International Journal of Infectious Diseases 16 (2012) e480–e486

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Association between the risk of congenital toxoplasmosis and the classification of toxoplasmosis in pregnant women and prenatal treatment in Brazil, 1994–2009

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ARTICLE INFO

Article history:
Received 29 November 2010
Received in revised form 12 January 2012
Accepted 13 January 2012

Corresponding Editor: Andy Hoepelman, Utrecht, the Netherlands

Keywords:
Risk factors
Congenital toxoplasmosis
Toxoplasmosis in the pregnant woman
Toxoplasmosis treatment
Classification of Lebech

SUMMARY

Objectives: The objectives of this study were to analyze the association between the classification of toxoplasmosis in the pregnant woman (TP) according to the classification of Lebech et al. and the incidence of congenital toxoplasmosis (CT), also taking into consideration prenatal treatment.
Methods: A clinical cohort study of 524 children followed-up until 1 year of age was conducted. Adjusted odds ratios (OR) were estimated by logistic regression.
Results: Of 519 pregnant women, 61.3% were not classified due to the incompleteness of hospital records. Among the pregnant women classified as confirmed cases of TP ($n = 19$), the CT risk was six times greater than in the probable/possible group. No case of CT was identified in the group of pregnant women classified as unlikely to have TP. The children with no prenatal treatment (46.2% $n = 242/524$) presented a risk almost three times greater of CT than the treated children (OR 2.77, 95% confidence interval (CI) 1.54–4.97; $p = 0.001$). Complete prenatal treatment was identified as a protecting factor for CT (OR 0.35, 95% CI 0.19–0.65; $p = 0.001$).
Conclusions: A lack or incomplete prenatal treatment was identified as an important risk factor for CT in this study. The proportions of non-classified mothers and children with no prenatal treatment reflect the need to improve prenatal care in Brazil.

1. Introduction

Congenital toxoplasmosis (CT) can cause serious neurological and ocular sequelae, even among asymptomatic children. CT is a preventable and treatable infection,[1–4] and the identification of risk factors for transmission during pregnancy may help in the clinical management of suspected children. Well known risk factors are acute toxoplasmosis in pregnancy (TP) and the timing of occurrence (the later the appearance of the infection, the greater the chance of transmission).[5,6] Considering that 90% of women with TP are asymptomatic, the diagnosis of TP is based on the results of serological tests.

In Brazil, TP and CT screening is performed on an irregular basis, as there is limited access to laboratory tests. Although there are no guidelines from the Health Ministry, the clinical control of CT in the Federal District (FD) is guided by the *Manual of gestational and congenital toxoplasmosis*.[7] However, even in the FD the diagnosis of TP is difficult, particularly the systematic testing of IgG and IgA, and avidity testing for IgG antibodies. Thus, the diagnosis of TP is usually based on accessible tests (IgG and IgM), the results of which are not always conclusive in relation to the occurrence of infection.

Lebech et al. correlated various serological profiles to the probability of TP, classifying pregnant women as having either a confirmed or presumed (probable, possible, or unlikely) infection.[8] Because this classification is possible regardless of the systematic testing for IgG and IgA and avidity testing for IgG, it was considered to be more suitable for the present study. However, studies assessing the association between the classification of TP according to Lebech et al. and the occurrence of CT were not identified in the reviewed literature. There is also controversy regarding the role of prenatal treatment in reducing vertical transmission.[9–17]

Therefore, the objective of this study was to analyze the associations between the classification of TP and the risk of CT, and prenatal treatment and the risk of CT, in a clinical cohort of children identified during 15 years and followed-up until the age of 1 year at a reference service for CT in the FD. These results may help obstetricians and pediatricians in the appropriate diagnosis and treatment of pregnant women and children who are suspected to have CT, in relation to laboratory investigations and therapeutic interventions.

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1201-9712/$36.00 – see front matter © 2012 Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.
http://dx.doi.org/10.1016/j.ijid.2012.01.016

2. Methods

2.1. Study population

Eligible children ($n = 533$) were those whose mothers were considered suspected or definite cases of TP. All of the mothers had positive IgG tests. These mothers were referred to the pediatric infectious diseases unit of the Regional Hospital of Asa Sul (PID-HRAS) by their babies' pediatricians based on prenatal data regarding their serologic status (positive IgG). All mothers and babies referred to PID-HRAS were identified during the period from May l994 to October 2009 at the pediatric infectious diseases outpatient unit. This is the only referral service for the investigation, follow-up, and treatment of CT of the State Health Secretariat, FD. Of the 533 eligible children, nine were lost to clinical follow-up before diagnosis.

The diagnosis of CT was confirmed by the persistence of IgG antibodies up to 12 months of life. All of the children were examined at birth and underwent clinical follow-up performed by the infectious diseases specialist and ophthalmologist and laboratory testing starting within the first 3 months of life. Laboratory investigations were repeated according to the clinical criteria, and included complete specific serological tests, hemogram, radiology exams (X-ray of the skull and ultrasonogram (US) and computed axial tomography (CAT) scan of the brain), and study of the cerebrospinal fluid (CSF). Serological testing was repeated at 1, 3, 5, 8, and 12 months, or until IgG antibodies were negative.

