ASIAN PACIFIC JOURNAL OF ALLERGY AND IMMUNOLOGY (2003) 21: 127-130

SHORT COMMUNICATION

Seroprevalence of Cytomegalovirus Infection in Children Born to HIV-1 Infected Women

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SUMMARY **Cytomegalovirus (CMV) is a frequent opportunistic infectious agent in children infected with human immunodeficiency virus type 1 (HIV-1). It has been implicated as a factor in the progression of HIV-1 disease. The aim of the present study was to evaluate the prevalence of CMV infection in Thai children born to HIV-1 infected women. The prevalence of CMV infection was 13, 89 and 84% in HIV-infected children and 9, 61 and 75% in HIV uninfected at age ranges of 0-12, 13-36 and 37-79 months, respectively. The prevalence of CMV infection was significantly different between HIV infected children (89%) and HIV uninfected (61%) at the age of 13-36 months ($p < 0.05$). The presence of CMV IgM in some children of age < 1 year suggested that CMV infection could occur early in life. Early co-infection may be important as they remain a risk factor for reactivation of latent CMV infection throughout the course of the HIV diseases. Clinical monitoring and appropriate work up may be of benefit in the early diagnosis and treatment of CMV disease.**

Cytomegalovirus (CMV) is a DNA virus and member of the *Herpesviridae* family. The virus is ubiquitous and commonly infects persons of all ages worldwide. The prevalence of the infection, which increases with age, is higher in developing countries especially among the lower socioeconomic population than in the more developed ones. A study on the prevalence of CMV antibodies revealed a seroconversion rate of 83.7% in Thai children below the age of sixteen years, and 70.7% to 100% in adult blood donors and pregnant women.[1-5] Most CMV infections are inapparent, but this virus can also cause a number of clinical illnesses that vary in severity from mild to fatal. In normal immunocompetent persons, the infection is occasionally characterized by a mononucleosis-like syndrome. Among immunosuppressed individuals, including recipients of transplants and patients with acquired immunodeficiency syndrome (AIDS), a variety of clinical symptoms may manifest during primary CMV infection or reactivation. Pneumonia, retinitis and gastrointestinal diseases are common and can be fatal.[6] CMV-infection has been implicated as a cofactor in the progression of HIV-1 disease. Our objective was to determine the prevalence of CMV infection in Thai children born to HIV-1 infected women.

MATERIALS AND METHODS

Patient population

One hundred and sixty children born to HIV-1 infected women who were receiving health care services at Chulalongkorn Memorial Hospital between October 1993-July 1998 were studied. The patients were recruited after informed consent was obtained from their parents. After reviewing their clinical status and the diagnosis of HIV infection, these children were categorized into HIV-infected children, and

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HIV-uninfected children.

Diagnosis of HIV infection

HIV infection in children can be diagnosed by positive anti-HIV antibody test at the age of 18 months onwards. In younger children, the infection can be diagnosed by the presence of other laboratory evidence such as HIV p24 antigen and/or HIV DNA or by the presence of other HIV associated conditions or AIDS.

Diagnosis of CMV infection

A child who had a positive serologic test for IgG or IgM at the age of 12 months onwards, was considered CMV-infected.[7] In children younger than 12 months, however, the infection was diagnosed by a positive serologic test for IgM (anti-CMV IgM).

Detection of anti-CMV IgG and IgM

All sera were examined for the presence of anti-CMV IgG and IgM using the Vironostika test kit assay (Organon-Teknika, Belgium). The principle of the test for anti-CMV IgG is a sandwich system, while the anti-CMV IgM is based on an antibody-capture sandwich system. For the anti-CMV IgG assay, microwells were coated with murine monoclonal antibody to CMV, to which in the first step inactivated CMV antigen was added. Diluted serum (1:100) was then added to react with the bound CMV antigen. The immune complexes were detected by sheep anti-human IgG labeled with horseradish peroxidase (HRP) and substrate (tetramethylbenzidine hydrochloride; TMB). In contrast to the anti-CMV IgG assay, IgM antibodies from diluted serum (1:100) bound to anti-human IgM which was coated on the wells. The CMV antigen and the anti-CMV labeled with HRP were then added. The immune complexes were detected by adding the TMB substrate. The enzymatic reactions of both tests were determined by an ELISA reader.

Statistical analysis

Demographic data were presented by using mean, range and percentage. Categorized variables were analyzed by the chi-square test and the Mann-Whitney test. Non categorized variables were analyzed by Student's t test. The level of significance was set at the p-value of 0.05.

