Ocular Outcome of Brazilian Patients With Congenital Toxoplasmosis

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Background: Retinochoroiditis is the most frequent manifestation of congenital toxoplasmosis. We aimed to describe the ocular outcome and factors that may influence the visual prognosis of these patients.

Methods: Cohort of patients with confirmed congenital toxoplasmosis seen between 1996 and 2017 in Porto Alegre, southern Brazil.

Results: Seventy-seven patients were included, of which 65 (85.5%) were identified by routine screening. Median age at the end of the follow-up was 10 years (minimum 2, maximum 25). Retinochoroiditis was present in 55 patients (71.4%). New retinochoroidal lesions developed after the first year of life in 77.8% of the patients who began treatment after the fourth month of life, compared with 35.2% among those treated before 4 months of life (relative risk = 0.45, 95% confidence intervals: 0.27–0.75, $P = 0.02$) and 33.3% among those treated before 2 months of life (relative risk = 0.42, 95% confidence intervals: 0.25–0.72, $P = 0.01$). There was a peak incidence of new retinochoroidal lesions between 4 and 5 years and another peak between 9 and 14 years, the latter only among girls. Thirty-four patients with retinochoroiditis were followed up for 10 years or more, and the school performance was appropriate in 28 (82.4%).

Conclusions: The high incidence of new retinochoroidal lesions during the follow-up period indicates the importance of long-term follow-up of patients with congenital toxoplasmosis. Initiating treatment within the first 4 months of life, especially within the first 2 months, was a protective factor against the later development of retinochoroiditis. Despite the usual favorable prognosis, the high morbidity of congenital toxoplasmosis in Brazil was confirmed.

Key Words: toxoplasmosis, congenital infections, chorioretinitis, visual acuity, risk factors

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Retinochoroiditis is the most frequent manifestation of congenital *Toxoplasma gondii* infection, and even infants without any abnormal findings are at a remarkable risk of developing ocular lesions in the short or long term.[1–5] It is recommended that after confirmation of congenital toxoplasmosis in the fetus, neonate, or infant, treatment be initiated as soon as possible and maintained for 1 year postnatally, even in asymptomatic patients.[1,4–8]

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Retinochoroidal lesions caused by congenital toxoplasmosis tend to be more severe, and their recurrence tends to be more frequent among children from North and South America when compared with other regions such as Europe.[9–11] Nevertheless, despite several relevant studies on the outcome of patients with congenital toxoplasmosis, there is a paucity of studies with extended follow-up in Brazil.[12–14] Long-term follow-up is crucial to provide reliable information on the course of diseases in different geographic scenarios, helping the formulation of guidelines and policies.

This study aimed to describe the ocular outcome and to investigate the previous history, clinical aspects, and treatment data that may influence the visual prognosis of congenital toxoplasmosis.

METHODS

Retrospective cohort study with data collected from the records of patients seen between 1996 and 2017 at the congenital infections outpatient clinics (public and private sectors) of Hospital São Lucas at Pontifical Catholic University of Rio Grande do Sul (HSL-PUCRS), in Porto Alegre, southern Brazil. All patients with congenital toxoplasmosis identified within the first year of life received specific drug therapy (pyrimethamine, sulfadiazine, and folinic acid), in addition to other therapeutic measures when indicated, such as systemic corticosteroids, neurosurgic procedures, and motor and visual stimulation, in compliance with current guidelines.

The inclusion criteria were follow-up for at least 12 months of life and persistence of anti-*T. gondii* immunoglobulin (Ig) G up to this age. Cases with insufficient records were excluded from the study. Variables related to the ocular outcome, such as presence of retinochoroiditis and other ocular findings, location and number of lesions, recurrence of lesions, and visual quality, were assessed. Other variables included perinatal history, suspicion, and diagnosis of congenital toxoplasmosis, clinical picture, data on treatment within the first year of life, neuropsychomotor development, and school performance.

