Risk factors for *Toxoplasma gondii* infection in mothers of infants with congenital toxoplasmosis: Implications for prenatal management and screening

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Objective: The purpose of this study was to determine whether demographic characteristics, history of exposure to recognized transmission vehicles, or illness that was compatible with acute toxoplasmosis during gestation identified most mothers of infants with congenital toxoplasmosis.

Study design: Mothers of 131 infants and children who were referred to a national study of treatment for congenital toxoplasmosis were characterized demographically and questioned concerning exposure to recognized risk factors or illness.

Results: No broad demographic features identified populations that were at risk. Only 48% of mothers recognized epidemiologic risk factors (direct or indirect exposure to raw/undercooked meat or to cat excrement) or gestational illnesses that were compatible with acute acquired toxoplasmosis during pregnancy.

Conclusion: Maternal risk factors or compatible illnesses were recognized in retrospect by fewer than one half of North American mothers of infants with toxoplasmosis. Educational programs might have prevented acquisition of *Toxoplasma gondii* by those mothers who had clear exposure risks. However, only systematic serologic screening of all pregnant women at prenatal visits or of all newborn infants at birth would prevent or detect a higher proportion of these congenital infections.

Congenital toxoplasmosis is a disease that affects an estimated 500 to 5000 newborn infants in the United States each year. Most infected infants have no apparent physical abnormalities at birth, but, without treatment, most of the infected infants will have significant morbidity that is related to chorioretinitis, hydrocephalus, or neurologic damage by the end of
adolescence. Treatment of infected infants in the first year of life substantially improves outcomes, and treatment of a mother with acute toxoplasmosis during pregnancy can prevent vertical transmission or initiate treatment of the congenitally infected fetus. Therefore, strategies for early recognition of maternal or infant infection and the institution of effective treatment could have a substantial impact on the incidence and morbidity that are associated with this congenital infection.

In the Chicago Collaborative Treatment Trial, we have followed up a cohort of infants who were referred to us for congenital toxoplasmosis over the past 20 years. In the present study, we have analyzed the mother’s history of exposure to potential vehicles of transmission of T. gondii and the history of illness that is compatible with acquired toxoplasmosis during gestation. This analysis defines the potential for prevention of congenital toxoplasmosis through educational efforts, obstetric management of illness during pregnancy, selective maternal screening, or universal maternal or neonatal screening.

Material and methods

Between 1983 and 1998, a total of 131 infants and children were referred to the Chicago Collaborative Treatment Trial with laboratory-confirmed congenital toxoplasmosis. Of the 131 patients, 122 patients were referred as infants within the first months of life. All studies that involve the Collaborative Treatment Trial participants are approved by the University of Chicago’s Institutional Review Board in accordance with National Institutes of Health guidelines.

In the course of multidisciplinary evaluations of these infants, demographic data were acquired, and mothers were questioned regarding their possible exposure to recognized vehicles of transmission of T. gondii and their history of compatible illness during pregnancy. Specifically, demographic data were acquired with regard to maternal residence, maternal age, maternal race/ethnicity, family’s Hollingshead index (a measure of socioeconomic status), and method of payment for care. Age and race/ethnicity distributions were compared with those of the general US population using χ² tests. Mothers were questioned regarding their exposure to cats. Specifically, they were asked whether they owned a cat, had emptied a litter pan, had gardened, had exposure to sand boxes, or had any combination of the above. Mothers were also questioned regarding their possibility of exposure to raw meat, specifically whether they had a history of preparation of foods with raw meat, had eaten any dishes that contained raw or undercooked meat, or had consumed any other raw foods (such as unpasteurized milk or raw eggs). The nature of exposure during pregnancy and the trimester in which it may have occurred were questioned specifically. Mothers were also asked about the occurrence of any illness during pregnancy that was compatible with infection and were queried specifically regarding fever or night sweats, flu-like illness or myalgia, headache, or lymphadenopathy.

For referred children, congenital infection was confirmed with standard laboratory tests in a reference laboratory (J. Remington, Toxoplasma Serology Laboratory, Palo Alto) that included the Sabin-Feldman dye test, immunoglobulin M, immunoglobulin A, and immunoglobulin E enzyme-linked immunosorbent assays or immunosorbent agglutination assays (ISAGA); subinoculation or polymerase chain reaction (PCR) of blood, amniotic fluid, or cerebrospinal fluid, or compatible findings in infants who were born of acutely infected mothers when other diagnoses were excluded. Maternal infection with T. gondii was documented with serologic tests that included the Sabin-Feldman dye test, immunoglobulin M, immunoglobulin A, or immunoglobulin E enzyme-linked immunosorbent assay or ISAGA, and the differential agglutination test.

