ORIGINAL ARTICLE

Symptomatic toxoplasma infection due to congenital and postnatally acquired infection

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Aims: To determine the incidence and severity of symptomatic toxoplasma infection presenting during childhood due to congenital or postnatally acquired infection.
Methods: Between 2002 and 2004, newly diagnosed children (<16 years) with signs or symptoms of congenital or ocular toxoplasmosis were reported by clinicians to the British Paediatric and Ophthalmic Surveillance Units or by toxoplasma referral laboratories. Confirmed cases were estimated to have a greater than 50% probability of congenital and/or ocular toxoplasmosis, based on clinical and serological findings.
Results: Thirty eight children had confirmed toxoplasma infection. Twenty two (58%) were classified with congenital infection (cumulative incidence for England and Wales 3.4/100 000 live births; 95% CI 2.4 to 4.8), of whom 2 (9%) were stillborn, 7 (32%) live births had intracranial abnormalities and/or developmental delay (5 of whom had retinochoroiditis), and 10 (45%) had retinochoroiditis with no other abnormalities reported. A further 16 (42%) children were classified as infected after birth; all had retinochoroiditis.
Conclusions: The low burden of symptomatic congenital toxoplasmosis combined with the lack of evidence of an effective treatment support current policy not to offer prenatal or neonatal screening for toxoplasma infection. Primary prevention strategies need to address acquisition of infection in childhood which accounts for half the ocular disease due to toxoplasma infection in children in the UK and Ireland.

Toxoplasmosis is caused by a ubiquitous protozoan parasite that is ingested in undercooked meat or in contaminated soil or water.[1] When the mother first acquires toxoplasma infection during pregnancy, the parasite can infect the fetus, causing death or serious neurological impairment in up to 5% of infected children.[2–4] Inflammation and scarring of the retina and choroid (retinochoroiditis) is the most frequent permanent manifestation of congenital toxoplasma infection and can develop at any age.[2] By 12 years old, 35% of congenitally infected children have retinochoroiditis, though many lesions will be asymptomatic and only detectable by ophthalmoscopy.[5]

Information on the burden of symptomatic congenital toxoplasma infection is needed to evaluate the potential benefits of screening.[6] Prenatal screening has been a mandatory part of antenatal care in France for over a decade, and is routinely offered in Italy, Belgium, Spain, and Austria.[7 8] Elsewhere (Denmark, Massachusetts, and parts of Brazil) neonatal screening is offered.[9–11] In the UK, the policy is not to offer screening, pending better evidence on the frequency and severity of disease as well as on the effectiveness of treatment.[6] In response, we conducted a national surveillance study of symptomatic toxoplasma infection in children presenting to clinicians. We asked clinicians to report children with suspected congenital toxoplasmosis and any children with ocular sequelae, regardless of whether they thought it was due to toxoplasma infection before or after birth. The results therefore provide information on the incidence and severity of neurological and ocular sequelae due to congenital and postnatally acquired toxoplasmosis in children.

METHODS

Reporting and data collection

We asked paediatricians, ophthalmologists, and toxoplasma referral laboratories to report any child (<16 years) or stillbirth with suspected toxoplasma infection for a 24 month period from July 2002. Active monthly reporting, in which clinicians state whether they have seen a case or not, was coordinated by the British Paediatric and the British Ophthalmic Surveillance Units, or directly with the referral laboratories.[12 13] The reporting definition for paediatricians included any stillborn child with suspected congenital toxoplasma infection, any child with unexplained retinitis, hydrocephalus, intracranial calcification, microcephaly, or microphthalmia, infants with unexplained hepatosplenomegaly and lymphadenopathy, or any child under 2 years with toxoplasma specific IgM, IgA, or IgG antibodies (after this age antibody responses are more likely to reflect acquired infection). Ophthalmologists were asked to report any retinitis or other ocular findings consistent with toxoplasmosis. Referral laboratories were asked to report any clinical samples from children or stillbirths meeting the above criteria. The number of therapeutic abortions for toxoplasmosis in England and Wales during the study period was requested from the Department of Health.

Notifying clinicians were asked to provide clinical data and laboratory results using a standard questionnaire. As referral laboratories had limited clinical data, we contacted the referring paediatrician or ophthalmologist for further information.

This study was approved by the London Multi-Centre Research Ethics Committee in July 2002.

Case definition

We classified all children reported during the two year study period according to whether or not they had probable (>50% probability) or definite congenital toxoplasmosis and/or toxoplasmic retinochoroiditis. We used the classification developed by Lebech and colleagues[14] with modifications (see appendix; available on the *ADC* website: http://www.archdischild.com/supplemental), which incorporates clinical and serologic findings, including prenatal test results where available. Immune compromised children were excluded. Classifications were performed independently by two assessors (RG and MS) and discrepancies were resolved by discussion.

