AIDS in 5 to 15 years. A

fraction of patients, about 5% to 10%, progress more rapidly (rapid progressors), and another fraction, perhaps 5%, show no evidence of progression over many years (non-progressors) (Reynold et al, 2006). Individuals who have been infected with HIV for a long period (10 years), whose CD4+ T cell counts are in the normal range and have remained stable over years, and who have not received antiretroviral therapy are considered to be long-term non-progressors (Fauci et al., 2001).

Three major mechanisms of CD4+ T-lymphocyte killing by HIV have been suggested: direct virus-mediated cytolysis, virus-induced apoptosis, and indirect killing through immune effector mechanisms. Direct virus-mediated cytolysis has been demonstrated in vitro and syncytium formation may accelerate the cytolytic process. Here infected cells are killed because of viral replication in these cells, disrupting the cell membrane (Fauci et al., 2001). The turnover rate of CD4+ T lymphocytes is correspondingly turbulent. Each day in an infected patient, up to 109 new virions are made and about 109 CD4+ T lymphocytes are killed and replaced (Hu et al., 1996). Recent data shows that the destruction of billions of CD4+ T cells overwhelms the immune systems regenerative capacity. Loss of CD4+ T cells results in a loss of recognition of antigens that are presented on class II MHC molecules. With gradual decrease of CD4+ T cells, Th1 function is damaged with loss of cell-mediated immune functions and Th2 functions are impaired with gradual loss of humoral responsiveness to newly presented foreign
antigens (Reynold et al, 2006).

Syncytia formation gives chance for the spread of HIV from cell to cell which result in the death of uninfected cells. CD4+ T lymphocytes from infected patients undergo apoptotic death when HIV proteins, probably leading to their suicide, distort cellular regulation. Apoptosis perhaps reflects the high rate of ongoing immune activation in HIV-infected persons. Immune destruction of infected cells may not likely to be a central mechanism of CD4+ T-lymphocyte depletion: because sometimes persons with weak immune responses show more rapid depletion and more rapid clinical disease progression (Reynold et al, 2006). The model, which is currently supported, stated that a concerted effect of the different mechanisms is responsible for the depletion of CD4+ T cells in HIV infection (McCune, 2001).

TB-HIV CO-PATHOGENESIS

Infection with HIV constitutes the strongest risk factor for development of TB in subjects with latent MTB infection. Due to the high incidence of both HIV and MTB infection in the developing countries, TB has emerged as the most common opportunistic infection (OI) in HIV-infected patients worldwide (WHO, 2006). Thus, the interaction of these two pathogens currently and in the future will potentiate morbidity and mortality associated with either. Globally, more than one-third of HIV positive individuals are co infected with MTB and 12% of AIDS deaths are attributed to TB (Raviglione, 2003). In Africa, HIV is the single most important factor determining the increased incidence of TB in the past 10 years (WHO, 2006). HIV/AIDS accounted for 32% of the estimated 141,000 cases of tuberculosis in Ethiopia in 2005 (MOH, 2005).The progressive loss of CD4+ T cells in HIV-infected patients is the basis of increased TB incidence since CD4+ T cells are considered to be the primary cellular component involved in immune protection against TB via their ability to produce IFN γ, activate macrophages, and kill infected cells. Furthermore, CD4+ T cells are believed to be required either for primary activation of CD8+ T cells or for the maintenance of immune protective CD8+ T cells (Janssen et al., 2003).Clinical TB accelerates the progression of underlying HIV disease by stimulating HIV infected macrophages and CD4+ lymphocytes to produce more viruses. A cohort study undertaken to assess the effect of TB on the natural history of HIV infection in patients from a high TB prevalence setting (Badri et al., 2001), demonstrated a significantly reduced survival and an increased frequency of AIDS-defining illness in HIV-infected patients with TB. The median time of progression to AIDS according to this study, in patients free of AIDS at baseline, was 6 months for tuberculosis cases compared to 14.5 months for patients with HIV but no TB (comparison group). Mortality rate was significantly higher in TB cases compared to the comparison group (Badri et al., 2001).

Furthermore, TB has been shown as one of the leading opportunistic diseases diagnosed in patients with AIDS as well as the most common cause of death in autopsied African patients with AIDS . In one observational cohort study of HIV infected adults in South Africa (Day et al., 2004), viral load was compared between patients experiencing episode of TB and those non-TB control group. The result revealed that the mean HIV viral load was higher in the TB group than in the non-TB control group showing that an episode of TB could have some effect on HIV disease progression or HIV transmission at the population level (Day et al., 2004). On the other hand, HIVpositive patients with active TB, who receive anti-TB therapy and HAART, are just as likely as HAART-treated HIV-positive patients without TB to benefit from antiretroviral therapy .

