Long-Term Ocular Prognosis in 327 Children With Congenital Toxoplasmosis

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ABSTRACT. *Objective.* **Retinochoroiditis is the most frequent consequence of congenital toxoplasmosis. Early diagnosis and treatment are believed to reduce the risk of visual impairment. We report on the clinical evolution of ocular lesions and final visual function in a prospective cohort of congenitally infected children who were identified during monthly maternal prenatal screening.**

Methods. **The study included 327 congenitally infected children who were monitored for up to 14 years at the Croix Rousse Hospital in Lyon, France. Data on date of maternal infection; time and type of therapy; antenatal, neonatal, and postnatal work-ups; and ocular status were analyzed.**

Results. **All mothers but 52 had been treated. Pyrimethamine and sulfadiazine was given in utero to 38% of children and after birth to 72% of newborns. Fansidar was given for an average duration of 337 days in all but 2 children. After a median follow-up of 6 years, 79 (24%) children had at least 1 retinochoroidal lesion. In 23 (29%) of them, at least 1 new event had been diagnosed up to 10 years after detection of the first lesions: reactivation of an existing lesion (1 case), new lesion in a previously healthy location (19 cases), or both (3 cases). Fifty-five children had lesions in 1 eye; of the 45 children for whom final visual acuity data were available, 31 (69%) had normal vision. Twenty-four children had lesions in both eyes; of the 21 for whom final visual acuity data were available, 11 had normal vision in both eyes. None had bilateral visual impairment.**

Conclusions. **Clinicians, parents, and elder children with congenital infection should be informed that late-onset retinal lesions and relapse can occur many years after birth but that the overall ocular prognosis of congenital toxoplasmosis is satisfactory when infection is identified early and treated accordingly.** *Pediatrics* **2004; 113:1567–1572;** ***Toxoplasma gondii, congenital, ocular, eye, cohort, prenatal screening, prevention.***

ABBREVIATION. Ig, immunoglobulin.

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Received for publication Oct 13, 2003; accepted Feb 2, 2004.

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Congenital toxoplasmosis results from the transplacental transmission of the protozoan *Toxoplasma gondii*. Most infected newborns have no clinical signs but are at risk of developing visual impairment as a result of retinochoroiditis in childhood or adolescence.[1,2] Ocular lesions have been reported in as many as 80% of untreated, congenitally infected children.[3–6] The most effective approach to prevent ocular lesions caused by congenital toxoplasmosis remains controversial. Additional data are necessary to determine to what extent the available preventive options (prevention of maternal infection, early treatment of infection in pregnant women, preventive treatment of infected infants, or treatment of existing lesions) are effective in reducing the risk of severe visual impairment. Because new lesions or recurrence of existing lesions may appear late after birth, long-term follow-up studies are necessary to estimate the definite ocular prognosis.[7]

The longest follow-up of children identified through detection of maternal infection in pregnancy is reported by Couvreur at al.[8] Of 172 children, 41 (24%) had at least 1 retinal lesion after a follow-up of 2 to 11 years despite a 12-month postnatal treatment with pyrimethamine and sulfadiazine. However, no data were available on visual acuity, and no clear distinction was made between detection of new lesions and reactivation of existing lesions. We report on the clinical evolution of ocular lesions and the final visual function in a prospective cohort of 327 congenitally infected children who were identified through monthly prenatal screening, received a diagnosis and were treated early according to a standard protocol, and were monitored for 6 months up to 14 years.

METHODS

Patients

Between 1988 and 2001, a total of 1506 consecutive pregnant women were monitored at the Croix-Rousse Hospital in Lyon, France, for an acute *Toxoplasma* infection detected during pregnancy through the French prenatal screening program. Fifty-three pregnancies ended with spontaneous abortion ($n = 22$), stillbirth ($n = 4$), or termination as a result of suspected or proven fetal infection ($n = 27$). The remaining 1453 pregnant women gave birth to 1466 live-born infants (26 twins), 1384 (94%) of whom could be followed up until infection was ruled out (1026 of 1384 [74%]) or confirmed (358 of 1384 [26%]). Among the 358 infected children, 31 were excluded because they had been followed up for <6 months at the study endpoint (March 31, 2002). The long-term study thus included 327 children.

Definition and Monitoring of Maternal Infection

As previously described,[9] maternal infection was defined as the appearance of specific immunoglobulin (Ig) G in previously seronegative women or as a significant rise in IgG in women with specific IgM. Standard maternal treatment was spiramycin (3 g/day) until delivery. When infection occurred after the 32nd week of pregnancy or when antenatal diagnosis was positive, 3-week courses of sulfadiazine (3 g/day) and pyrimethamine (50 mg/day) were alternated with 3-week courses of spiramycin.

