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Long-term ocular outcome in congenital toxoplasmosis: A prospective cohort of treated children

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Summary *Objectives:* Congenital toxoplasmosis remains a public health problem throughout the world. Long-term longitudinal studies are still needed to argument controversial screening and treatment strategies and to enable to accurately counsel parents.
Methods: We conducted a prospective cohort study over 16 years in Marseilles, France. Seronegative pregnant women underwent monthly serological testing. Children were treated antenatally with rovamycine as soon as maternal infection was detected and with pyrimethamine and sulfadoxine in case of positive *Toxoplasma* PCR on amniotic fluid. Postnatal treatment with pyrimethamine and sulfadoxine was systematically prescribed for one year and possibly continued at the physician discretion.
Results: 127 children were included. 24 children (18.9%) presented ocular lesions causing visual impairment in eight cases. Eleven children (8.7%) presented with ocular lesions at birth, mostly macular. Sixteen children (12.6%) developed ocular lesions during follow-up, mostly peripheral. The first ocular lesion could occur as late as 12 years after birth. No significant risk factor of chorioretinitis was identified including gestational age at infection, type of antenatal treatment and shorter postnatal treatment.
Conclusions: These results confirm the overall good prognosis of congenital toxoplasmosis in Europe but highlight though a low risk of late ocular manifestation. Chorioretinitis affected 18.9% of children suffering from congenital toxoplasmosis despite antenatal and neonatal

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screening associated with early treatment. Long-standing follow-up is needed because first lesion can occur as late as 12 years after birth. Late lesions were less often macular but nevertheless caused sometimes visual impairment.

Introduction

Congenital toxoplasmosis remains a public health problem throughout the world.[1] In sole France around 300 cases are notified each year to the National Reference Centre (https://www.chu-reims.fr/professionnels/cnr-toxoplasmose-1/rapports-dactivite/). Knowing about the prevalence and severity of late manifestations is a prerequisite to deliver appropriate information and counselling to anxious parents. In previous reports, 7%—33% of overall European patients and 27—92% of American patients developed ocular lesions.[2—12] Chorioretinitis could even occur after the age of 10 years.[7—9] Reported risk factors of chorioretinitis included early gestational age at infection,[1,7,13] delayed or absent antenatal treatment,[14—16] and presence of extra-ocular toxoplasmosis lesions,[2,13] but their actual significance remained debated.[2,17] Quality of life and visual acuity appeared preserved in a recent French report[18] but prognosis appeared more severe in American cohorts.[5,6,11,19,20] Because reported long-term outcome varied, optimal strategies for screening, treatment and follow-up remain debated.[1,2,17,19,21,22] Multicentre studies were indeed often difficult to interpret because of too short follow-up and variations between centres due to population heterogeneity and management specificities.[3,4,17] As to the few available monocentre studies,[7,9,13] they might be impacted by specific management or population characteristics, or by changes of diagnostic procedures and treatment regimen during the study period. There is therefore a need for additional long-standing monocentre cohort studies. We prospectively studied a cohort of patients suffering from congenital toxoplasmosis in Southern France who benefited from homogenous diagnostic and treatment procedures.

Patients and methods

Study population

This prospective study was conducted from January 1995 through December 2010 in the academic hospital of Marseille, France. Inclusion period ended in December 2008 to obtain a two-year follow-up. The academic hospital of Marseille is the reference centre for diagnosis and treatment of congenital toxoplasmosis in an area inhabited by more than 3.000.000 people where 2009 incidence of congenital toxoplasmosis was 2.5 cases per 10.000 live births according to French national reference centre. Congenital toxoplasmosis was diagnosed if *Toxoplasma* PCR was positive on amniotic fluid, if synthesis of specific anti-*Toxoplasma* antibodies (IgA, IgM, and/or IgG) was proven at birth or during the first year of life, and/or if specific antibodies were still present after the age of 12 months.