Incidence estimation

The cumulative incidence of symptomatic toxoplasma infection was based on children born in England and Wales between 1987 to 2004 who were classified as probable or definite congenital or ocular toxoplasmosis and therapeutic abortions for toxoplasmosis. The rest of the British Isles was excluded due to non-response from the Toxoplasma Reference Laboratories in Scotland and Ireland (Eire), and few reports from ophthalmologists in Northern Ireland or Eire. We assumed that the incidence of congenital toxoplasma infection was constant for the entire 15 year birth cohort and calculated a weighted sum of the mean incidence for each year of age. Ninety five per cent confidence intervals were estimated using the Poisson distribution.

RESULTS

Case ascertainment

A total of 181 suspected cases were notified during the 24 month study period. Questionnaires requesting further information were returned for 122 notifications relating to 105 children (29/181 were notification errors and 30/181 were not returned). Sixty four of 105 children first presented during the study period, but two were excluded due to immune compromise. Of the 62 cases that met the reporting definition, 38 were classified as probable or definite congenital toxoplasma infection or toxoplasmic retinochoroiditis, or both. The remaining 24 cases were classified as possible or unlikely toxoplasma infection as none had clinical or serological evidence of congenital infection in the fetus or child: 10 live births and 7 miscarriages or still births had evidence of maternal infection during or before the first half of pregnancy and no other abnormalities; 2 children with intracranial lesions were toxoplasma IgG negative; 1 child born at 32 weeks with an intracranial cyst and hydrocephaly had negative toxoplasma IgA and IgM but positive IgG at 7 months; and 4 children had retinochoroiditis due to other causes.

Ophthalmologists reported more cases (n = 23, 19 by ophthalmologists alone) than paediatricians (n = 8, 4 by paediatricians alone). The Toxoplasma Reference Laboratory in Swansea reported all cases identified by laboratories (n = 13, 8 by laboratories alone). At the time of presentation, most cases were resident in England and Wales, 2 were in Scotland, 2 in Ireland, and none were resident in Northern Ireland.

Clinical findings

Most children presented with ophthalmic signs (31/38) and of these, half (16/31) were classified as postnatally acquired toxoplasmosis. Overall, 22/38 (58%) were classified with congenital infection, including 7 children with no ophthalmologic signs, all of whom presented in infancy, and 3 children with retinochoroiditis who presented after 4 years old. All children with postnatal infection presented with retinochoroiditis after the age of 4 years; 14/16 (88%) first presented at 10 or more years.

Table 1 summarises the clinical characteristics. Nine (41%) children with congenital toxoplasmosis either died in utero or had abnormal neurological findings (table 1). Two children (both congenitally infected) had bilateral visual impairment of <6/12 or worse. Half (7/14) the children with congenital infection diagnosed in infancy were given anti-toxoplasma treatment.

Table 1 Clinical characteristics of cases reported in the UK and Ireland in 2002 to 2004

	Timing of infection	
	Congenital (n = 22)	Postnatal (n = 16)
Neurological sequelae, bilateral visual impairment in live born children, or fetal death	9	0
Fetal death	2*	0
Neurological abnormality	2†	0
Neurological abnormality and retinochoroiditis	5‡¶	
Retinochoroiditis alone	10¶	16
Any clinical signs	19§	16
Specific IgG antibodies detected	13/15**	11/11††
Anti-toxoplasma treatment		
Prenatal	1	0
Postnatal	8	6
Ethnic group	12 White	7 White
	2 Asian	3 Asian
	1 Other	2 Black
	7 unknown	4 unknown

*One child had hydrocephalus.
†One child had microcephaly, the other intracranial calcification but no abnormal neurological findings.
‡Three children had developmental delay but no intracranial lesions reported (one developed retinochoroiditis for the first time at 11 years). One child had intracranial calcification, hydrocephalus, and developmental delay, and one had intracranial calcification with no developmental outcomes reported.
¶Two children had bilateral visual impairment <6/12 Snellen.
§Three children reported by the laboratory had no further clinical details.
**13/15 tested positive for IgM or IgA in infancy or IgG after 12 months; 2/15 positive for IgG during infancy had no further information.
††All 11 tested IgG positive.

Table 2 Cumulative incidence of symptomatic toxoplasma infection during childhood per 100 000 live births: present study and published estimates (95% CI)

Outcome	Present study*	Predicted from other studies
Congenital toxoplasma infection		
Any (n = 21)	3.43 (2.38, 4.78)	2†‡ 2¶
Neurological impairment (n = 5)	0.82 (0.36, 1.60)	0.4†§
Ocular disease (n = 13)	2.11 (1.31, 3.23)	3†**
Postnatally acquired ocular toxoplasmosis (n = 11)	1.62 (0.93, 2.62)	Not available
Any ocular disease (congenital or postnatally acquired, n = 24)	3.73 (2.63, 5.14)	2.9††