Results

Demographic parameters

Hollingshead indices

Congenital toxoplasmosis was found to affect infants who were born to families of all socioeconomic classes (Table I), although our population had a higher than predicted proportion of Hollingshead indices 1 and 2.

Payment for care

The method of payment for medical care and type of health insurance in referred families was comparable to that of the US population as a whole (Table I).

Hometown size

One half the families were from urban settings, approximately one quarter each from suburban or rural hometowns (Table I).

Maternal age and ethnicity

The median maternal age was 25 to 29 years (Table II). Ethnicities are shown in Table III, with an over-representation of Asian/Pacific Islander subjects and an underrepresentation of African American subjects. Age differences were not statistically significant compared to the general US population, but racial differences were.

Risk factors

Although 75% of women who were delivered of an infant with congenital toxoplasmosis could recall a conceivable exposure, only 39% of the women specifically recalled
exposure to cat litter or raw meat dishes (Table IV). Surprisingly, 25% of the women could not identify any possible exposure to cats or any ingestion of even undercooked meat.

Compatible clinical illness

Although 48% of the mothers noted an illness that might have included toxoplasmosis as a cause, only 27% of the women recalled fever or night sweats, and only 23% of the women recalled lymphadenopathy (Table V). Fifty-two percent of the mothers could not recall an infectious illness of any kind during pregnancy.

Overall, 60 mothers (48%) recognized signs and symptoms that were considered typical of toxoplasmosis or had known, specific risk factors (Table VI).

Prenatal serologic testing

Only 10 women (8%) had serologic tests for toxoplasmosis before delivery of their infant. Of these 10 women, 3 women were American expatriates living in France who were tested during their pregnancies as a component of routine obstetric care. Interestingly, all 3 of these women also recalled compatible symptoms (eg, lymphadenopathy, malaise, myalgia, fever, chills, or “flu-like” illness), but screening occurred as part of the standard practice of care in France and not because of their symptoms. Of the remaining 7 women, all had compatible illness and/or identified risk factors; however, 1 woman was tested because of ascites that was noted on prenatal ultrasound scans in both her twins; 3 women were tested only because their physicians were looking for the cause of compatible illness and/or identified risk factors, and 3 women were tested because their physicians used routine screening practices.

Comment

This study addresses whether a report of exposure to epidemiologic risk factors or etiologic investigation of a compatible illness during pregnancy would lead to the identification of most or all women who are at risk for transmitting *T gondii* to their unborn babies. If the identification of most such women could identify most infected infants, then serologic screening would not be
needed. Simply obtaining a careful history would lead to appropriate testing and management. Our data demonstrate that a careful history would identify, at most, 48% of mothers who have acquired toxoplasmosis during pregnancy. Thus, only serologic screening would have identified the rest.

Implications of our findings for prevention with education are clear. Even if education about the risks of toxoplasmosis became a component of standard obstetric practice, only approximately one half of the women had risk factors that might have been recognized and thus could have been eliminated by education. Our observation that only 8% of women in our study were screened for toxoplasmosis during pregnancy is consistent with the relatively infrequent screening of pregnant women in the United States for this disease. In France and Austria, where educational measures have been incorporated into routine obstetric care, reductions in rates of infection by 50% have been reported. Thus, other measures appear to be necessary to prevent or identify a higher proportion of cases of this congenital disease.

Our study is retrospective, because we elicited histories only from women whose infants already had been diagnosed with congenital toxoplasmosis. In many instances, the babies had substantial handicaps, and their mothers were knowledgeable about toxoplasmosis and understandably actively seeking explanations for their infection. Thus, the bias in ascertainment of risk behaviors and compatible illness in our experience is in favor of the identification of a higher proportion of mothers with risk factors. It is likely that the proportion of these women who reported risk exposures or compatible illnesses, if queried prospectively, would have been considerably lower. The degree to which US populations of pregnant women are aware of the risks of exposure to cats and cat excrement and of consuming raw or undercooked meat was not addressed specifically in our study and deserves further investigation. There are no means for determining percentages of women with similar symptoms and risk factors in a demographically comparable, concomitant control group during the past 20 years. This type of control group, established prospectively, might have helped identify whether any factor was seen more commonly in the mothers in our studies or whether nothing in the history was distinctive. However, this information was not available and does not effect the conclusion of this work.