The mothers of the eligible children were classified into five groups according to the probability of TP, using the classification of Lebech et al.,[8] modified by the authors, as follows: (1) Definite: seroconversion – both samples taken after conception; positive culture from maternal blood; confirmed congenital infection in offspring. (2) Probable: seroconversion – first sample taken within 2 months before conception; significant rise of IgG titers, and presence of IgM and/or IgA; high IgG titers, presence of IgM and/or IgA and onset of lymphadenopathy during pregnancy; high IgG titers and presence of IgM and/or IgA in the second half of pregnancy. (3) Possible: stable high IgG, without IgM, in the second half of pregnancy; high IgG and the presence of IgM and/or IgA in the first half of pregnancy. (4) Unlikely: stable low IgG, with or without IgM; stable high IgG, without IgM, in early pregnancy. (5) Not classified: non-quantified IgG antibody results.

The authors modified the classification of Lebech et al. by excluding the fifth group ('not infected') and creating a new group 'not classified' to prevent the exclusion of a large number of mothers. The 'not infected' group was defined by Lebech et al. as: seronegative (during pregnancy); maternal preconception seropositive sample; positive IgM and/or IgA without the appearance of IgG. This group was excluded by the authors because all eligible children were born from a mother suspected of TP.

Prenatal treatment aims to prevent transplacental transmission of *Toxoplasma gondii* and to treat fetuses that are possibly infected. The therapeutic regimens studied were: (1) spiramycin (2 tablets every 12 h) for 21 days; (2) pyrimethamine (2 tablets once a day, at the same time) associated with sulfadiazine (2 tablets every 6 h) and with folinic acid (1 tablet three times a week); (3) regimens 1 and 2 alternately every 21 days.

Other variables related to treatment that were analyzed were the trimester in which treatment was initiated and the duration of treatment. Treatment was considered continuous when given until delivery.

2.2. Study design

This historical cohort study was based on medical records of clinical and laboratory data related to pregnancy and the follow-up of the children.

2.3. Data analysis

Data analysis included descriptive and analytic stages. In the descriptive stage, the incidence of CT was studied for each group of pregnant women classified according to the classification of Lebech et al.[8] Prenatal treatment data were described with the corresponding 95% confidence intervals (95% CI) based on the exact method.

In the analytic stage, associations between the selected explanatory variables (classification of TP according to the classification of Lebech et al.[8] and data on prenatal treatment) and CT were estimated using logistic regression models. Crude and adjusted odds ratios (OR) were estimated along with their respective 95% CI. For the statistical significance of the hypothesis tests, the accepted type 1 error was 5%. Stata software (version 10) was used for all the analyses.[18]

The research protocol conforms to Brazilian Resolution No. 196/96 concerning ethical aspects of research on human beings. The study was approved and authorized by the director of the Regional Hospital of Asa Sul and by the Research Ethics Committee of the State Health Secretariat, FD.

3. Results

Among 519 mothers analyzed ($n = 5$ mothers of twins) it was not possible to classify 318 (61.3%) of them according to the classification of Lebech et al.[8] due to incomplete information about serological tests (Table 1). Nineteen (3.7%) mothers were classified as definite, 111 (21.4%) as probable, 46 (8.9%) as possible, and 25 (4.8%) as unlikely cases of TP.

Overall, the incidence of CT in this study was 11.3% ($n = 524$). The CT incidence was larger for pregnant women classified as definite cases (42.1%, 95% CI 19.90–64.31%) compared to the other groups of mothers classified as probable cases (10.8%, 95% CI 5.03–16.59%) and possible cases (19.6%, 95% CI 8.10–31.03%) of CT. For these latter two groups, the classification of Lebech et al.[8] had limited discriminatory power to identify CT. In contrast, there were no CT cases among mothers classified as unlikely cases of TP.

Children whose mothers were listed as definite cases of TP ($n = 19$) had a risk almost four times greater of having CT than those born to mothers listed as presumed cases ($n = 182$). In the first group, 63.2% ($n = 12/19$) received specific prenatal treatment during pregnancy, and in the second group, 55.5% ($n = 101/182$) received such treatment (data not presented).

Among children treated during the prenatal period, the probability of CT was 6.7% (95% CI 3.81–9.66%) in contrast to the group that was not treated, in which the probability rose to 16.7% (95% CI 11.76–21.57%). Thus, children who were not treated during the prenatal period showed a risk 2.8 (95% CI 1.54–4.97) times greater of been a CT case than those who were treated.

The risk of CT among untreated children and those who had no record of receiving prenatal treatment was rather similar, indicating that in this latter group, the majority of children were probably untreated during the prenatal stage (Table 1).

Among the 19 pregnant women listed as definite cases of TP, 12 were treated, six were not, and one had no information regarding treatment (data not presented). The transmission rate of CT in the group of definite cases when treated was 41.7% ($n = 5/12$) and when untreated was 33.3% ($n = 2/6$). The rates of CT transmission were even lower among probable, possible, and unlikely cases ($n = 182$) when untreated (17.3%, $n = 14/81$) or when treated prenatally (6.0%, $n = 6/101$) (data not presented).

The rate of CT among children whose mothers were given regimen 1 of prenatal treatment (spiramycin; $n = 210$) was 8.1% (95% CI 4.41–11.78%). This rate decreased to 2.9% (95% CI 0–8.38%) among children whose mothers received regimen 2 ($n = 35$) and to 0% among children whose mothers were given regimen 3 ($n = 18$).