Definition and Monitoring of Congenital Infection

Fetal infection was diagnosed using mice inoculation of cord blood and amniotic fluid as standard tests until 1994 and using polymerase chain reaction and inoculation of amniotic fluid thereafter. Our standard protocol at birth included funduscopic examination; skull radiograph; head ultrasonography; and systematic serologic testing for IgM, IgA, and IgG in umbilical cord and neonatal blood. As previously described,[9] clinical, neurologic, and ophthalmologic examinations were performed and a blood sample was taken for serologic testing to detect anti–*Toxoplasma*-specific IgG using indirect immunofluorescence and anti–*Toxoplasma*-specific IgM using immunosorbent agglutination assay every 3 months for the first 2 years of life, every 6 months during the third year, and annually thereafter, with no age limit.

Children were considered to be infected when they had persistent IgG (indirect immunofluorescence) after the first year of life or an increase in IgG during the first year of life or at least 2 criteria among the following: 1) positive mice inoculation of amniotic fluid or fetal blood, positive PCR on amniotic fluid, positive specific IgM and IgA in fetal blood; 2) positive IgM (index >2) after birth (immunosorbent agglutination assay; Biomérieux, Marcy l'Etoile, France), positive IgA (>0.70) after birth (enzyme-linked immunosorbent assay; SFRI, Bordeaux, France); and 3) patent signs of toxoplasmosis.

Neonates with confirmed or suspected congenital toxoplasmosis were given a 3-week course of pyrimethamine (3 mg/kg every 3 days), sulfadiazine (25 mg/kg every 8 hours), and folinic acid (50 mg every 7 days orally) and underwent weekly hematologic and renal monitoring. Spiramycin (100 mg/kg/day) was then administered until the child weighted 5 kg (at ~2 months of age), after which time a 12-month treatment course of the combination pyrimethamine (1.25 mg/kg every 10 days)/sulfadoxine (25 mg/kg every 10 days; Fansidar) and folinic acid (50 mg every 7 days) was administered with monthly hematologic surveillance. In the event of active retinal lesions being detected at the end of this period, treatment with Fansidar was resumed for 3 months.

All eye examinations were performed by experienced ophthalmologists, who recorded their findings on a standardized form. All forms were reviewed retrospectively by an external committee, and the following data were extracted: 1) date of examination; 2) visual acuity; 3) abnormalities relating to the anterior and posterior segments of both eyes after pupillary dilatation, using direct ophthalmoscopy and/or a 3-mirror-lens system for direct and wide-field lenses (90 diopter) for indirect visualization of the retina at the slit lamp, depending on the child's age and compliance and on the examiner's preference; and 4) date, size, location, activity, evolution, and treatment of each new event. Reactivation of an existing lesion or detection of a new lesion in a previously healthy retina was distinguished and both considered as secondary events. Under 3 years of age, visual acuity was assessed using Parinaud charts and was considered as normal when >2.[10] Snellen charts were used in elder children, and visual acuity was considered as normal when >20/25. These data were added to a computerized database that already contained the date of maternal infection (in weeks of gestation); the dates, types, and doses of treatment given during pregnancy and after birth; and the results of antenatal (fetal ultrasound, fetal blood, and amniotic fluid analyses) and neonatal work-ups (umbilical cord and peripheral blood analyses; neurologic, radiologic, and ophthalmologic examinations).

Statistical Analysis

Results were expressed as percentages for qualitative covariates and as means (±standard deviation and range) for quantitative variables when normally distributed but otherwise as median values and interquartile ranges. *T* test, Mann-Whitney or Kruskal-Wallis nonparametric tests, variance analysis, Pearson χ^2, or Fisher exact tests were used when appropriate.

The baseline date was either the date of birth, if congenital toxoplasmosis had been diagnosed before or at birth, or the date of diagnosis. Time to the first occurrence of retinochoroiditis after the diagnosis of congenital toxoplasmosis was taken to be the interval between baseline date and first detection of retinochoroiditis or time from baseline date to last ophthalmologic examination in children without retinochoroiditis. Hereafter, it was expressed as age.

The incidence density of the first occurrence of retinochoroiditis was calculated for each year after the baseline date and was expressed as the ratio of the number of first occurrences each year weighted by the length of observation. Incidence was expressed for 100 person-years.