Neuropsychomotor development was evaluated during pediatric consultations, using the Denver developmental screening test, whereas the data on school performance were obtained from parents' reports. School performance was assessed only in those patients with 10 years of age or older, and it was deemed appropriate when the child was attending the grade expected for his/her age. The laboratory tests were carried out at the clinical laboratory of HSL-PUCRS, and serum analyses were performed using the microparticle enzyme assay (MEIA) (Imx, Abbott, Abbott Park, IL) up to 1998 and the enzyme-linked fluorescence assay (ELFA) (VIDAS, bioMérieux, Brazil) for the other periods. The neuroimaging exams were performed at the hospital's imaging center.

Ophthalmologic examinations were carried out by several ophthalmologists, indicated by the pediatric team from among pediatric ophthalmology specialists. All examinations were conducted with an indirect ophthalmoscope after mydriasis. Eye examinations were performed, in general, on a monthly basis in the first year of life, every 4–6 months up to school age, and annually thereafter,

but periodicity could vary depending on the available resources of families.

Macular or paramacular retinochoroidal lesions were considered as central lesions. Visual acuity was assessed by an ophthalmologist in patients older than 3 years and described as %. According to the international classification, visual acuity can be classified as normal (≥80%), mild visual loss (<80%≥30%), poor vision (<30%≥5%), and blindness (<5%).[15] In children younger than 3 years or in patients in whom visual quality was reported by the patient or by the family, the terms "normal vision," "good vision," or "able to follow small objects" were regarded as normal vision; the term "abnormal" was regarded as undetermined visual loss; the descriptions "able to follow light" and "peripheral vision only" were regarded as poor vision; and "total loss" was regarded as blindness. Bilateral poor vision or unilateral or bilateral blindness were regarded as severe visual loss.

To assess the effect of the time at which postnatal treatment was initiated on the later development of retinochoroiditis, a smaller sample was used, which included only those patients followed up for at least 5 years of life and excluded those who had not received any treatment during the first year of life.

Statistical analyses were performed using EPI INFO version 7.2.2.16. Continuous numerical variables were described as median and interquartile range (IQR) or as mean and standard deviation, whereas categorical variables were described as absolute number and percentage. The χ^2 test (or Fisher's exact test) was used to assess the associations between variables and outcomes of interest for categorical variables, and Student's *t* test or Mann-Whitney/Wilcoxon test was used for continuous variables. A $P<0.05$ was considered to be significant.

The study was approved by the institutional Research Ethics Committee. Since this study was a retrospective one, a consent form did not have to be signed by the patients or their legal guardians. An agreement for data usage was signed by the researchers. All guidelines established in Resolution no. 466 of December 12, 2012, issued by the National Health Council, linked to the Brazilian Ministry of Health, and the 1994 Declaration of Helsinki and its later revisions, which regulate research studies that include humans, were followed.

RESULTS

Sampling

In the study period, 537 neonates, infants, or children with suspected or confirmed congenital toxoplasmosis were referred to the aforementioned centers. In 425 cases, congenital toxoplasmosis was ruled out or the patients were lost to follow-up before confirmation of the diagnosis. Of the 112 patients with confirmed congenital toxoplasmosis, 26 were lost to follow-up before 12 months of life and 9 were excluded because of incomplete data records. Thus, the sample comprised 77 patients, corresponding to 75 pregnancies (2 twin pairs) (see Figure, Supplemental Digital Content 1, http://links.lww.com/INF/E143).

Demographic and Perinatal Data, Suspicion, Diagnosis, and Treatment

Congenital toxoplasmosis was suspected during routine screening (prenatal, neonatal, or of parturient women) in 65 (84.4%) of the cases. Among the 33 infants detected by newborn screening, 31 (93.9%) mothers had more than 6 prenatal visits. Twenty-seven mothers had been diagnosed during pregnancy, and, among them, 20 (74%) received prenatal treatment (13 with spiramycin and 7 with pyrimethamine, sulfadiazine, and folinic acid). More perinatal data are shown in Table, Supplemental Digital Content 2, (http://links.lww.com/INF/E144).

