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Japanese encephalitis vaccination in HIV-infected children with immune recovery after highly active antiretroviral therapy

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Abstract

HIV-infected children are vulnerable to infections by vaccine preventable pathogens. However, they have poorer responses to childhood immunization than healthy children. The objectives of this study are to determine the prevalence of Japanese encephalitis (JE) protective antibody in HIV-infected children with immune recovery after highly active antiretroviral therapy (HAART) and evaluate response to JE revaccination. JE neutralizing antibody titer of plasma was determined by a plaque reduction neutralization assay. An antibody titer of more than 1:10 was defined as protective antibody. Children who did not have protective antibody to JE were enrolled to receive a two-dose JE revaccination during the study. There were 96 children with mean age of 9.7 years (S.D. 2.6) and mean CD4 percentage of 25 (S.D. 5) who participated in the study. Forty-four children (46%) had protective antibody to JE. A two-dose JE revaccination was administered to 50 children who did not have JE antibody. At 1 month after revaccination, 44 children (88%) developed protective antibody. This study demonstrated that there is a low prevalence of JE protective antibody in HIV-infected children despite history of JE primary childhood vaccination. However, the majority of HIV-infected children with immune recovery after HAART can develop protective antibody after JE revaccination.

Keywords: Japanese encephalitis virus; Human immunodeficiency virus (HIV); Protective antibody

1. Introduction

Japanese encephalitis virus is a mosquito-borne flavivirus. Japanese encephalitis (JE) is the leading cause of viral encephalitis in Asia. JE occurs in annual epidemics in many Asian countries including China, Vietnam, Thailand, Laos, India, Sri Lanka and Indonesia [1]. The estimated incidence of JE in Thailand ranges from 1.5 to 2.5 per 10,000 populations. It is highest in the northern region, and lowest in the central region. The age specific rate is highest in children 5–9 years of age [2]. The case fatality rate of JE ranges from 17 to 25% in various region [3,4]. Approximately 50% of the survivors have neurologic sequelae with frank motor deficits, or severe cognitive and language impairment [3]. JE is preventable through immunization with safe and effective inactivated vaccines with efficacy of 91–94% [5,6]. Since 1992, inactivated JE vaccine has been included in the childhood Expanded Program on Immunizations (EPI) vaccination schedule for children in Thailand. The primary series consists of two doses given 1–2 weeks apart for children around 18 months of age. The first booster dose is administered 1 year later. The second booster dose is administered as an optional dose in the following 4–5 years.

Human immunodeficiency virus (HIV) infection destroyed $CD4^+$ T-cells which provided a critical help to B-cells in the production of antibodies against T-cell-dependent

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antigens and in the differentiation of B-cells into memory cells [7]. Several studies report poorer immune response to vaccine in HIV-infected children compared to the general population [7,8]. Rojanasuphot et al. reported a low response to JE vaccine among HIV-infected children after primary vaccination with two doses of JE vaccine. The response rate was only 36% compared to 67% among uninfected children [9].

The introduction of highly active antiretroviral therapy (HAART) has resulted in immune recovery [10] and reduction of morbidity and mortality in HIV-infected children [11]. However, information about the persistence of JE antibody after primary series vaccination in these children is limited. Whether revaccination after immune recovery is necessary remains unknown. We hypothesized that the majority of HIV-infected children had no JE protective antibody and were at risk of JE infection even after the commencement of HAART. The aims of this study were (1) to determine the prevalence of JE protective antibody in HIV-infected children with immune recovery after HAART and (2) to assess efficacy of JE revaccination in HIV-infected children after receiving HAART.

2. Patients and methods

2.1. Study design and patient population

The study had a two-step design. The first phase was a cross-sectional study to determine the proportion of HIV-infected children who had a protective antibody to JE virus. Children who had no JE protective antibody were enrolled to the second phase of the study. The second phase was an intervention study to determine a proportion of children who were able to produce a protective antibody to JE virus after having received a two-dose JE revaccination.

This study was conducted at Chiang Mai University hospital, Chiang Mai, Thailand from March 2005 to March 2006. The inclusion criteria were (1) HIV-infected children aged >5 years, (2) had been severely immunosuppressed (nadir CD4 lymphocyte percentage ≤15), (3) had shown evidence of immune recovery, defined as CD4 lymphocyte percentage >15 for at least 3 months after receiving HAART and (4) had a history of JE vaccination. The exclusion criteria were children who (1) received immunosuppressive agents within 3 months or (2) received blood component transfusion within 6 months prior to the study. The study protocol was approved by the research ethics committee of Chiang Mai University. Written informed consent was obtained from each child's parent or guardian before enrollment.

2.2. Study procedures

2.2.1. The first phase—to determine the prevalence of JE protective antibody

A cross-sectional study to evaluate the prevalence of JE protective level was performed in March 2005. Past illnesses and immunization data were collected by medical record review and caregiver interview. The history of HIV-related illness and antiretroviral treatment was obtained by medical record review. The clinical stage of HIV disease was determined according to the 1994 US Centers for Disease Control and Prevention revised classification [12]. CD4 lymphocyte count and plasma HIV RNA level before starting HAART and at 24-week intervals after HAART were abstracted from medical records. A single blood drawing was performed to measure JE neutralizing antibody. Patient who had no JE protective antibody, defined as a neutralizing antibody titer of ≤1:10, were enrolled to the second phase of a study.

2.2.2. The second phase—to determine the efficacy of JE revaccination

Two subcutaneous 0.5 mL doses of the inactivated JE vaccine—Beijing strain (produced by the Thai Government pharmaceutical organization) were given 6 months apart. Subjects had blood drawn at 2 months after first dose, prior to second dose and at 1 month after second dose of JE revaccination. Since response to JE vaccine might differ between children who had had dengue infection and those who had not, blood specimens were measured for both JE and dengue antibody levels.

2.3. Safety assessment

Vaccine safety and tolerability were monitored by the use of a vaccine report card supplied to parents or guardians. The cards solicited daily recording of injection-site adverse events and systemic adverse events on the day of vaccination and for 72 h thereafter. They were also asked to notify the study physician immediately if unexpected or severe reactions occurred.

2.4. Laboratory tests

JE and dengue neutralizing antibody titer of plasma were determined at the Center for Vaccine Development, Mahidol University, Bangkok by a plaque reduction neutralization (PRNT50) assay modified from Russell et al. [13]. Plaque count was determined by using LLC-MK_2 plaque assay single overlay technique. Briefly, sera were thawed and heat-inactivated by incubation at 56 °C for 30 min. Serial dilutions of serum were made (1:10, 1:40 and 1:160). An equal volume of diluted Japanese encephalitis (Beijing), Dengue 1 (16007), Dengue 2 (16681), Dengue 3 (16562) and Dengue 4 (1036) viruses contain about 40–60 pfu/0.2 mL/well was added to each serum dilution tube. Following incubation at 37 °C for 60 min, 0.2 mL was removed from each tube and inoculated onto triplicate 6-well plates of confluent LLC-MK_2. Each plate was incubated at 37 °C for 90 min and the monolayers were then overlaid with 4 mL of 3.0% carboxy methyl cellulose/MEM. Plates were incubated for 7 days at 37 °C with 5% CO_2, then plaques were counted. The endpoint neutralizing plaque dilution was determined from the dilution series