SPECIAL ARTICLE

Aids in Infants and Children

by

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Abstract

Children are infected by HIV, 80% vertically, from HIV infected mothers mostly near or at delivery. Because heterosexual transmission of HIV among adults is more and more important it is estimated that at the end of this century there will be totally more than 10 million HIV infected children.

Three quarters of HIV-infected babies show non specific symptoms at the early phase, including failure to thrive, chronic diarrhea, recurrent bacterial infections, mucocutanous infection.

Cytotropism of HIV to nerve cells results in inflammation, nerve cell damage and neuronal loss. Progressive neurologic abnormalities and developmental milestone regression or developmental retardation will be the results. Pneumocystics carinii infection has worse prognosis than lymphocytic interstitial pneumonia which more commonly occurred in HIV infected children. Diarrhea is a troublesome problem in children wityh AIDS. Kaposi's sarcoma and secondary cancer are rare in pediatric AIDS. Anemia and thrombocytopenia is common among AIDS children. In developing countries children with AIDS die within the year following the appearance of the symptoms, whereas asymptomatic HIV-infected children will live longer with high risk of recurrent and opportunistic infections.

The hallmark of AIDS in children is the same as in adults, i.e. the decrease of the number and function of CD4 lymphocytes. This in turn influences the functions of otherimmunocompetent cells and loss of immunity is the result. Many things are still unexplainable in children AIDS.

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The management applied now has proved to increase the quality of life, although it is not curative. Zidovudine is effective in alleviating some clinical problems, but needs further study. Routine immunization including BCG, DPT, polio and measles should be carried out on HIV infected children as usual. Only BCG is not done on children with clinical manifestations of AIDS.

AIDS affects the whole family, including non-infected children. The destruction of the families by AIDS will result in abandoned children who roam the streets of cities - who face the additional hazard of HIV infection trough sexual abuse and intravenous drugs. By the year 2000 there will be 10-15 million orphaned children due the death of one or both parents.

Paris Declaration on Women, Children and AIDS in 1989 recommended efforts of prevention and control of HIV/AIDS for women and children. Only by working together - pooling our efforts, resources and imagination - have we the best chance of bringing the pandemic under control.

Keywords : vertical transmission - CDC classification - CD4 lymphocyte - zidovudin - immunization - abondaned and orphaned children - Paris Declaration.

Introduction

Aquired immunodeficiency syndrome (AIDS) was firstly described in adults among homosexuals in USA in 1981. At the beginning of AIDS epidemic the spread of the disease in children and infants seemed remote. But thereafter AIDS was reported from all over the world affecting all ages (1). In the era of globalization, especially facilitated by tourism, no country can consider itself immune. After the etiology of AIDS was discovered in 1983 and then named human immunodeficiency virus (HIV) and the mode of transmission understood, it is becoming clearer that children are not impossible to be infected. The main risk factors of transmission are (2) :

1. high numbers of sexual partners
2. a history of sexualy transmitted disease (STD)
3. a sexual partner with AIDS orAIDS-related complex (ARC) 4. blood transfusion.

Children were infected chiefly vertically from HIV-infected mothers and through blood transfusion. HIV infection in children results in immunologic defect as in adults but AIDS in children differs from adults in two respects : 1. bacterial infections and lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia are accepted as indicative of AIDS in children. 2. The laboratory criteria are more stringent for children under 15 months old.

AIDS does not mean only a disease but it is very injurious to the growth and development of affected children. It destructs also the life of unaffected children as well. The purpose of this paper is to elaborate the knowledge of AIDS in children.

Epidemiology and Transmission in Children

The pandemic of AIDS sweeping the world cuts across conventional boundaries of nationality, sex, and age. Children are not free from HIV infection.

The first indication of spread to children came from investtigators in California, who reported transfusion-associated AIDS in a 20-month old white boy. The

prematurely born infant had received multiple transfusions of irradiated blood products during his stay in the nursery. One of the donors was a homosexual man who, although symptom -free at the time of his donation, subsequently developed AIDS and died. At the age of four months the child developed hepatosplenomegaly, neutropenia, autoimmune hemolytic anemia, thrombocytopenia, hyperglobulinemia, in vitro evidence of T cell dysfunction, and opportunistic infection [1].