Clinical and serologic criteria for initiating postnatal treatment of the infants are summarized in Table, Supplemental Digital Content 3 (http://links.lww.com/INF/E145). Seventy-three infants (94.8%) had been treated with pyrimethamine, sulfadiazine, and folinic acid in the first year of life. Treatment was initiated within the first 4 months of life in 63 patients (81.8%) and within the first 2 months of life in 57 patients (74.0%). Although the total length of the initial treatment was 12 months in almost all of the 73 patients diagnosed in the first year, the time of treatment within the first year of life varied according to the age of diagnosis and the interruptions. Thus, in these 73 patients, the median total length of treatment was 12.0 (IQR 12.0–12.0) months, while the median time of treatment within the first year of life was 10.5 (IQR 8.0–11.0) months, and the mean was 9.3 ± 2.6 months.

Twelve infants (representing 16.4% of 73 diagnosed in the first year of life and 30.8% of 39 with retinochoroiditis in the first year) received systemic corticosteroids in the first year of life, including 10 (83.3%) due to active retinochoroiditis (see Table, Supplemental Digital Content 3, http://links.lww.com/INF/E145). In subsequent years, systemic corticosteroids were used in the presence of active retinochoroiditis. Corticosteroids (1 mg/kg/d of prednisone or prednisolone) were started 48 hours after the specific therapy, maintained until the ocular lesions were healing, and then gradually withdrawn over a period of 1 week. The average time of corticosteroid use in each course was 2 months. No intraocular or topic therapy was prescribed.

Fifty-eight patients (79.5%) had some drug-related adverse effects. The most frequent adverse reaction was neutropenia, treated with escalation of folinic acid dose or with temporary discontinuation of pyrimethamine (see Table, Supplemental Digital Content 3, http://links.lww.com/INF/E145). No severe infection that could be attributed to neutropenia was observed. There were no severe drug-related adverse effects.

Clinical Picture at Baseline, Neurologic and Hearing Disorders

Data on these topics are described in Text and Table, Supplemental Digital Content 4, http://links.lww.com/INF/E146.

Follow-up Period

Median age at the end of the follow-up period was 10 years, IQR 6–14 years, minimum (min.) 2, maximum (max.) 25 years. No significant difference in age was observed at the end of the follow-up period between girls (median 10, IQR 5–15, min. 3, max. 23) and boys (median 11, IQR 6–14, min. 2, max. 25 years) ($P=0.74$). Age at the end of follow-up was higher in patients with ocular lesions (median 11, IQR 6–15, min. 2, max. 25 years) than in those patients without such lesions (median 7.5, IQR 4–10, min. 3, max. 20 years) ($P=0.02$).

Frequency and Time of Onset of Ocular Lesions

Fifty-four patients were examined by an ophthalmologist within the first 2 months of life when retinochoroiditis was detected in 19 (35.2%), all with central lesions (either macular or paramacular) and 8 (14.8%) with active lesions. Of the 35 patients without ocular lesions within the first 2 months, 8 (22.8%) were diagnosed with cicatricial peripheral retinochoroiditis within the first year of life; and another 12 cases of retinochoroiditis were diagnosed in infants in which the first ophthalmologic examination was only performed between 2 and 11 months of life. Therefore, at the end of the first year of life, 39 (50.6%) patients had already been diagnosed with retinochoroiditis.

At the end of follow-up, 55 (71.4%) patients had been diagnosed with retinochoroiditis, with or without other ocular manifestations. Two patients presented with ocular alterations without retinochoroiditis, 1 with strabismus only, and another 1 with strabismus and bilateral optic neuritis. Findings that cooccurred with retinochoroiditis included: strabismus in 30 patients (39.0%), optic neuritis in 4 (5.2%) (bilateral in 1), vitritis in 5 (6.5%) (including 2 cases of vitreous bands), nystagmus in 4 (5.2%), and microphthalmos in 3 (3.9%).