Laboratory procedure and follow-up

As mandatory in France, all pregnant women in the region underwent an initial *Toxoplasma* serology. Seronegative pregnant women were tested every month using IgM ELISA, confirmed by IgM immunosorbent agglutination assay (ISAGA) if positive, and IgG ELISA. Maternal seroconversion was defined either by the appearance of specific IgG anti-toxoplasmic antibodies in a previously seronegative pregnant woman or by a significant rise in IgG anti-toxoplasmic antibodies in the presence of specific IgM antibodies more than two months after conception. Amniocentesis was performed at least one month after seroconversion and always later than the 18th weeks of pregnancy. If *Toxoplasma* infection was detected in the last three months of pregnancy, amniocentesis could be performed immediately. The 10 mL obtained were analysed using both mouse inoculation and *Toxoplasma* PCR.

At birth, cord blood was used to perform IgG ELISA, IgM and IgA ISAGA, and comparison of mother and child IgG and IgM serologic profiles by Western Blot (each additional band found by Western Blot in cord blood but not in the maternal serum represented the synthesis of specific antibody by the neonate). All children also underwent physical examination, transfontanellar ultrasound, and fundus examination. Positive neonatal results were always controlled in the first three weeks of life. Children with negative prenatal and neonatal diagnosis benefited from another serologic, clinical and ophthalmological examination a month after and then every three months until *Toxoplasma* serology became negative. Congenital toxoplasmosis was diagnosed during follow-up if synthesis of specific antibodies was demonstrated in a child by a rise in specific IgG titre using ELISA and/or by the apparition of specific IgM and/or IgA antibodies using ISAGA, confirmed by the apparition of new specific antibodies using IgG Western Blot (each additional band found by Western Blot in a child's follow-up serum but not in a previous sample represented the synthesis of specific antibody by the child). Positive results were always controlled on a second blood sample Children with congenital toxoplasmosis underwent clinical and ophthalmological examination every three months for two years, then every six months for one year, and then yearly. Chorioretinitis was clinically defined by the apparition of typical lesions on a fundus examination performed by an expert ophthalmologist.

Treatment

For infections later than 30 weeks of gestational age, pyrimethamine (1 g) and sulfadoxine (50 mg) were immediately given every 10 days associated with folinic acid (50 mg). For earlier infections, mothers were treated with spiramycin (9 millions SI units per day) as soon as seroconversion was confirmed or isolated IgM anti-*Toxoplasma*

antibodies were detected. If PCR on amniotic fluid was positive, spiramycin treatment was stopped and pyrimethamine and sulfadoxine were administered. Otherwise, spiramycin was pursued until delivery. After birth, infected children were treated with pyrimethamine (1.25 mg/kg) and sulfadoxine (25 mg/kg) every week, associated with folinic acid (50 mg every week). Treatment was planned for one year, and might be pursued at the physician discretion.

Statistics

Statistical analyzes were performed using the software R© 2.10.1 (The R foundation for Statistical Computing), using Chi-square and Fisher exact tests. $P < 0.05$ was considered to be statistically significant.

Results

127 children were included. Twelve additional cases of foetal infection following maternal seroconversion were demonstrated by Toxoplasma PCR on amniotic fluid and/or on foetal samples. These 12 foetal infections led to five terminations of pregnancy because of major neurologic involvement and seven spontaneous foetal deaths. Maternal characteristics are presented in Table 1. All untreated mothers were infected in the last month of their pregnancy. Maximum follow-up was 12 years (median: 4 years). Congenital toxoplasmosis was always diagnosed before the age of nine months: *in utero* in 30% of children, in the first three weeks of life in 66 additional children (52%), before the age of two months in 9 additional children (7%), and later for 11% of children (Table 2). All antenatal diagnoses were confirmed by postnatal analyses. All children without antenatal diagnosis presented later with evidences of a synthesis of specific anti-Toxoplasma antibodies (IgA, IgM, and/or IgG) by two distinct techniques or more.

121 children (95.3%) were treated for 1 year or more, including 19 (15%) who were treated for two years or more. Mean duration of treatment was 16 months (median: 12 months). Five children presented with side effects of pyrimethamine and sulfadoxine: neutropenia in 2 cases (1 month interruption), anaemia in one case (1 month interruption), vomiting in one case (1 month interruption), and diffuse rash in one case (treatment not reintroduced). Parents decided to interrupt treatment in five additional cases.