In the course of the study, several additional observations and demographic factors were noted. First, the proportion of African American women with infants who were infected with toxoplasmosis in the study was quite low, representing only 2% of the total, whereas the proportion of African American women in the US population is 12% ($P < .001$). Whether this low prevalence is due to different exposure rates, to poorer

<table>
<thead>
<tr>
<th>Table IV</th>
<th>Recognized maternal risk factors for 131 women with infants with congenital toxoplasmosis</th>
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<tbody>
<tr>
<td>Variable</td>
<td>N (%)</td>
</tr>
<tr>
<td>Cat exposure</td>
<td></td>
</tr>
<tr>
<td>Any cat exposure</td>
<td>80 (65)</td>
</tr>
<tr>
<td>Own cat</td>
<td>36 (29)</td>
</tr>
<tr>
<td>Emptied litter pan</td>
<td>18 (15)</td>
</tr>
<tr>
<td>Garden/sandbox</td>
<td>33 (27)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
</tr>
<tr>
<td>No cat exposure</td>
<td>43 (35)</td>
</tr>
<tr>
<td>Maternal raw or undercooked meat exposure</td>
<td></td>
</tr>
<tr>
<td>Any raw meat exposure</td>
<td>62 (50)</td>
</tr>
<tr>
<td>Preparation with raw meat</td>
<td>45 (37)</td>
</tr>
<tr>
<td>Ate raw or undercooked meat</td>
<td>38 (31)</td>
</tr>
<tr>
<td>Ate raw meat dishes</td>
<td>15 (12)</td>
</tr>
<tr>
<td>Ate raw milk or eggs</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
</tr>
<tr>
<td>No raw meat exposure</td>
<td>61 (50)</td>
</tr>
<tr>
<td>Combined risk factors</td>
<td></td>
</tr>
<tr>
<td>Any cat or raw meat exposure</td>
<td>91 (75)</td>
</tr>
<tr>
<td>No cat or raw meat exposure</td>
<td>31 (25)</td>
</tr>
<tr>
<td>Cat litter or raw meat dishes</td>
<td>47 (39)</td>
</tr>
<tr>
<td>No cat litter or raw meat dishes</td>
<td>75 (61)</td>
</tr>
</tbody>
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<tr>
<th>Table V</th>
<th>Maternal illness during pregnancy in 131 mothers with congenitally infected infants</th>
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<tbody>
<tr>
<td>Illness</td>
<td>N (%)</td>
</tr>
<tr>
<td>Fever or night sweats</td>
<td>33 (27)</td>
</tr>
<tr>
<td>Flu-like illness or myalgia</td>
<td>32 (26)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>29 (23)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
</tr>
<tr>
<td>Any infectious illness</td>
<td>60 (48)</td>
</tr>
<tr>
<td>No maternal illness</td>
<td>63 (52)</td>
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</tbody>
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<tr>
<th>Table VI</th>
<th>Summary epidemiologic factors of maternal exposure and illness history</th>
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<tr>
<td>Factor</td>
<td>Percentage</td>
</tr>
<tr>
<td>Any exposure to cats</td>
<td>65</td>
</tr>
<tr>
<td>Any exposure to undercooked or uncooked meat</td>
<td>50</td>
</tr>
<tr>
<td>Any exposure to cats or undercooked or uncooked meat</td>
<td>75</td>
</tr>
<tr>
<td>Specific exposure to cat litter or uncooked meat</td>
<td>39</td>
</tr>
<tr>
<td>Unexplained febrile illness or lymphadenopathy during pregnancy</td>
<td>48</td>
</tr>
<tr>
<td>Exposure to cat litter, uncooked meat, or toxoplasmosis-like illness during pregnancy</td>
<td>48</td>
</tr>
</tbody>
</table>
quality of primary health care for African American women and infants, or possibly to a genetically based, increased resistance to the transmission of the disease remains to be determined. If the lower than expected proportion of African American infants is due to poorer quality of health care, systematic screening would help to remedy the problem of differential access to proper diagnosis and health care. Second, despite reporting nonspecific symptoms of infection to their physicians (such as prolonged fever or lymphadenopathy), many of the women indicated that toxoplasmosis was seldom considered as a possible explanation of the symptoms. This observation points out the importance of greater recognition by obstetricians of the pediatric implications of maternal infection and infectious symptoms during pregnancy.27