In little more than a decade, over 1.5 million children have been infected by HIV - including more than 500,000 children below the age of 5 years who have developed AIDS and died - from a total of at least 8 to 10 million HIV infected people worldwide [2]. The pandemic is currently growing at the rate of around 5000 new infections per day. WHO's projection of the number of men, women and children expected to be infected with HIV by the year 2000 is 30-40 million, more than 10 million of which will be children [3]. Developing countries will have close to 90% of world total AIDS cases. While sub-Saharan Africa is still the hardest hit region, with over 7 million adults and children infected, since the start of the pandemic, the virus is now showing dramatic epidemic spread in South and South-East Asia, whereas at least 1 million people have already been infected [4]. As of early 1991, about 70% of all global HIV infections are estimated to have been spread by sexual intercourse between men and women. By the end of the century, it is projected that over 80% all HIV infections will result from heterosexual intercourse. Children are infected by HIV, chiefly through vertical transmission from infected mothers. With more than 3 million women estimated to be infected, the problem of perinatal transmission has become serious.

Because 80% of transmission of HIV in children are through vertical transmission, it is not surprising that serologic survey on HIV-infected children has been used to study the epidemiology of HIV among the mothers [5,6]. The transmission can occur in utero across the placenta or - in most cases - nearly or during the labor [7,8]. It is estimated that 25-50% of infants born by seropositive mothers will be infected. Perinatal transmission could conceivably be regulated by immune response of the mother to virus-encoded proteins. Maternal antibiodies to the immunodominant hypervariable loop in gp120 may reduce the rate of perinatal transmission. HIV antigen can be detected in amniotic fluid, and fetal tissues from a pregnancy terminated at 15 weeks' gestation [9]. Because heterosexual transmission is more and more important, the transmission from man to woman and vice versa is increasing. Failure of HIV antenatal screening for coming mothers therefore, will result in perinatal associated cases to continue to increase [10,11]. In the 1990s there will be more than 10 million HIV infected newborns and this occurs especially in the developing countries [4].

Transmission via breast feeding is very rare, but some cases have been reported [2,9,11,12]. Live virus has been cultured from breastmilk of HIV seropositive mothers, although many children are breastfed by infected mothers but none of them are infected.

HIV transmission in children can also occur by transfusion, especially in children who get multiple transfusions (e.g. thalassemia, hemophilia) with unscreened blood, by unsterilized or inadequately sterilized syringes and needles (in mass immunization or medical practice in some countries), by sexual abuse, and possibly ritual scarification and other traditional practices in which the skin is broken. Out of 1094 pediatric AIDS reported in Rumania in December, 1990,

39,2% are recipients of blood or blood product, in 57,4% the transmission is unknown but it is suspected that many of them are infected by unsterile equipments or needles [13]. Ninety percent of HIV infected blood recipients will be infected. In industrial countries screening of blood supply for antibody to HIV has been highly effective, and new infections due to transfusion of blood products are now extremely rare, thought it is not the case in the developing countries [10].

There is no evidence that HIV is transmitted by bite or casual contact with AIDS children. AIDS is not transmitted by vectors like mosquito or other insects.

Clinical Manifestation

AIDS is the late phase of HIV infection. In HIV-1-infected children, progression to disease is bimodal : some children develop AIDS during the first year of life, and others progress to AIDS at a later age [11,14].

In the early phase 75% of HIV infected children are asymptomatic or show non-specific symptoms and signs including growth failure, microcephaly and craniofacial abnormalities. Many non-specific signs and symptoms can occur, alone or in combination, during the course of HIV infection, and these include failure to thrive, recurrent infection, thrush, diarrhea, and lymphadenopathy [1]. In countries with high prevalence of AIDS, children with above mentioned signs and symptoms or with LIP, unexplained neurologic abnormalities or developmental milestones regression should be suspected suferring from HIV infection [9,10,15].