Overall, 24 children (18.9%) developed toxoplasmic chorioretinitis. Specific characteristics of these children are presented in Table 3. First ocular lesion was detected before the age of two years in 75% (18/24) of affected children and before the age of five years in 92% (22/24) of affected children (Fig. 1). The association of ocular lesions with possible risk factors is presented in Table 4. No statistically significant association was found. Lesions detected at birth were associated with a higher risk of macular involvement (8/11 lesions) than lesions detected during follow-up (5/20 lesions) (Odd Ratio: 7.4 [1.2—61.6], $p = 0.02$). Toxoplasmic chorioretinitis was responsible for bilateral visual impairment in one case and unilateral visual impairment in seven other cases. Visual impairment could occur late: it affected one child who developed his first ocular lesion at the age of 12. In this case, congenital toxoplasmosis was diagnosed at birth because synthesis of IgM, IgA, and IgG was demonstrated in cord blood and in

Table 1 Characteristics of mothers of children suffering from congenital toxoplasmosis.

Median age at delivery (range)	28 years (16—40)
Gestational age at infection	
<15 weeks	9%
15—28 weeks	37%
>28 weeks	51%
Date unknown	3%
Maternal treatment	
No treatment	20%
Spiramycin only	41%
Spiramycin then pyrimethamine and sulfadoxine	35%
Pyrimethamine and sulfadoxine only	4%
Median delay of initiation after infection (range)	3 weeks 2—18

Table 2 Number of the 127 children found positive by each diagnostic technique.

Antenatal diagnosis (38 children)	
Toxoplasma PCR on amniotic fluid	38 (30%)
Diagnosis during the first three weeks of life (104 children)[a]	
Specific IgM and/or IgA (ISAGA)	94 (74%)
Specific IgM (ISAGA)	72 (57%)
Specific IgA (ISAGA)	83 (65%)
Specific IgG and/or IgM synthesis according to Western Blot	89 (70%)
Specific IgG synthesis	48 (38%)
Specific IgM synthesis	82 (65%)
Specific antibodies synthesis found by ISAGA and/or Western Blot	104 (82%)
Diagnosis between three weeks and two months of life (9 children)	
Specific IgM and/or IgA (ISAGA)	7 (6%)
Specific IgM (ISAGA)	7 (6%)
Specific IgA (ISAGA)	5 (4%)
Specific IgG synthesis demonstrated by successive Western Blot	9 (7%)
Diagnosis after the age of two months (14 children)	
Specific IgG synthesis demonstrated by successive Western Blot	14 (11%)
Rise in specific IgG titre[b] (ELISA)	14 (11%)
Persistence of specific IgG antibodies after one year	14 (11%)

ISAGA: Immunosorbent agglutination assay; ELISA: Enzyme-linked immunosorbent assay.
[a] Including patients with antenatal diagnosis.
[b] Rise was considered significant if IgG titre at least doubled on two successive samples.

Table 3 Occurrence of ocular lesions in children suffering from congenital toxoplasmosis according to possible risk factors.

Gender	
Male	12/63 (19%)
Female	12/64 (19%)
Neurological toxoplasmosis lesions	
Presence	4/11 (36%)
Absence	20/116 (17%)
Maternal seroconversion	
<15 weeks	3/11 (27%)
15–28 weeks	9/47 (19%)
>28 weeks	12/65 (18%)
Maternal treatment	
No treatment	4/25 (16%)
Spiramycin only	11/52 (20%)
Spiramycin then pyrimethamine /sulfadoxine	9/45 (20%)
Pyrimethamine/sulfadoxine	0/5 (0%)
Spiramycin started less than 4 weeks after infection	11/51 (22%)
Spiramycin started more than 4 weeks after infection	9/46 (20%)
Duration of postnatal treatment (excluding children with lesions at birth)	
Interrupted before 12 months	1/5 (20%)
12 months	4/51 (8%)
Continued after 12 months	8/60 (13%)

control serum using ISAGA and Western Blot, and IgG were still detected at the age of one year.

Six children (25%) presented more than one occurrence of chorioretinitis, including one who relapsed twice. The initially spared eye was affected in two cases. Three of these six children presented no ocular lesion at birth. The maximum delay between first and second chorioretinitis occurrence was 8 years.

Eleven children (8.7%) exhibited neurologic manifestations: isolated cerebral calcifications in seven cases, white substance modifications on MRI in one case, ventricular dilation in two cases, bilateral temporal microabscesses in one case, and language development disorder in two cases. Four of these 11 children also exhibited ocular lesions.