Other new epidemiologic observations have been made recently and suggest the possibility of additional modes of transmission of T gondii in North America. A high number of sea otters have died off the coast of California since 1995, and investigators have found that T gondii infection is 1 of the causes.28 The suggested epidemiologic factor is that the otters ingest Toxoplasma oocysts in sea water, where oocysts can persist up to 6 months, concentrated in mussels or other shellfish. Researchers hypothesize that oocysts infect shellfish through cat excrement in litter that people discard into toilets or watershed areas, which then arrive in coastal waters where otters live. Similarly, a large community epidemic of toxoplasmosis took place in Victoria, British Columbia, in 1995.29 No conventional transmission vehicle was identified, but case-control studies showed significant associations between acute infection and residence in the distribution system of one reservoir that supplied unfiltered water to greater Victoria. A recent study from Brazil, where toxoplasmosis is hyperendemic, also supports the hypothesis of transmission by unfiltered drinking water.30 In our study, we did not ask about the consumption of shellfish33 or of sources of water consumption in our inquiries about possible risk factors.

There have been economic analyses, Cochran Database reviews, and metareviews concerning screening programs for toxoplasmosis and their outcomes.1,9,32-40 Some of these have assigned equal value to well-performed studies and to dissimilar cohorts in studies that sometimes are designed, controlled, performed, or interpreted inadequately. Some of these analyses have noted the absence of perfectly designed and performed prospective, placebo-controlled, randomized studies with long follow-up, which included economic analyses, that clearly document savings in costs and efficacy of newborn infant or maternal screening.33-36 Some authors who reviewed these available data have concluded that, in the absence of better prospective studies, it may be too costly or unwarranted to perform universal screening or even testing and treatment at all, even to prevent suffering, health care–related costs, loss of productivity, and limitation in quality of life that are associated with untreated congenital toxoplasmosis.36 Some authors have commented that such screening could cause anxiety because of false-positive test results or unnecessary pregnancy terminations caused by serologic testing that was not confirmed in a high-quality reference laboratory or to counseling that was suboptimal.34 In contrast, other analyses have concluded that screening, in conjunction with careful confirmation in a high-quality reference laboratory and knowledgeable and caring counseling is important to facilitate identification and treatment.19,20,32,37-43 We critically reviewed these analyses and the concerns they raise. We conclude that there is rigorous and careful work that indicates that systematic detection of this infection in pregnant women and the treatment of the infected fetus, as described9,37-40 results in improved outcomes for affected children. Careful confirmation of serologic testing in a high-quality, reliable reference laboratory and knowledgeable and empathetic medical care and counseling are essential parts of this process.

From our analysis of the risk factors and illnesses in mothers of congenitally infected children, we conclude that the most effective way to prevent or detect a higher proportion of infants with this congenital infection is by systematic serologic screening. It is difficult to imagine that any informed mother or father would choose not to include this screening in their prenatal care, considering that almost all untreated infants who are infected with T gondii in utero experience ophthalmologic and/or neurologic disease34 and that treatment of the fetus and infant clearly reduces these risks.11-21

An implication of our data is that education of pregnant women concerning risk factors for acquiring Toxoplasma during gestation would be useful in the prevention of congenital toxoplasmosis. Also, although uncommon,19 the recognition of signs and symptoms of this infection by obstetricians is important for prevention. Another implication of our findings is that only systematic serologic screening would detect a substantial proportion of mothers who are infected during gestation and those fetuses and infants with congenital toxoplasmosis. For many of these mothers, risk factors and signs or symptoms were not identified. Thus, our approach to prevention also is to include serologic screening to prevent congenital toxoplasmosis. Delays in treatment have been shown to result in more severe clinical manifestations. Therefore, our approach to how frequent serologic screening is performed, without limitation of resources, includes preconception testing of women and the identification of women who are infected acutely during pregnancy with an initial test for Toxoplasma infection at the first prenatal visit in the first trimester. Thereafter, monthly testing of seronegative
women to identify seroconversion and testing of newborn infants to identify congenital infection should be performed. We recognize that this optimal approach may not be economically feasible at this time in the United States, where seroprevalence is relatively low, resources are limited, and automated testing procedures are not widely available. In this country, testing seronegative pregnant women once each trimester (e.g., at 8–10, 18–20, and 28–30 weeks’ gestation)\(^3\) and all newborn infants might be considered.\(^4\) However, it should be recalled that the best outcomes derive from monthly screening approaches.\(^9,36,39\)