RESULTS

Among the 160 children recruited, 82 were boys and 78 were girls, with an age range of 3-79 months, (mean 21 months). Of these, 77 were HIV-1 infected and 83 were HIV-1 uninfected. CMV-IgG antibodies were detected in 65 (84.4%) of the 77 HIV-infected children and in 51 (61.9%) of the 83 HIV-uninfected children (p = 0.002). CMV-IgM antibodies were detected in 7 (9%) of the 77 HIV-infected children and in 4 (4.8%) of the 83 HIV-uninfected children (p = 0.45) (Table 1). Among the 11 children who were CMV-IgM antibody positive, 6 children were below the age of one year. The remaining 5 children were in the age group of 13-36 months. All children were CMV-asymptomatic. Seroprevalence of CMV antibodies was 80, 89 and 84% in HIV-infected children and 56, 61 and 75% in HIV-uninfected in the age ranges of 0-12, 13-36, and 37-79 months, respectively (Table 2). The prevalence of CMV antibodies was significantly different between HIV-infected children (89%) and HIV uninfected (61%) at the age of 13-

Table 1 Characteristics of study population and prevalence of CMV antibodies

	HIV-infected N = 77	HIV-uninfected N = 83	p-value
Age (months)			
Mean ± SD	23 ± 17.79	20 ± 11.4	0.2027[a]
Median	16	18	
Boys:girls	34:34	48:35	0.1162[b]
Anti-CMV IgG positive	65/77 (84.4%)	51/83 (61.9%)	0.002[b]
Anti-CMV IgM positive	7/77 (9%)	4/83 (4.8%)	0.451[b]

a = Student's t test
b = Chi-square test

36 months ($p < 0.05$) only. The prevalence of CMV infection among different groups of children is shown in Table 3.

Antibody titers of > 1:100 were considered positive. Individual titers ranged from 1:100 to 1:6,400. The geometric mean titer (GMT) was 1:639.49 and 1:601.36 in HIV infected and HIV uninfected, respectively ($p = 0.067$).

DISCUSSION

The prevalence of antibodies to CMV varies in different populations and in different places.[1,8] The results of our study are generally consistent with those of other reports from developing countries where CMV infection occurs early in life both among normal and immunocompromised children.[9] In our sample, 56-80% of children from both groups acquired antibodies to CMV in the first year of their life. Maternal antibody probably was accounted for the presence of antibodies in some infants. The results from a recent study indicated a high prevalence of CMV infection in Thai adults. It varied from 86% in college students, 97% in blood donors and up to 100% in pregnant women.[5,10] The significant difference in the prevalence of CMV infection in HIV-infected children and HIV-uninfected children in the age range of 13-36 months may be caused by the different practices of child rearing, socioeconomic status or the immunodeficiency caused by HIV.[11] Our findings were similar to a study performed by Kovacs *et al.*[7] which reported that HIV-1 infected infants had higher rates of CMV infection acquired perinatally or during the first four years of life.

The presence of IgM antibody to CMV in 4.8-9% of sera in children below the age of one year suggests that CMV infection can occur very early in life. CMV has been implicated as a cofactor in the progression of HIV-1 disease and the pathogenesis of AIDS.[12,13] CMV and HIV-1 infect the same cell. The viral gene products and the cellular proteins of each virus can activate the other virus *in vitro*.[14] Recent quantitative analyses of CMV infection and CMV viremia in both children and adults have shown a correlation between CMV infection and rapid progression of HIV-1 disease.[15,16] Early co-infection may also be an important risk factor for reactivation of latent CMV infection throughout the course of the HIV disease. Clinical monitoring and appropriate work up may be of benefit in the early diagnosis and for timely treatment of CMV disease.

ACKNOWLEDGEMENTS

We are grateful to the Thailand Research Fund and the Center of Excellence, Viral Hepatitis Research Unit, Chulalongkorn University, for their generous financial sup-

Table 2 Seroprevalence of CMV-antibodies among different group of children born to HIV-1 infected women

Age group (months)	HIV-infected CMV positive/no. tested (%)	HIV-uninfected CMV positive/no. tested (%)	*p*-value
0-12	24/30 (80)	12/22 (56)	0.09
13-36	25/28 (89)	30/49 (61)	0.02
37-79	16/19 (84)	9/12 (75)	0.65

Table 3 Seroprevalence of CMV infection among different groups of children born to HIV-1 infected women

Age group (months)	HIV-infected CMV positive/no. tested (%)	HIV-uninfected CMV positive/no. tested (%)	*p*-value
0-12	4/30 (13)	2/22 (9)	0.49
13-36	25/28 (89)	30/49 (61)	0.02
37-79	16/19 (84)	9/12 (75)	0.65
Total	45/77 (58.4)	41/83 (49.3)	≤ 1

ports. We would also like to thank the Venerable Dr. Mettanando Bhikkhu of Wat Nakprok, Bangkok, for editing the paper.

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