For all analyses, differences were considered to be significant if $P < .05$. Statistical analyses were performed using Stata v7.0 (Stata Corp, College Station, TX).

RESULTS

Study Population

A total of 327 children who were born to 324 mothers were included in the analysis. None of the mothers or the children were immunocompromised. Most mothers had acquired infection during the second or third trimester. All pregnant women had been treated, except for 52, in whom infection was diagnosed at delivery. Congenital infection was diagnosed during pregnancy in 27% of the cases and at birth in 50%. In the remaining 77 (23%) cases, infection was revealed by an increase in IgG during the first year of life (median: 6 months). Pyrimethamine and sulfadiazine were administered in utero in 38% of cases and after birth in 72% of newborns. Fansidar was given for an average duration of 337 days (±23) in all but 2 children (Table 1).

Length of Follow-up

At the final examination, children were aged between 6 months and 14 years. Sixty percent ($n = 195$) of the children were followed up for at least 5 years, and 23% ($n = 74$) were followed up for at least 10 years. The median length of the follow-up was 6 years (interquartile range: 3–10).

Findings at the Final Ophthalmologic Examination

At the final examination, 79 (24%) children had at least 1 retinochoroidal lesion (187 lesions total). Fifty-five children had lesions in 1 eye; of the 45 children for whom final visual acuity data were available, 31 (69%) had normal vision. Twenty-four children had lesions in both eyes; of the 21 for whom final visual acuity data were available, 11 had normal vision in both eyes. None of the children had bilateral visual impairment. In the 24 children with known unilateral visual impairment, visual acuity ranged from 20/25 (2 patients) to 20/400 (10 patients; Tables 2 and 3).

Age at Diagnosis of the First Retinal Lesions

Of the 327 children, 9 (3%) had a retinal lesion during their first month of life and 38 (12%) had at least 1 lesion during their first year. Half of the initial lesions were diagnosed before 1 year of age, 58% before 2 years, 76% before 5 years, and 95% before 10 years. Thirteen percent (25 of 187) of lesions were active at the time of detection. Thirty lesions were

TABLE 1. Characteristics of the Study Population

Mothers of children with congenital infection (*n;* mean age)	324 (28 ± 5)
Trimester of maternal infection (*n* [%])	
First	18 (6)
Second	88 (27)
Third	218 (67)
Treatment during pregnancy (*n* [%])	
No treatment (diagnosis made at delivery)	52 (16)
Treatment according to standard protocol	272 (84)
Spiramycin alone	149 (46)
Pyrimethamine + sulphadiazine	19 (6)
Spiramycin then pyrimethamine + sulphadiazine	104 (32)
Infected children (*n* [gender ratio (f/m)]	327 (0.96)
Length of follow-up (y; median [IQR])	6 (3–10)
Time at which congenital infection was diagnosed (*n* [%])	
Before birth	87 (27)
At birth	163 (50)
After birth [median: 6 (1–32) months]	77 (23)
Postnatal treatment (*n* [%])	
No treatment	2 (1)
Treatment according to standard protocol	325 (99)
Pyrimethamine + sulphadiazine immediately after birth	237 (73)
Fansidar after a body weight of 5 kg was attained	325 (100)

IQR indicates interquartile range.
Data relate to maternal infection, time of diagnosis of congenital infection, and treatment during pregnancy or after birth.

TABLE 2. Final Ophthalmologic Findings in the 327 Children With Congenital Toxoplasmosis

	No. of Children	%
Ocular lesions	79	24
Location		
Peripheral	38	48
Macular	31	39
Peripapillary	8	10
Peripapillary + macular	2	3
Side		
Right eye	32	41
Left eye	23	29
Both eyes	24	30
No. of lesions		
One eye	55	70
1 lesion	46	59
2 lesions	5	6
3 lesions	4	5
Both eyes	24	30
No ocular involvement	248	76

diagnosed in children who were treated with Fansidar (Table 4, Fig 1).

The incidence density was highest during the first year of life and lowest between the fourth and sixth years. A peak was observed between 7 and 8 years as a result of the detection of new lesions in 7 children. Of these, 5 had inactive lesions and 4 had peripheral lesions. This distribution was similar to that observed for lesions detected at a younger age.

