CONGENITAL TOXOPLASMOsis TRANSMitted BY hUMAN IMMUNODEfiCiENCY-virus INFECTED WOMEN

ABSTRACT

We report the occurrence of congenital toxoplasmosis in three infants born to HIV-infected women who had high anti-toxoplasma IgG and negative IgM during pregnancy. We briefly reviewed available literature and discussed the possible transmission mechanisms of congenital toxoplasmosis among HIV-infected pregnant women. Serum samples were tested for Toxoplasma gondii IgM and IgG antibodies using commercial enzyme immunoassay and IgG-avidity tests. In the first case, fetal death occurred at 28th week of gestation. In the second case, congenital toxoplasmosis was diagnosis at 6th month of life; and in the third case, an HIV-infected newborn, congenital toxoplasmosis was asymptomatic. These cases point out to the possibility of enhanced maternal-fetal transmission of T. gondii infection by HIV-infected women chronically infected, which may have important public health consequences, considering that increasing frequency of HIV-infection has been observed among women of childbearing age around the world.

Keywords: congenital toxoplasmosis, human immunodeficiency-virus, prevention, AIDS.

INTRODUCTION

Toxoplasma gondii is a ubiquitous obligatory widely-distributed intracellular protozoan. Once infected, the host normally acquires lifelong immunity induced by the persistence of the parasite in an encysted form. Maternal immunity appears to protect against fetal infections. If anti-T. gondii IgG antibody is confirmed before pregnancy, then the woman is not at risk for a congenitally infected fetus. Congenital toxoplasmosis is usually the result of maternal acquisition of T. gondii for the first time during gestation. However, vertical transmission of toxoplasmosis as a result of reactivation has been described in immunocompromised women and more rarely in immunocompetent women.

Clinical manifestations of congenital toxoplasmosis are numerous, including intracranial calcifications, convulsion, psychomotor retardation, strabismus, chorioretinitis, microcephaly, and hydrocephaly observed in infancy or later. However, most neonates with congenital toxoplasmosis are asymptomatic or with subclinical presentation of the disease at birth.

There is limited data on medical literature about the frequency of T. gondii vertical transmission among HIV-infected women. In Brazil, the prevalence of seropositivity for T. gondii is 50% to 80% in women of childbearing age. Although T. gondii infection is highly prevalent in Brazil, there are only two reports of congenital toxoplasmosis documented among HIV-infected women.

In this paper we describe serological and clinical findings of three cases of congenital toxoplasmosis diagnosed among 113 HIV-exposed infants followed at the Infectious Diseases Department of Antônio Pedro University Hospital, since 1998, in Niterói, Rio de Janeiro, Brazil. Seventy per cent of HIV-infected mothers had serologic evidence of anti-T. gondii IgG during pregnancy. Blood samples were taken serially for HIV routine diagnostic purposes, and some serum samples from the three patients were tested retrospectively for the present study.

CASES REPORT

First case: A 26-year-old caucasian woman was diagnosed with HIV-infection in May 2004, at 14 weeks’ gestation of her third pregnancy. Routine prenatal testing revealed Anti-T. gondii IgG positive and anti-T. gondii IgM negative. She was asymptomatic and had never...
been treated with antiretroviral drugs. Initial CD4 cell count was 291/mm³ and viral load was 65,000 copies/mL (4.81 log) by nucleic acid sequence based amplification (NASBA). From the 22nd week of gestation onwards, she was started on zidovudine, lamivudine and nevirapine for prophylaxis of HIV-infection vertical transmission. At 21 weeks’ gestation (July 2004) another toxoplasma serology was done and the result revealed IgG positive (2,320 IU/mL; cut-off: 8 IU/mL) and IgM negative by enzyme linked fluorescent assay (ELFA) (VIDAS® Toxo IgG II and IgM, Biomérieux SA, France). The anti- T. gondii Ig-avidity was high (0.586; cut-off: 0.3) (VIDAS® Toxo IgG Avidity, Biomérieux SA). At 28 weeks’ gestation (August 2004), she was admitted to the hospital with fever, flank pain, and pyuria. She received cefazolin for treatment of urinary tract infection. Her laboratory exams showed anaemia, and toxoplasma serology was positive for IgG (2,488 IU/mL) and negative for IgM antibodies by ELFA. Ultrasonography revealed fetal death and delivery was induced. Fetal autopsy showed hepatosplenomegaly and anasarca. Microscopic analysis of heart sections stained with hematoxylin and eosin (HE) revealed pericarditis and anasarca. Microscopic analysis of heart sections stained with hematoxylin and eosin revealed pericarditis and myocarditis, with acute and chronic inflammatory infiltration and micro-elements morphologically compatible with T. gondii trophozoites. Placental histology showed diffuse necrotizants villoisitis with trophozoites. Immunostaining with polyclonal antibody anti-T. gondii (rabbit anti-T. gondii; code no.: B1013, Dako, Denmark) of heart and placenta tissue sections confirmed HE microscopic analysis. Her toxoplasma serology repeated in October 2004 was positive for IgG antibodies (2,262 IU/mL) by ELFA. Six months after, the IgG titre by ELFA was lower (1,232 IU/mL). Both sera were negative with the IgM-ELFA and showed high avidity IgG antibodies.