*Figures differ from table 1 as numerator is children (<16 yeas) *born* in England and Wales and first presenting during study period. Includes two therapeutic abortions for toxoplasmosis.
†Assumes birth prevalence of congenital toxoplasma infection = 1/10 000 (0.7/10 000 live births in Massachusetts,[26] 0.8/10 000 Sweden,[27] based on neonatal screening studies that were assumed to detect 70% of congenitally infected infants).[10 27]
‡Assumes risk of neurological or ocular symptoms by 5 years = 20%.[2 3 5]
¶Based on national surveillance study in 1989: 14 cases (not all severe) identified in one year in England and Wales.[28]
§Four per cent of live born children with congenital toxoplasmosis had serious neurological impairment or died in early life (unpublished data from EMSCOT cohort, Freeman and Gilbert).
**Assumes risk of ocular lesions by 12 years of age is 30% in children identified by prenatal screening. Only a proportion of lesions are likely to be symptomatic.[5 24 25]
††From surveillance study of ophthalmologists in a population of 7 million. Figure gives cumulative incidence by 15 years for British born children. Lifetime incidence was 18/100 000 (10.8, 25.2).[29]

The cumulative incidence rates for congenital and postnatally acquired ocular toxoplasmosis are given in table 2. Incidence estimates include two terminations reported for the year 2000 as we were not granted access to abortion figures for subsequent years. The weighted average denominator population was 646 739.

DISCUSSION

The burden of disease due to symptomatic congenital toxoplasma infection was low. Most children presented with ocular manifestations and less than half had serious neurological manifestations or died in utero. Half of the ocular toxoplasmosis seen in children was estimated to be due to infection acquired after birth.

Our study is likely to have missed some children who were not reported by clinicians or whose condition was never diagnosed as due to congenital or postnatally acquired toxoplasmosis. In particular, we underestimated the overall burden of disease due to postnatal infection as we confined reporting to ocular disease. Postnatal infections resulting in fever and lymphadenopathy were not included as clinicians rarely test for toxoplasma antibodies in such cases. We could not quantify the degree of under-ascertainment using capture-recapture analysis as laboratories, paediatricians, and ophthalmologists were not equally likely to see the same children.[15] However, our results are consistent with rates for symptomatic congenital and postnatal acquired disease extrapolated from previous surveillance studies (table 2).

Our findings have important implications for screening programmes for congenital toxoplasmosis. The low burden of disease resulting in visual or neurological impairment, combined with the high cost (estimated at more than £50 million per year for the UK) and the lack of evidence for a clinically important effect of treatment on mother to child transmission or clinical manifestations during infancy, make prenatal screening hard to justify in any setting.[4 6 7] Neonatal screening is likely to yield fewer benefits, as few symptomatic children presented with retinochoroiditis occurring for the first time after birth, and hence few would stand to benefit from postnatal treatment. As there is no evidence for a protective effect of postnatal treatment on subsequent ocular disease it is not surprising that less than half of those with retinochoroiditis were treated (6/16 in the postnatal acquired, and 6/15 in the congenital group).[16 17] Most of the infants presenting with serious neurological signs or intracranial calcification during infancy were treated (4/6).

Potential harms of screening and treatment include the burdensome administration of toxoplasma antimicrobial therapy during pregnancy and throughout infancy, neutropenia which leads to treatment being stopped temporarily in 5–30% of children and 2% of pregnant women,[7 9] fetal loss due to prenatal diagnosis, and unnecessary treatment or termination of pregnancy due to false positive results.[18 19 23] There is also evidence that the diagnosis of congenital toxoplasma infection itself generates significant anxiety: at 3–4 years after birth, parents of infected children were twice as likely to have significant levels of anxiety about their child's current and future health than parents of uninfected children born to mothers infected with *T gondii* during pregnancy.[3] In summary, screening is likely to do more harm than good to the health of children.

What is already known on this topic

- In the late 1980s, the incidence of symptomatic congenital toxoplasma infection was estimated to be 2/100 000 live births
- Toxoplasmic retinochoroiditis is the most common manifestation of congenital toxoplasma infection but can also be caused by postnatally acquired infection

What this study adds

- The burden of symptomatic congenital toxoplasma infection remained low (3.4/100 000 live births) and less than half of them had serious sequelae
- Over half of the toxoplasmic retinochoroiditis in children was estimated to be due to postnatally acquired infection. Public health attention should be focused on primary prevention of infection in childhood

Our results highlight the need for preventive strategies to shift from the present focus on screening to primary prevention of infection acquired during childhood. Over 40% of disease seen in our study was due to postnatally acquired disease. However, the true burden due to infection acquired in childhood may take years to manifest as ocular disease in adulthood or disseminated disease in immune compromised individuals. The annual incidence of infection in children in the UK is estimated to be more than twice the rate in adulthood, yet information is lacking on how and when children acquire infection.[20] We know that eating undercooked meat is the major risk factor for infection in European pregnant women and that risk reduction measures involve a range of interventions from farm to fork.[1] In children, other factors, such as soil and water contamination, may be more important, and may require different approaches to prevention.[21 22]

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