Secondary Events

Among the 79 children with at least 1 lesion, 23 (29%) had at least 1 new event: reactivation of an existing lesion (1 case), lesion in a previously healthy location (19 cases), or both (3 cases). Reactivations at the borders of preexisting scars were diagnosed up to 12 years after detection of the first lesions and additional lesions up to 10 years. Time between involvement of the first and the second eye ranged from 1.5 to 10 years (median: 2 years). No association was found between the occurrence of new events and the age at which the initial lesion was detected ($P = .8$), activity ($P = .5$), or location ($P = .2$). The presence of >1 lesion in the first eye was predictive for the involvement of the partner eye ($P < .0001$; Table 5).

Other Manifestations of Congenital Toxoplasmosis

At the final pediatric examination, 71% (232 of 327) of children were free of any lesions and 18% (60 of 327) manifested no sequelae except retinochoroiditis. In the other 11%, at least 1 pathologic sign was detected: cranial calcifications were detected in 31 children, hydrocephalus was detected in 6, and microcephalus was detected in 1. Three children with hydrocephalus had moderate psychomotor retardation; the other 3 had normal development and school progression. Two children with calcifications had 1-time seizures that remained isolated despite the lack of long-term antiepileptic therapy (Table 6).

DISCUSSION

Our goal was to report on the long-term outcome of children who were congenitally infected with toxoplasmosis and were identified during monthly prenatal screening and therefore benefited from the earliest possible diagnosis and treatment. This information is necessary to assess the efficacy of prenatal screening and is essential for clinicians who have to advise future parents about the risk of lesions in their children.

In our cohort, 79 (24%) of 327 children developed retinal lesions over a median 6-year follow-up period. Among the 66 children for whom visual acuity was reported, 64% had no visual impairment. None had bilateral impairment despite bilateral lesions in 30% of the children. Only 9 (11%) received a diagnosis of retinochoroiditis during the first month of life. Half of the lesions were diagnosed after 1 year of age.

These data obviously contrast with earlier studies

TABLE 3. Visual Acuity and Associated Ophthalmic Abnormalities as a Result of Congenital Toxoplasmosis in the 79 Children With at Least One Retinal Lesion

	n	Visual Acuity								
		20/20	20/25	20/30	20/40	20/60	20/100	20/200	20/400	Unknown
Unilateral disease	55	31(S + MO = 1)	-	2(S = 1)	1(S + MO)	3(S + MO = 1)	-	2(S = 1)	6(S = 1)	10(S = 3)
Bilateral disease	24	11	2	1	1	-	1	1(S = 1)	4(S = 1; S + MO + RD = 1; S + MO + RD + OA + C + H = 1)	3(S = 1)

S indicates strabismus; MO, microphtalmia; RD, retinal detachment; OA, optic nerve atrophy; C, cataract; H, hyalitis.

on children with congenital toxoplasmosis, who were not treated or received treatment for a shorter period. In the study by Wilson et al,[3] 11 of 13 children who had been asymptomatic at birth and received no treatment postnatally received a diagnosis of retinal lesions between 1 month and 9 years of age. Koppe et al[4] reported the occurrence of lesions in 9 of the 11 subjects followed for 20 years. Four children had severe visual impairment, including 2 of the 5 newborns who received treatment at birth.

It generally is recognized that extensive management in utero and after birth certainly helps decrease the severity of the infection and the risk of ocular lesions. Indeed, compared with Wilson et al and Koppe et al, Mets et al[11] reported a better outcome in 79 children who were treated at birth or perinatally with pyrimethamine and sulfadiazine for 1 year, but even so, 29% of their cases had bilateral visual impairment. Eighteen historical controls who had entered the study after 1 year of age all had retinochoroidal lesions.

Our data should not be used to draw any conclusions about antenatal screening because factors other than therapy certainly influence the observed outcomes. This is demonstrated by the report by Guerina et al[12] of an outcome similar to ours in children who were identified during neonatal screening. Another evidence of the influence of factors other than therapy is the higher prevalence of children with eye lesions in 2 reports based on French children who were also identified through prenatal screening. In the first study, by Couvreur et al,[8] based on 172 children who received pyrimethamine and sulfadiazine for 1 year after birth, the proportion of children with lesions (24%) was the same after a median follow-up of 4 years as in our study after a median follow-up of 6 years. Thirty-eight (22%) children had lesions diagnosed at birth, whereas only 11% of children in our study had lesions detected within the first month of life. However, exact comparison is impossible because of the lack of information on the exact date of maternal infection and on visual acuity as well as the lack of clear distinction between detection of new lesions and reactivation of existing lesion. In the second study, Brezin et al[13] reported a higher prevalence of retinochoroiditis at a younger age in 18 children who were born from mothers who were infected in the first half of pregnancy and who all were treated in utero and for 1 year after birth with pyrimethamine and sulfadiazine. At an ophthalmologic examination performed at a median age of 4.5 years (1–11), 7 (39%) children had at least 1 lesion, including 4 who had bilateral lesions. One child had bilateral visual impairment. No data were available on the age at detection of lesions. Also, the selection of early maternal infections and the small number of subjects limit the comparison with our data and might partially explain the differences in outcome.