Discussion

This longitudinal observational study benefits from several strengths. First, diagnostic and treatment procedures enabled to obtain an homogeneous cohort: postnatal treatment recommendations did not change over the study period, and the same diagnostic procedures were used contrary to previous works where the successive use of mouse inoculation (associated with a 3–6 weeks diagnosis delay) and *Toxoplasma* PCR induced differences in the timing and frequency of use of antenatal treatment.[7,9] A long-standing follow-up could be obtained: half of the children were followed for more than 4 years, with a maximum of 12 years. Last, no significant recruitment bias can be feared since all French pregnant women benefit from a mandatory

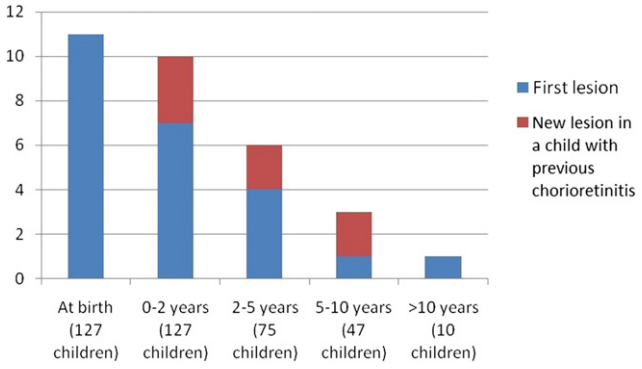

Figure 1 Time of occurrence of the 31 ocular lesions observed in children born with congenital toxoplasmosis.

antenatal and neonatal screening program. In an area inhabited by over 3.000.000 people, all *Toxoplasma* PCR on amniotic fluid and children serology at birth are performed in our laboratory which belongs to the national reference centre. It can therefore be assumed that almost all regional cases of congenital toxoplasmosis were included in the study.

Our first finding of interest is that the ocular lesion can occur for the first time after the age of ten years in children suffering from congenital toxoplasmosis. The causal relation with congenital toxoplasmosis was highly probable in this case where congenital toxoplasmosis was demonstrated at birth following a late maternal infection. Indeed, such late occurrence was previously reported in France[7,9] and North America.[5,6,8] Moreover, the lifetime risk of chorioretinitis related to postnatal infection may be as low as 3/10.000 persons in Europe.[23] This risk is even lower at young age.[24] On the other hand, in patients with evocative lesions and no prior follow-up, or in areas where several *Toxoplasma* genotypes circulate, the risk of late chorioretinitis due to congenital toxoplasmosis should not bring physicians to overdiagnose congenital toxoplasmosis by disregarding the importance of postnatal infection.[23,24]

Despite this risk of delayed manifestations, long-term outcome was most often good: 81% of children did not develop chorioretinitis and only 6% suffered from visual impairment. Previous European cohorts provided similar results: 7–33% of children presented with ocular lesion, lower numbers being associated with shorter follow-ups.[3,4,7,9,25] Congenital toxoplasmosis most often involved peripheral retinal area in previous works as in our study[9,11] and therefore had little impact on quality of life and visual performance.[18] We showed additionally for the first time that late lesions were more likely to be peripheral and therefore not associated with impairment of visual acuity, in line with the good long-term functional prognosis.[18] However, severe lesions associated with visual impairment can occasionally occur late as illustrated by our findings. We believe therefore that children suffering from congenital toxoplasmosis should be monitored as long as possible, and not only for the first years as sometimes suggested.[22]

Beside chorioretinitis, congenital toxoplasmosis was sometimes associated with other ocular abnormalities including microphthalmia, cataracts and strabism.[26] Only three children presented with such manifestations in our

Table 4 Characteristics of ocular lesions in children suffering from congenital toxoplasmosis.