TB AND HIV DIAGNOSIS

Presumptive diagnosis of TB is commonly based on the finding of acid fast bacillus (AFB) on microscopic examination of a diagnostic specimen such as a smear of expectorated sputum or of tissue (for example, a lymph node biopsy or fine needle aspiration). Definitive diagnosis depends on the isolation and identification of MTB from a diagnostic specimen (in most cases a sputum) using Mycobacterial Culture on Lowenstein-Jensen or Middle brook 7H10 media by incubating

at 370C under 5% CO2.

Skin testing with PPD is most widely used in screening for MTB infection. The test is of limited value in the diagnosis of active TB because of its low sensitivity and specificity. False-negative reactions are common in immunosuppressed patients. Positive reactions are obtained when patients have been infected with MTB but do not have active disease and when persons have been sensitized by non-tuberculous mycobacteria or Bacilli Calmette-Guerin (BCG) vaccination. In the past years, new diagnostic methods like Enzyme-linked immunospot (ELISPOT) and Enzyme-linked immunosorbent assay (ELISA) for the diagnosis of infection with MTB have been developed. The ELISPOT and ELISA detect the secretion of γ-interferon by mononuclear cells in venous blood, specific for MTB peptides, ESAT-6 and CFP-10. These tests are more sensitive and specific for the diagnosis of MTB infection and are superior to the tuberculin skin test (TST) in patients with immunosuppression (Ferrara et al., 2006). ESAT-6 and CFP-10 are peptides that mediate MTB virulence .Radiographic Procedures and clinical sign and symptoms can also be used in the process of diagnosing TB. The initial suspicion of pulmonary TB is often based on abnormal chest radiographic findings in a patient with respiratory symptoms. Of the clinical features, cough is reported less frequently in HIV patients, probably because of weak cough reflex due to debilitated condition of the patients in advanced disease, absence of cavitations, and less endobronchial irritation (MOH, 2005).

For HIV diagnosis currently different testing methods can be used. These methods detect the presence of infection by detecting one of the following: HIV antibody, HIV antigen, combined HIV Ab/Ag, HIV viral nucleic acid and HIV virus by viral culture method. HIV antibody detection can be done using ELISA methods, rapid tests and western blot assay methods. For surveillance as well as diagnostic purpose in developing countries, WHO recommends alternative testing strategies using combination of ELISA or rapid tests (WHO, 2001).

The close relationship between clinical manifestations of HIV infection and CD4+ T cell count has made measurement of the latter a routine part of the evaluation of HIV-infected individuals. The CD4+ T cell count provides information on the current immunologic status of the patient (Fauci et al., 2001). Patients with HIV infection should have CD4+ T cell measurements performed at the time of diagnosis and every 3 to 6 months thereafter (DHSS Panel, 2005). CD4+ T cell count is stated in treatment guidelines for determining when to start or change ART and for deciding when to initiate prophylaxis for opportunistic infections (MOH, 2005). According to most guidelines, a CD4+ T cell count <500/mm3 is an indication for consideration of initiating antiretroviral therapy, and a decline in CD4+ T cell count of >25% is an indication for considering a change in therapy (Fauci et al., 2001). In the Ethiopian setting currently clinical symptoms and CD4+ T-cell count of <200 cells/mm3 are in use for initiating antiretroviral treatment (MOH, 2005). In untreated HIV patients or in patients in whom therapy has not adequately controlled virus replication, the CD4+ T cell count falls below a critical level after a variable period and the patient becomes highly susceptible to opportunistic diseases (Fauci et al., 2001). Different opportunistic infections occur at different CD4+ T cell levels in HIV/AIDS patients. Unlike most other opportunistic infections (OIs) associated with AIDS, TB can occur at relatively high CD4+ counts .

TB-HIV CO INFECTION IN ETHIOPIA

Varying HIV seropositivity rates among tuberculosis patients have been reported in different parts of the world and even within a country. Several studies done elsewhere globally have reported TB-HIV co-infection rates ranging from <1% up to as high as 65% (Vander Werf et al., 2006). Similarly, studies from Central, North and Southern part of Ethiopia revealed varying rates of HIV seropositivity in active TB patients ranging from 6.6% to 52.1% (Kassu et al., 2007). On the other hand, very limited studies in Ethiopia tried to assess the immune status of patients when they develop active TB .

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