Specific care was taken in our study to avoid distortions of findings as a result of selection or detection biases. Although not population based, our study nevertheless can be considered as unselected, owing to the exhaustive inclusion of cases identified

TABLE 4. Incidence Density of the First Occurrence of Retinochoroiditis Estimated Every Month of the First Year, Every Trimester Over the Second Year, and Every Year Thereafter*

Time at Assessment (Months After Baseline)	Children-Months at Risk	Children Diagnosed With First Lesion	Incidence Rates Per 100 Months	95% Confidence Intervals
First year				
0–1	322	9	2.80	1.46–5.38
1–2	318	0	0.00	—
2–3	315	3	0.95	0.31–2.95
3–4	310	5	1.61	0.67–3.87
4–5	306	3	0.98	0.32–3.04
5–6	304	2	0.66	0.16–2.63
6–7	299	3	1.00	0.32–3.11
7–8	295	4	1.35	0.51–3.61
8–9	291	2	0.69	0.17–2.75
9–10	287	2	0.70	0.17–2.79
10–11	284	3	1.06	0.34–3.27
11–12	279	2	0.72	0.18–2.87
Second year				
12–15	820	4	0.49	0.18–1.3
15–18	790	3	0.38	0.12–1.18
18–21	764	0	0.00	—
21–24	747	1	0.13	0.02–0.95
Following years				
Third (24–36 mo)	2713	8	0.29	0.15–0.59
Fourth (36–48 mo)	2357	4	0.17	0.06–0.45
Fifth (48–60 mo)	1989	2	0.10	0.03–0.40
Sixth (60–72 mo)	1726	2	0.12	0.03–0.46
Seventh (72–84 mo)	1448	4	0.28	0.10–0.74
Eighth (84–96 mo)	1146	7	0.61	0.29–1.28
Ninth (96–108 mo)	864	2	0.23	0.06–0.93
10th (108–120 mo)	679	0	0.00	—
11th (120–132 mo)	484	1	0.21	0.03–1.47
12th (132–144 mo)	315	1	0.32	0.04–2.25
13th (144–156 mo)	171	2	1.17	0.29–4.68

* Incidence rates are calculated as the number of first occurrences weighted by the number of children-months at risk at each endpoint and are expressed for 100 children-months.