Pulmonary disease accounts for most of the morbidity and mortality associated with HIV infections in children. Pneumocystis carinii pneumonia (PCP) is the most important opportunistic pathogen. Lymphoid interstitial pneumonia (LIP) may also occur and may be difficult to distinguish from PCP. Children with PCP are more often febrile, have more often tachypnea with retractions, and have auscultatory finding of diminished breath sounds, wheezes, and rhonchi. Other opportunistic infections can occur, among others chronic interstitial pneumonia, disseminated CMV, candida esophagitis.

Encephalopathy may procede other manifestations, a progressive loss of developmental milestones or arrest in development being perhaps the most early signs. It is considered a primary persistent and progressive retroviral infection of the brain. Central nervous system (CNS) involvement is a bad prognostic sign. HIV virus infects the central nervous system (CNS) in 90% patients dying from AIDS. CNS involvement is a serious problem in children under 2 years old, while most HIV-infected children will not have a normal psychomotor development between the ages of 2 - 6 years. Cohen et al. [16] reported that the over all intelligence of seropositive hemophilic children (even as long as 8 years after HIV-1 infection through blood transfusion) didn't differ from that of seronegative hemophiliacs. But differences were found on school achievement and on tasks that require motor speed, visual scanning, and cognitive flexibility.

Hematologic involvement is common among children with HIV-infection, especially anemia and thrombocytopenia. There may be bleeding from mucosal sites. Peripheral blood smears may show large atypical lymphocytes with increased cytoplasm and basophilia.

Gastrointestinal and hepatobiliary dysfunction is common and may appear as : candida esophagitis, non-specific villus atrophy with malabsorption, periodic abdominal distension and pain, enterocolitis,

pseudomembranous necrotizing jejunitis, hypergastrinemia with hypochlorhydria, non-specific evaluations of transaminases, and biliary obstruction. Gastrointestinal dysfunction is a major problem; persistent diarrheal disease and disaccharidase intolerance are common in children with HIV infection. Dehydration is not uncommon. Careful attention to dietary intake may be required to ameliorate clinical symptoms and to maintain adequate nutrition [17].

Many children with HIV infection develop skin disease. A non-specific intermittent eczematoid eruption and candida dermatitis are common, but many other dermatologic manifestations have been found.

Cardiovascular disease is also not uncommon, i.e congestive cardiomyopathy which may show congestive failure and AIDS arteriopathy which affects the medium-sized vessels of many organs. Severe cardiovascular impairment occurs in children with AIDS and this may account for the fatal outcome in some cases.

Renal involvement has been observed in a few children with AIDS. The usual presentation is that of nephrotic syndrome with peripheral edema, hypoalbuminemia, and renal insufficiency.

HIV-infected children shows hyperglobulinemia but functionally they are hypoglobulinemia. They easily suffer from infections by opportunistic pathogens, especially pneumocystic carinii pneumonia (PCP), chronic interstitial pneumonia, disseminated CMV, candida esophagitis.

In the developing countries the situation is worse, where most of HIV-infected children die within the year following the appearance of the symptoms [11]. These children seem have no future either due to the progressive and fatally ended disease, poor health problems or psychosocial and economical problems.

Diagnosis

CDC classification of pediatric HIV infection is as follows (1,9) :

p-0 Indeterminate infection

p-1 Asymptomatic infection
- A Normal immune function
- B Abnormal immune function
- C Immune function not tested

p-2 Symptomatic infection
- A Nonspecific findings
- B Progressive neurological disease
- C Lymphocytic interstitial pneumonitis
- D Secondary infectious diseases
- E Secondary cancer
- F Other diseases attributable ot HIV

P-0 includes asymptomatic perinatally infected infants under 15 months with positive antibody test as only evidence of HIV infection. P-1 includes perinatally infected infants more than 15 months or infants under 15 months infected by non-perinatal routes of transmission.