Second case: A 30-year-old caucasian woman was diagnosed with HIV-infection in September 2005, on the 12th week of her third pregnancy. Routine prenatal testing revealed anti-T. gondii IgG positive (1/512; cut-off: 1/16) and IgM negative by EIA. At 21 weeks’ gestation (March 2006), she was submitted to a cesarean-section because of fetal suffering. An apparently healthy girl was born, and zidovudine was given to the newborn for 6 weeks to prevent HIV infection. The baby was followed up by the Pediatric Department and in June 2006 she started presenting nistagmus. On clinical exam there were strabismus, neurodevelopmental delay and hepatosplenomegaly. Laboratory screening revealed anti-T. gondii IgG (107 IU/mL) and a positive IgM by ELFA. Funduscopy showed chorioretnitis in her left eye and the skull radiography was normal. The child was treated with sulfadiazine, pirimetamine, and folinic acid for 6 months. During follow-up visits, chorioretinal scars were seen in funduscopic reevaluation and intracranial calcifications on brain CT scan. Anti-T. gondii serology by ELFA revealed IgG positive (99 IU/mL) and IgM negative. The child had a serology for HIV negative at the 11th month of life, being considered HIV-uninfected. Placenta histology showed intervillositis, extensive villitis and chorioamnionitis.

Retrospectively, the mother’s serology showed a significant increase in Anti-T. gondii IgG titre by ELFA from 364 IU/mL in November 2005 to 3,616 IU/mL in March 2006. Both sera were negative with the IgM-ELFA and had high avidity IgG antibodies. During follow-up visits, maternal anti-T. gondii serology still showed high levels of IgG antibodies detected by ELFA: July 2006 – IgG: 6,138 IU/mL; January 2007 – IgG: 2,970 IU/mL; October 2007 – IgG: 2,188 IU/mL. All serum samples tested for IgM antibodies by ELFA were negative and also had high avidity IgG antibodies anti-T. gondii.

Third case: A 16-year-old afro-descend adolescent was diagnosed with HIV-infection in 2003 during her first pregnancy. Her follow-up visits were at irregular intervals, and antiretrovirals were given only for prophylaxis of HIV-infection vertical transmission during pregnancy. Her toxoplasma serology had always been positive for IgG and negative for IgM antibodies since 2003. In February 2008, she sought for medical advice as she was at 33 weeks’ gestation. She had pruritus, anaemia, and her toxoplasma serology was positive for IgG antibodies (204 IU/mL) and inconclusive for IgM by ELFA. In March 2008 (36 weeks’ gestation), she complained of progressive visual impairment affecting the left eye, and ophthalmologic examination showed uveitis due to toxoplasmosis. Her toxoplasma serology was positive for IgG antibodies (198 IU/mL) and negative for IgM by ELFA. The VIDAS IgG-avidity test was high (0.391). She was treated with sulfadiazine, pirimetamine, and folinic acid for ocular toxoplasmosis and zidovudine for prophylaxis of HIV-infection vertical transmission. Her CD4 cell count was 171/mm³ and the viral load was 333,129 copies/mL (5.523 log) by b-DNA technique. She was submitted to an elective cesarean-section at 38 weeks’ gestation. A healthy girl was born, and laboratory showed toxoplasma serology positive for IgG antibodies (172 IU/mL) and positive for IgM by ELFA. Cerebrospinal
fluid examination revealed pleocytosis (20 cell/mm³, 100% neutrophil predominance), elevated protein (129 mg/dL). Funduscropy and skull radiography were normal. The child was discharged from hospital receiving drugs for treatment of congenital toxoplasmosis and to prevent HIV infection. The baby was followed up by the Pediatric Department. In May 2008, her HIV viral load was positive (163,000 copies/mL; 5.21 log) by b-DNA technique. In June 2008, she had oral candidiasis and her CD4 cell count and viral load were, respectively, 1,407/mm³ and more than 500,000 copies/mL. Her clinical and laboratory status was compatible with aids, and antiretroviral treatment was started in July 2008.