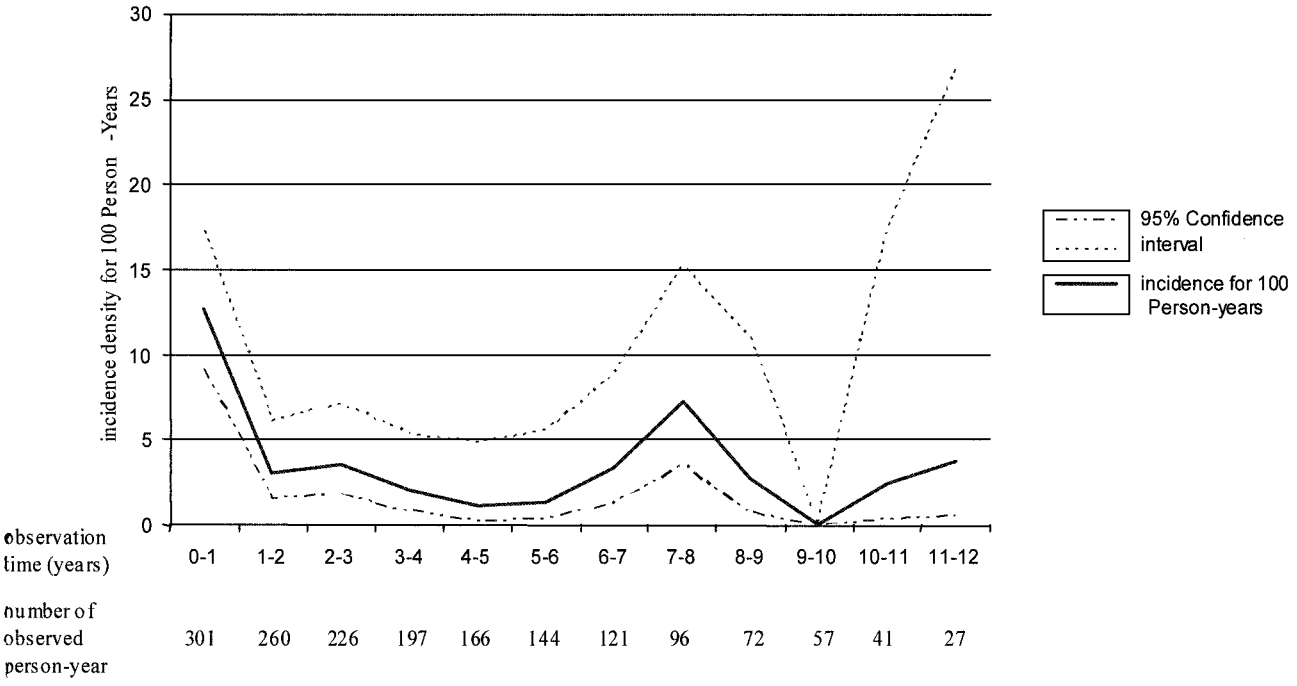

Fig. 1. Incidence density of first ocular lesion after diagnosis of congenital toxoplasmosis.

during prenatal screening, regardless of age at the time of maternal infection and severity of the congenital infection. The importance of an unbiased selection is demonstrated by the difference in outcome in this cohort compared with that in an earlier series of 121 children who were monitored at our center before monthly screening of seronegative pregnant women became mandatory in France.[14] In our previous study, lesions were detected between birth and 1 year of life in 85% of children with retinal disease

TABLE 5. New and Secondary Events Detected After Birth in the 327 Children With Congenital Toxoplasmosis

	No. of Children	%
Secondary events	23	29
New ocular lesion	19	24
Reactivation of old lesions	1	1
New and reactivated lesions	3	4
No secondary events	56	71

TABLE 6. Organ Manifestations of Congenital Toxoplasmosis at Final Examination in the 327 Infected Children

	No. of Children	%
Organ manifestations	95	29
Eye alone	60	18
Central nervous system*	35	11
Cerebral calcifications	31	9
Hydrocephalus	6	2
Microcephalus	1	<1
No organ manifestations	232	71

* Including retinochoroiditis in 19 children.

compared with 50% in the more recent cohort. The increased proportion of early lesions in the first series probably reflected the preferential referral of children who were deemed likely to have clinically manifest congenital toxoplasmosis. Furthermore, unlike other studies in which distinction between acquired and congenital infection was difficult,[15,16] we included only confirmed cases of congenital toxoplasmosis. Moreover, all cases were managed prenatally and postnatally according to a standard protocol. In the absence of a widely accepted standard treatment regimen and the lack of data demonstrating a better efficacy in vivo or tolerance or both sulfadiazine and pyrimethamine versus Fansidar,[17] we opted for the latter, more convenient strategy. There is no evidence that the outcome would have differed significantly if we had used sulfadiazine and pyrimethamine.

Finally, our lengthy follow-up period permitted the detection of lesions that otherwise would have been overlooked. The large number of eye examinations performed in each child over time decreased examination bias and increased the reliability of detection, known to be highly variable after a single assessment.[18] As our study was not designed as an experiment but was based on routinely collected data, examinations were not performed by a single ophthalmologist but in several institutions and private practices. However, all ophthalmologists had experience in examining young children. Use of a standardized form reduced imprecision in the reporting of relevant information. Normal acuity was adapted to the child's age, and although we cannot exclude the possibility that minor impairments were overlooked, we do not believe that these would have significantly altered our findings.

The delayed onset of lesions is an important consideration in clinical counseling and in any study that uses ocular outcome as an endpoint. The follow-up will be extended until a sufficient number of adolescents and young adults are available to assess whether the risk of ocular lesions increases in puberty or in pregnancy and to analyze the functional consequences of ocular lesions and their impact on social life. We are also currently searching for prognostic factors to identify subgroups that are at higher risk of developing eye lesions.

In the meantime, clinicians and parents should be informed that, despite early diagnosis of congenital toxoplasmosis and treatment, relapses and late-onset ocular lesions can occur late after birth. They cannot be predicted at the present time but fortunately do not lead to severe visual impairment.

ACKNOWLEDGMENT

This study was performed at the Department of Parasitology, Hôpital de la Croix-Rousse, Lyon, France.

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