At present, laboratory evidence for HIV infection relies on antibody detection by an enzyme-linked immunoabsorbent assay (ELISA) screening test which is confirmed by Western blot tests. This is not a specific indicator of HIV infection in young children, as transplacental transfer of maternal antibodies can be detected in the infant's circulation for 18 months after birth. In exceptional circumstances, maternal antibodies can persist up to 22 months of age without clinical evidence of HIV infection in the child. Standard ELISA and Western blottests cannot distinguish between maternally derived and infant-derived antibodies. Furthermore Western blot test is frequently difficult to interprete if only one or two bands appear; there are disagreements among laboratories and interpreters [9,11,18,19,20]. Children under

15 months of age who are exposed to HIV during the perinatal period and show positive HIV antibody are grouped into indeterminate infection if other tests, i.e. HIV culture, immunoglobulin titer, CD4/CD8 ratio are not done. Positive antibody test in children are interpreted as manifestation of HIV if other laboratory tests are positive [9,11].

Without a definitive virological diagnosis, the monitoring of immunoglobulin, CD4/CD8 ratio, and clinical signs could identify HIV infection in 48% of infected children by 6 months, with specificity of more than 99% [14]. After the ages of 18 months, a positive HIV-antibody test is indicative of HIV infection. With children as with adults, antibody testing is the best laboratory diagnostic test [11].

An alternative test, based on the fact that elevated serum IgA concentration is found as early as 3 weeks after birth, is antiviral anti IgA Western Blot and dot blot assays with recombinant HIV-1 proteins. Anti-HIV IgA was proved present in nearly all infected infants 5-27 weeks after birth and was not present in the uninfected infants or the control subjects, either by the anti IgA Western blot or dot blot assays. It was an effective method for detecting viral infection in newborns and young children [21].

Pathomechanism

The clinical, immunological, and virologicalcorrelationsof transmission and disease progression are not known. We still lack precise information on immunological aspects of pediatric AIDS, although qualitative and quantitative defects of CD4 lymphocytes also seem to be the hallmark of pediatric AIDS [11,22]. The period between the infection and the manifestation of AIDS is shorter in vertical transmission than in blood transmission [11].

Symptomatic HIV-infected children harbored more virus in their plasma and peripheral blood mononuclear cells (PBMCs) than the asymptomatic ones. But the relatively rapid progression to symptomatic disease of the majority of vertically infected patients is likely not due to the a higher load of replicating virus in the blood, because the titer of the virus in the symptomatic children is about the same as in adults [23,24].

The European Collaborative Study [14] recorded a direct relation between total plasma immunoglobulin (specifically a high IgM) and subsequent rapid disease progression. The extent of host immune reactivity, which may be genetically determined, is a powerful factor in the pathogenesis of HIV-associated disease [25]. Brenner et al. [26] reported that syncytium inhibition (SI) antibodies in children with AIDS were associated with a more benign outcome. Among children with both Western blot positive and had higher SI titres the prognosis seemed to be much better than among those who were Western blot positive but whose SI titers were absent or low. Deficient cytotoxic T lymphocyte (CTL) development to gag protein of HIV-1 can, in part, explain the more rapid onset of symptomatic disease following vertical HIV infection. Circulating HIV-1 gag-specific cytotoxic responses of 1. response to all stimuli, 2. response to ALLO and PHA but not to recall antigens 3. response to PHA but not to recall antigens or ALLO, and 4. response to none of these stimuli. Thus distinct patterns of CD4 lymphocyte dysfunction exist in children infected by HIV type 1 and correlate with higher frequency of infections. Comparisons of in vitro CD4 lymphocyte responses to these stimuli may be useful for detecting early functional CD4 lymphocyte defects and for monitoring progression of the disease. There is a close association between CD4

lymphocyte count and progression to AIDS. By applying a simple linear model for decline CD4 lymphocyte counts over a time, it can be suggested that differences in the time at which patients with HIV will progress to AIDS can largely be explained by differences in rates of decline of CD4 lymphocyte counts [29].