**DISCUSSION**

Although not proved, our first case was possibly a reactivation of latent *T. gondii* infection. There was a possibility of acquired infection in the first 14 weeks of gestation; since absence of specific IgM is characteristic for HIV-infected patients. Fetal death may support this hypothesis of newly acquired infection. However, the sharp rise in specific IgG suggests remote infection, because in HIV-infected patients the serum levels of antibodies against existing infections increase, but the humoral response to recently introduced antigens decreases.

Our first case indicates that congenital toxoplasmosis may occur in children of HIV-positive mothers who are not severely immunocompromised as a result of toxoplasmic reactivation. Even though no serology to *T. gondii* infection was available before the present gestation, negative IgM and high IgG-avidity antibodies are compatible with primary infection before the pregnancy, although HIV-infected pregnant women may present newly acquired *T. gondii* infection without seroconversion to specific IgM. The other two cases were both severely immunocompromised and their antibody test results clearly showed *T. gondii* infection acquired before pregnancy. In the three cases, congenital toxoplasmosis was probably due to reactivation of latent maternal infection, although reinfection with a different strain of *T. gondii* is also possible.

The second case alerts for the necessity of doing tests for congenital infections in newborns of HIV-infected mothers. The opportunity of treating infant since birth, or even before birth, must not be lost. This case, in which CT scan showed intracerebral calcifications, alerts to very low sensitivity of skull radiography to congenital toxoplasmosis. This infant was treated for only 6 months because when she was 1-year-old there were no signs of active infection.

Although HIV-infected pregnant women chronically infected with *T. gondii* may transmit the infection to the fetus, the risk is low and certainly less than 5%. Some authors advocate that women with CD4 less than 100 cells/mm³ who are Anti-*T. gondii* IgG positive should be treated with adequate prophylaxis during pregnancy to attempt to interrupt transmission of *T. gondii* from chronically infected women to fetus. They suggest this advice may be also appropriate for HIV-uninfected patients who are severely immunocompromised for other reason. Other study suggests that the risk of maternal-fetal transmission is not sufficient high to justify routine anti-toxoplasmosis chemoprophylaxis for HIV-infected pregnant women, although the authors highlight the need of further research on this issue.

The lack of an established risk of maternal-fetal infection, particularly in countries like Brazil where there are high seroprevalence rates of *T. gondii*, may explain the current obstetric management of these patients without the prescription of anti-toxoplasmosis chemoprophylaxis in chronically infected women.

Our report shows the need for special attention to maternal titles of anti-*T. gondii* antibodies during HIV prenatal care even in women chronically infected with *T. gondii* and also in those not severely immunocompromised. A high concentration of *T. gondii*-specific IgG and a positive result for *T. gondii*-specific IgM in immunocompetent patients usually indicate recent infection, because *T. gondii*-specific IgG increases rapidly in the acute infection. Conversely, a low concentration of *T. gondii*-specific IgG and no *T. gondii*-specific IgM is a sign a remote infection. These indications may not apply to HIV-infected pregnant women. If, as described for HIV-infected patients in general, it is true for HIV-infected pregnant women, the serum levels of antibodies against existing infections increase and the humoral response to recently introduced antigens decreases, then, high *T. gondii*-specific IgG concentrations may, paradoxically, indicate latent *T. gondii* infection, whereas low concentrations may indicate recent infection, when the risk of congenital toxoplasmosis may be high. A higher risk of congenital toxoplasmosis with low *T. gondii*-specific IgG concentration and negative specific IgM is worth of attention in order to not let a case of acute gestational toxoplasmosis unidentified in HIV-infected pregnant women. It also enhances the relevance of routine antibody screening for congenital toxoplasmosis in the newborn blood. The screening for IgM antibody is an important tool for the detection of newborns infected with *T. gondii* and it is mandatory in HIV-exposed infants.

Considering the increasing frequency that HIV-infection has been observed among women of childbearing age around the world and the severity of fetal lesions caused by congenital toxoplasmosis, the possibility of enhanced maternal-fetal transmission of this infection by HIV-infected women chronically infected with *T. gondii* may have important public health consequences, mainly in those countries with high seroprevalence rates of *T. gondii* infection.
**ACKNOWLEDGEMENTS**

We would like to thank Dr. Rosa Vieira and her team, from the Immunology Laboratory, Hospital Universitário Antônio Pedro (UFF), for carrying out the serological tests for toxoplasmosis.

**REFERENCES**