Location	
Bilateral involvement	4/24 (16%)
Macular involvement[a]	
Children with ocular involvement at birth	8/11 (73%)
Children with ocular involvement during follow-up	4/16 (25%)
Occurrence of several successive eye lesions	
All patients	6/24 (25%)
Retinochoroiditis detected at birth	3/11 (27%)
No lesion at birth	3/13 (23%)
Visual impairment	
Retinochoroiditis detected at birth	5/11 (45%)
No lesion at birth	3/13 (23%)
Additional ocular abnormalities (strabism)	
Children with retinochoroiditis	2/24 (8%)
Children free from retinochoroiditis	1/103 (1%)

[a] Total of 27 children because three children presented ocular lesion at birth and a new eye lesion during follow-up.

cohort. Central nervous system manifestations were even fewer: only two children developed language development disorders. This favourable outcome of children born alive with congenital toxoplasmosis is essential information to provide appropriate counselling to anxious parents. However, initial counselling during pregnancy should avoid excessive optimism taking into account the risk of spontaneous foetal deaths and of pregnancy termination because of major neurologic involvement.

No reliable predictor of ocular toxoplasmosis was identified. The higher risk previously associated with gender,[13,16] early gestational age at infection[13] and central nervous system involvement[2,13,16] was not confirmed. Gestational age at infection was already unrelated to ocular toxoplasmosis in previous European cohorts.[4] As previous studies,[2,14,27] our results showed similar outcomes whatever the type and delay of antenatal treatment. However, early antenatal treatment was previously associated with lower risk of materno-foetal transmission[4] and with better neurologic status of severely affected children.[3,15,28] These discrepancies might be related to the association between gestational age at infection and absence of treatment: women infected late in pregnancy remained often untreated because diagnosis was made too late to initiate treatment before delivery. This association between late infections, associated with a higher risk of foetal transmission,[1] and absence of treatment also explains the high proportion of untreated mothers in our cohort. This bias was suspected to mask the impact of antenatal treatment by confounding the higher risk of toxoplasmosis lesions in children infected early during pregnancy and the lower risk possibly associated with antenatal treatment.[1,21] Consequently results such as ours could illustrate that antenatal treatment of early infections enabled to obtain as good outcomes as those associated with late infections. The ongoing TOXOGEST (NCT01189448) trial will determine whether antenatal treatment with pyrimethamine and sulfadiazine is associated with better outcome than spiramycin.

Oppositely, the effectiveness of postnatal treatment by sulfadiazine (or sulfadoxine) and pyrimethamine is commonly acknowledged because of the better outcomes observed in cohorts of treated children.[1,5–7,17,20] While higher doses of pyrimethamine were not associated with better outcomes,[20] the optimal duration of postnatal treatment remains debated.[2] Our results showed similar outcomes whatever the treatment duration. These outcomes were similar to previous European reports using various treatment regimens.[3,4,7,9,25] Notably, 26% of children treated for 24 months developed chorioretinitis in a previous cohort.[7] Even shorter postnatal treatments (3 months) are currently evaluated by the TOSCANE (NCT01202500) clinical trial.

Weekly administration of pyrimethamine and sulfadoxine was well accepted and tolerated: 91% of children were treated for 1 year as planned, and treatment was permanently discontinued because of side effects in only one case. Previous studies reported a higher frequency of haematologic side effects responsible for discontinuation of treatment in case of pyrimethamine and sulfadiazine treatment,[29] especially in the lack of concomitant folinic acid administration. Our results using pyrimethamine and sulfadoxine are reassuring as haematologic side effects were rare and did not relapse when treatments were reintroduced. Similarly, no discontinuation of treatment was reported in a cohort of 107 children with congenital toxoplasmosis who were treated for 24 months with pyrimethamine, sulfadoxine, and folinic acid.[7]

It was previously considered that results such as ours did not support congenital toxoplasmosis screening programs in North America.[22] European cohorts indeed showed that significant functional impairment was rare. However, European results should not be used to determine adequate strategies elsewhere. First, in France, termination of pregnancy is often performed in case of demonstrated foetal neurologic involvement. This tends to underestimate the proportion of symptomatic children. Second, European *Toxoplasma gondii* type II strains might be less virulent than American or African strains.[1,11,19,30,31] Third, European reports over the last decades mostly involved children who benefited from antenatal and/or postnatal treatment. These factors can explain the discrepancy with American cohorts which showed that up to 92% of untreated children developed ocular lesions.[5,8,11,12,19] Overall, the reassuring European cohort results may be used to determine the prognosis of children suffering from congenital toxoplasmosis in France and in European countries with similar policies. Elsewhere, decision-making should only be based on rigorous local studies.

Acknowledgements/Conflict of interest

The authors declare no conflict of interest.

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