

High Burden of Congenital Toxoplasmosis in the United States: The Strain Hypothesis?

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(See the Major Article by McLeod et al, on pages 1595–605.)

Rima McLeod, the leading author of an article published in this issue of *Clinical Infectious Diseases* [1], has accumulated a unique and remarkable database on congenital toxoplasmosis in the United States through the National Collaborative Chicago-based Congenital Toxoplasmosis Study (NCCCTS), which began in 1981 and continues to date. In a recent study [2], she and colleagues at the reference Palo Alto Medical Foundation *Toxoplasma* Serology Laboratory (PAMF-TSL) revealed that severe clinical signs of congenital toxoplasmosis, including hydrocephalus, eye disease, or intracranial calcifications, occurred in 84% of 116 infants from birth to 180 days of age who had laboratory confirmation of congenital toxoplasmosis and in whom clinical information was available during a period of 15 years in the United States. The big question that needs to be answered is why these figures in the United States are in marked contrast with those reported in France, where roughly 90%

of children with congenital toxoplasmosis are free of lesions at birth.

There are obvious differences between France and the United States in the management of congenital toxoplasmosis that are likely to explain, at least partially, the different burden of the disease on both sides of the Atlantic. There is a national screening program at the prenatal and postnatal levels in France but not in the United States. The prenatal screening permits early detection of seroconversion in the mother and early diagnosis of infection in the fetus. In France, a prenatal treatment is offered during pregnancy with a double goal: to reduce the risk of mother-to-child transmission and, if fetal infection has occurred, to reduce the risk of intracranial and ocular damage in the child. Although the benefit of prenatal treatment is unclear and has yet to be evidenced in a large randomized controlled clinical trial, the lack of prompt diagnosis and treatment of the mother during gestation in the United States is a major factor that is likely to partly explain the worse outcome at birth in this country in comparison with the French data. The absence of prenatal and postnatal screening in the United States adds other biases in the comparison of data between both countries. In France, independent of clinical and imaging results, all cases of congenital toxoplasmosis

are laboratory confirmed in a score of reference laboratories across the territory. On the contrary, samples are sent to 1 reference laboratory in the United States (PAMF-TSL) when there are clinical signs in favor of congenital infection. This referral bias is likely to induce an underdiagnosis of congenitally infected infants free of lesions and may explain the overrepresentation of severe cases in the United States. Finally, because of this lack of screening, the gestational age at which maternal infection is acquired is not known in the United States. Keeping in mind that infection acquired by the mother early in gestation is clearly associated with more severe outcome in the child, this kind of information is sorely lacking when data on clinical severity are compared. Even if the French prenatal screening and the biases discussed above are of major importance to explain the better outcome of congenital toxoplasmosis in France, additional factors are required to fully explain such a huge difference with the US data.

Among these factors, attention has been focused on genetic variability among *Toxoplasma gondii* strains. The influence of strain in congenital toxoplasmosis has been clearly addressed in Brazil, where children with congenital toxoplasmosis have a 5 times higher risk than European children of developing

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eye lesions and their lesions are larger, more numerous, and more likely to involve the macula [3]. These stark differences are likely to be due to the predominance of more virulent genotypes of the parasite in Brazil, which are rarely found in Europe. To summarize, the genetic diversity of *T. gondii* strains is very high in Brazil where many different and atypical genotypes have been characterized in animals. Conversely, the genetic diversity is very poor in European *T. gondii* strains. For example, in France, roughly 95% of human and animal strains are highly similar and cluster in a clonal lineage named type II, whereas 5% of strains are genetically clustered in another clonal lineage named type III. Based on our experience in the French National Reference Center for genotyping *T. gondii* isolates, an accumulating body of data indicates that atypical strains are more likely to cause severe damage than type II strains in congenital toxoplasmosis and in immunocompetent people.

In this issue of *Clinical Infectious Diseases*, an article by McLeod et al [1] addresses for the first time to our knowledge the influence of the parasite strain on the severity of congenital toxoplasmosis in the United States. Because few *T. gondii* strains have been isolated from patients in the United States, the strategy of the authors has been based on serotyping rather than genotyping. Serotyping is a very attractive test because this technique bypasses the very complicated issue of isolating strains from human samples for performing genotyping analyses. However, the information provided by this test is limited to a yes-no question: Is the infection caused by type II strains or not? In other words, serotyping is a good test for identifying patients infected with type II strains, but sera of patients infected with other genotypes are solely identified as not exclusively II (NE-II) serotypes. This test is therefore useful in France, where 95% of strains are type II

strains but is useless in areas where there are many different atypical genotypes such as in Brazil. In this study, parasite serotype was determined for 183 congenitally infected infants and their mothers in the NCCCTS, 1981–2009. Contrary to what is observed in France, the results indicate that type II strains are not predominant in congenital toxoplasmosis in the United States: Type II serotypes were reported in 39% of cases, whereas NE-II serotypes were associated with 61% of cases. Furthermore, severe disease and eye severity at birth were more common in infants with NE-II serotypes than in those with type II serotypes.

The limitation of the study is the serotyping assay because this test is unable to determine which genotypes induce a NE-II serotype response. Are there many different and atypical genotypes such as in Brazil, or is there another new major lineage? The answer may come from recent studies conducted in animals. Of 169 isolates collected from wildlife in North America, type II and III strains accounted only for 30% and 10%, respectively, whereas another clonal lineage, named type X/A or haplogroup 12 (HG12) or the fourth lineage was identified in nearly 50% of the isolates [4]. This HG12 lineage has also been isolated in domestic animals and in 2 of the small sets of strains collected from patients in North America. Of note, HG12 appears to be endemic in North America because it has not been collected outside this area so far. Considering that toxoplasmosis is a zoonosis and that the same strains infect both animals and humans, it can be assumed that the HG12 strains are predominantly involved in the NE-II serotype response described in the study of McLeod et al [1]. The genetic makeup of this HG12 lineage suggests that it is the result of genetic recombination with a native North American isolate and an ancestral type II strain. One of the possible scenarios for North America would be that

type II strains were imported from Europe when household cats were introduced in North America by European colonists. The recombination of type II strains with a native strain in the wild would have given birth to the successful HG12 lineage in North America. Poor host adaptation of the European migrants to these new strains with a different genetic background may explain the higher pathogenicity of HG12 strains in humans.

All together, the data reported by McLeod et al [1] advocate for the overabundance of endemic *T. gondii* strains in the United States that are more pathogenic in congenital toxoplasmosis than the type II strains commonly found in Europe. The strain hypothesis needs therefore to be taken into consideration when trying to explain why the prevalence of clinical signs at birth in congenital toxoplasmosis is so different between France and the United States. With these new data available, the lack of national program or policy in the United States to address the burden of congenital toxoplasmosis becomes even more striking.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

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