HIV have cytotropism to nerve cells, involving white and gray matter of brain and medulla spinalis resulting in inflammation and damage. Peripheral nerve involvement is common in adults with HIV infection and is also reported in children; acute or chronic inflammatory demyelinating polyneuropathy and a predominantly secondary neuropathy with little histopathologic evidence of inflammation may occur [30]. It was reported by Everall et al. [31] that 38% neuronal loss of the frontal cortex was found in AIDS patients who died with encephalitis, minimal changes without opportunistic infection or brain neoplasm. The neuronal loss may be due to interaction between HIV gp120 protein coat and specific neurotransmitter for T peptide and vasoactive intestinal peptide. Decreased methylation may also induce neurological lesions. In HIV-infected patients a reduced brain S-adenosylmenthionin/S-adenosylhomocystein (methylation) ratio would inhibit methyltransferase enzymes leading to hypomethylation in the central nervous system and ultimately to neurological lesions. This process occurs early in the disease [32].

Management

The era of considering pediatric HIV infection an untreatable disease has passed. Management now routinely includes propylaxis of HIV-associated infections, anticipatory manegement of childhood illnesses, nutritional support, modification of immunization schedule, psychosocial support, and, most recently, antiretroviral therapy. Although current therapeutic intervention is not curative, it has improved the quality, if not the duration, of life for children who have HIV infection and has offered significant hope for the future [9,33].

Zidovudine has shown in adults to prolong survival of patients with clinical AIDS and to reduce the rate of disease progression among patients with ARC or asymptomatic patients with CD4 counts of < 500 cells/mm3. In children zidovudine therapy has shown improvement of the patient's sense of well being, height and weight gain, neurodevelopmental parameters as well as reduction of HIV core antigenemia (P24). Unfortunately the drug does not eradicate the HIV but acts as an inhibitor of viral DNA polymerases and chain synthesis terminator so that transcription of viral RNA to DNA does not occur [23,24,33,34,35]. High dose the drug shows side effects or toxic, especially in patients with advanced disease. Anemia and thrombocytopenia has limited the use of high dose zidovudine in children. Zidovudine in low dose is well tolerated, no hematologic side effect occurs, but positive effects on neurodevelopment status may not be achieved [36]. Because encephalopathy is a serious complication of HIV infection in children and a poor prognostic indicator, this is an important concern. It is still controversial the use of zidovudine therapy for symptom-free infants and children with CD4 lymphocytecounts >500/mm3. Mostly zidovudine is given to the infants and children with symptoms and with CD4 >500/mm3, but a substantial number of experts recommend therapy for symptom-free as well. Indications for antiretroviral therapy in infants and children will be the subject of future studies [37].

Psychosocial and Economic Effects

Children of AIDS families, although HIV-uninfected,face serious psychosocial problems. HIV-infected children face gloomy days of health, growth and development problems. Children with AIDS need hospitalization more frequently than adults patients. Conviser et al. (38) reported that children with AIDS need an averaged 4,35 hospital admissions per year, 60,69 days of hospitalization per year and an averaged cost of $ 37,110.

The overwhelming medical and psychological needs of women and children with AIDS may result in the neglect of the other children in those families. These children-who are obliged to take over many of the parental responsibilities-must face the death not only their sister or brother but also one or both parents as well.

The serious psychological and emotional affects of this disease on family functioning are further complicated by social stigmatization and discrimination associated with AIDS. Because of fear and rejection on the part of the larger community, families with AIDS may feel they must and indeed may be required to keep the fact of the disease secret from their extended family, friends and neighbours. The resulting isolation comes at a time when the family is in greatest need of external support and care [39].

Because of its lifestyle conections and deadliness, many have regarded AIDS as retribution for sexual deviation and drug abuse. A review of surveys by CDC found that only very small proportion of respondents believed in the possibility of casual transmission. Nonetheless, 53% favoures banning AIDS patients from health-care jobs, 43% from restaurants, and 43% from schools. In another survey, 80% of 219 parents of children at day-care centres expressed fears about the inclusion of HIV-infected children with their children [40].

HIV affects chiefly economic active age group. Their death will result in 10-15 million orphaned children at the end of this century and a number of old ages without life support. It is a serious problem and especially hit the developing countries which have been burdened by many problems. In many developing countries the budget for prevention of AIDS is less than the cost spent for an individual case of AIDS in USA [3]. Some countries in Africa, where the prevalence of AIDS is high, spent only 1% of national gross product (GNP) for health, whereas the fund for supplying zidovudine for AIDS patients or antibiotics for recurrent infections is enormous [41].