**T. gondii**—specific immunoglobulin G and M assays are used for screening pregnant women and newborn infants. Acute infection in the mother should be confirmed by a *Toxoplasma* serologic reference laboratory (e.g., in the United States: www.pamf.org/serology). *Toxoplasma*-specific immunoglobulin A, differential agglutination test, and avidity assays are used to document the timing of the acquisition of an infection during gestation more precisely. The avidity assay is an important, recently developed test that can be used in the first 12 to 16 weeks of gestation (based on the test kit used) to accurately date the acquisition of infection before conception.\(^41,42\) High avidity of *Toxoplasma*-specific antibody in a single serum that has *Toxoplasma*-specific immunoglobulin G and M antibodies and that has been obtained in the first 12 or 16 weeks of gestation indicates that infection has occurred before conception and therefore is not likely to threaten the fetus.

This approach to the diagnosis and treatment of women who are suspected or proved to have acquired the infection during gestation also includes fetal ultrasound scans and amniocentesis with PCR on the amniotic fluid at 18 weeks of gestation or thereafter to determine whether the fetus is infected. Whereas the specificity of PCR testing on amniotic fluid approaches 100%, the sensitivity is significantly less.\(^43\) Thus, a negative PCR does not rule out infection in the fetus definitively. If the PCR is negative, spiramycin is used to attempt to reduce the transplacental transmission of *T. gondii* to the fetus. When infection is acquired by the pregnant woman before mid gestation and there is no fetal infection that is documented by amniocentesis or suggested by fetal ultrasound scans, spiramycin is continued until term. If the fetus is determined to be infected, the administration of pyrimethamine and sulfadiazine to the mother provides treatment for the fetus as well. Dosages of these medicines for the pregnant woman are pyrimethamine (50 mg per day) and sulfadiazine (2 g, twice daily) with leucovorin (10 mg per day) for its marrow-protective effects. Pyrimethamine is not administered before 12 weeks of gestation.

Management of the pregnant woman who becomes infected later in gestation is controversial. Some physicians use the same approach as described earlier to differentiate the exposed and infected fetus. However, because the likelihood of transplacental transmission and an infected fetus is very high late in gestation, other physicians treat all such mothers and their infants with pyrimethamine, sulfadiazine, and leucovorin.

Our approach to newborn infants who are born to mothers who are suspected or proved to have acquired the infection during gestation is to evaluate the infant clinically and serologically, with an attempt to isolate the parasite from placental tissue.\(^3\) The results of that testing are used to determine whether the treatment of the infant should be initiated or continued. Testing for immunoglobulin M antibodies by a sensitive method like the immunoglobulin M ISAGA test and immunoglobulin A antibodies by enzyme-linked immunosorbent assay must be performed. Serologic testing and subinoculation of the placenta for the infant are performed by a *Toxoplasma* serologic reference laboratory. Treatment in utero reduces clinical manifestations, the ability to isolate the parasite from the placenta, and the serologic markers of infection in the newborn infant. The infected infant is treated throughout the first year of life.

Analyses of cost and efficacy of screening programs are important in public health policy decision making. Rigorous analyses clearly are needed. However, congenital toxoplasmosis eventually has devastating clinical consequences for nearly all infected infants.\(^44\) Early and aggressive antimicrobial therapy has a clear benefit.\(^21-21\) The disease occurs with an incidence that is comparable to or higher than a number of genetic and metabolic diseases (e.g., phenylketonuria, congenital hypothyroidism, and congenital adrenal hyperplasia) for which neonatal screening is mandated by law in most states.\(^44\) The data herein support the conclusion that “the time has come” to screen for acute acquired *Toxoplasma* infection in pregnant women and congenital toxoplasmosis in infants to prevent the potentially devastating outcomes from untreated disease.\(^25,32\)

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