Immunization and AIDS

Immunization is very important in children, but because AIDS children are immunocompromized it is thought that adverse reaction may appear, especially to live vaccines. The recommendation on the use of expanded immunization program (EPI) antigens is as follows [42] :

1. In countries where HIV infection is considered a problem, individuals, including individuals with asymptomatic HIV infection, should be immunized according to standard schedules. Individuals with clinical (symptomatic) AIDS should not receive BCG, but should receive the other vaccines (DPT, OPV/IPV, measles).

2. In areas where the risk of exposure to measles and poliovirus is high, the benefit of immunization outweighs the apparent low risk of adverse effect of

these vaccines, even in the presence of symptomatic HIV infection. IPV is an alternative to OPV for immunization of children with symptomatic HIV infection who may be at risk for OPV-associated paralytic poliomyelitis.

3. Evidence for an increased adverse reactions after BCG immunization among asymptomatic HIV-infected individuals remains inconclusive. Therefore for asymptomatic HIV-infected individuals where the risk of tuberculosis is high, BCG is recommended at birth or as soon as possible, Thereafter in accordance with standard policies for immunization of non-HIV-infected children. In a limited number areas, where the risk of tuberculosis is low, BCG is recommended as a routine immunization; BCG may be withheld from individuals know or suspected to be infected with HIV. For symptomatic HIV-affected individuals, BCG should be withheld.

4. Emphasizes of EPI recommendation to immunize children as early as possible in life. Vaccine associated adverse effects may be minimized and vaccine response may be optimized by beginning immunization before the progression of HI-induced immunosupression.

5. Endorses the simultaneous administration of multiple antigens such as BCG, DPT, Polio and measles vaccine when indicated.

Control and prevention

Children of AIDS family, either infected or not, need very much special care in various aspects. Educations on HIV infected children should be adjusted in accordance with the behavior, neurologic development, physical condition, and the expected type of interaction with other children. Asymptomatic HIV infected children should be allowed to attend school without restriction. For infected preschool-aged children and for some neurologically handycapped children who lack control of their bodily secretions or who display potentially hazardous behavior such as biting other children, and those who have uncoverable oozing lesion, a more restrictive environment is advisable until more is known about transmission in these setting (1).

The Paris Declaration on Women, Children and the Acquired Immunodeficiency Syndrome (AIDS) recommended many points of promoting and protecting the health of women, children and families with AIDS, including : mobilizing the necessary resources; enhancing the role and the social economic and legal status of women and children; multifaceted health educational programs for prevention of HIV infection/AIDS; prevent stigmatization and discrimination against people with HIV infection/AIDS; recognition of the problem of AIDS and HIV infection by developing and maintaining national epidemiological surveillance; HIV/AIDS prevention and control programs should be coordinated or integrated with all other programs; HIV testing is offered to women and children; support the families affected by AIDS including those who suffer from discrimination, that are not able to provide child care, or the abondoned or orphaned children; availability of and access to necessary health care; safe blood collection and transfusion sevices (3).

All the efforts can only be achieved by sharing among Government, Non Government Organizations, and community activities. Focused and nationwide interventions will have to be greatly expanded before they can have an epidemiological impact. Money spent on interventions at an early stage in the growth of the epidemic has a much greater impact than similar expenditure at a later stage in terms of the number of cases of infection prevented (3,11,41). Many countries realize the important of early prevention after it is too late.

Conclusion

AIDS affects adults as well as children. High transmission among adults results in more infected children. The signs and symptoms of AIDS in children differs a little with those in adults, although the hallmark in both age group is the same. Central nervous system involvement affects harmfully very much the development of infected children. Many problems of children AIDS are still unexplainable.

Curative intervention is still unavailable, although the management now has greatly improvemed the quality of life of AIDS patients. EPI antigens should be given to asymptomatic HIV-infected children.

Family destruction by AIDS, abandoned orphaned children due to death of one or both parents, stigmatization, discrimination and rejection by community are among the serious problems of AIDS.

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