Among the 55 patients with retinochoroiditis, the first lesion was diagnosed within the first year of life in 39 (70.9%), within the second year in none, and between 2 and 11 years of age in 16 patients (29.1%). Twenty-two patients had new lesions after the first one, totaling 39 cases of relapse from the third year to the third decade of life. Adding up the 16 retinochoroidal lesions that appeared for the first time after the first year of life, there were 55 episodes of new lesions after the first year of life among 29 patients (see Figure, Supplemental Digital Content 5, http://links.lww.com/INF/E147). As with initial lesions, there was no case of recurrence in the second year of life.

Considering the presence of retinochoroiditis in the first year alone, the rate was slightly higher in boys (18/34; 52.9%) than in girls (21/43; 48.8%), without statistical significance ($P=0.72$). However, the episodes of retinochoroiditis after the first year of life (initial episodes+relapses) were more frequent in girls (36/55 episodes; 65.4%) than in boys (19/55 episodes; 34.5%) ($P<0.01$). There was a peak incidence of new retinochoroidal lesions (both initial and relapses) between 4 and 5 years of age, and another peak between 9 and 14 years, the latter only among girls (Fig. 1).

Symptoms Concomitant With the Appearance of Retinochoroidal Lesions

None of the children who developed new retinochoroidal lesions before 7 years of age complained about symptoms (23 episodes). From this age onward, symptoms were reported by patients during 24/32 (75.0%) episodes. The most frequent symptom was myodesopsia (commonly known as "floaters"), followed by blurred vision, headache, localized pain, and distorted vision. Some patients reported more than 1 symptom. In all cases, the symptoms ceased with drug treatment for 2–4 months. Preexisting lesions, which had already healed, did not change with treatment. After the acute phase of relapses, there was no permanent deterioration of vision.

Visual sequelae, such as blind spots (scotoma), peripheral vision only, and poor peripheral vision, were reported by some patients during the chronic phase. However, some older children and adolescents with retinal lesions that could indicate visual field impairment did not perceive it.

Location and Number of Retinochoroidal Lesions

Central lesions were predominant during the first year, being detected in 39/60 (65.0%) eyes. Lesions that developed later (including relapses), where instead predominantly peripheral, appearing in 31/44 (70.5%) eyes ($P<0.001$).

In the last ophthalmologic examination, central lesions were distributed evenly on both sides: 28 in the right eyes (19 macular and 9 paramacular) and 25 in the left eyes (17 macular and 8 paramacular), affecting 53 eyes in 40 patients with central lesions. Regarding the number of all retinochoroidal lesions, there was 1 lesion in 11 patients, 2 lesions in 13 patients, 3 lesions in 14 patients, between 4 and 9 lesions in 10 patients, and 10 or more lesions in 4 patients. There was no information about the number of lesions in 3 medical records. Figure, Supplemental Digital Content 6, http://links.lww.com/INF/E148, shows the location of retinochoroidal lesions in the last assessments of the 55 patients.

Treatment of Toxoplasmosis in the First Year of Life versus Development or Recurrence of Retinochoroiditis

The mean duration of treatment for congenital toxoplasmosis within the first year of life was higher in patients without development or recurrence of retinochoroiditis after the first year (9.6±2.8 months) than in those patients who developed new lesions after this age (7.7±3.8 months) ($P=0.01$).

A smaller sample, used to assess the influence of the age at which treatment was initiated on later development of retinochoroiditis, included 63 patients who received some treatment in the first year and were followed up at least until their fifth year of life. In this sample, early treatment was a protective factor against the later development of retinochoroiditis. Seven of 9 (77.8%) patients who began treatment between the 5th and 10th months of life developed new retinochoroidal lesions after the first year, when compared with 19/54 (35.2%) patients who began treatment before 4 months of age (relative risk=0.45, 95% confidence intervals: 0.27–0.75, $P=0.02$) and to 16/48 (33.3%) patients who began treatment before 2 months

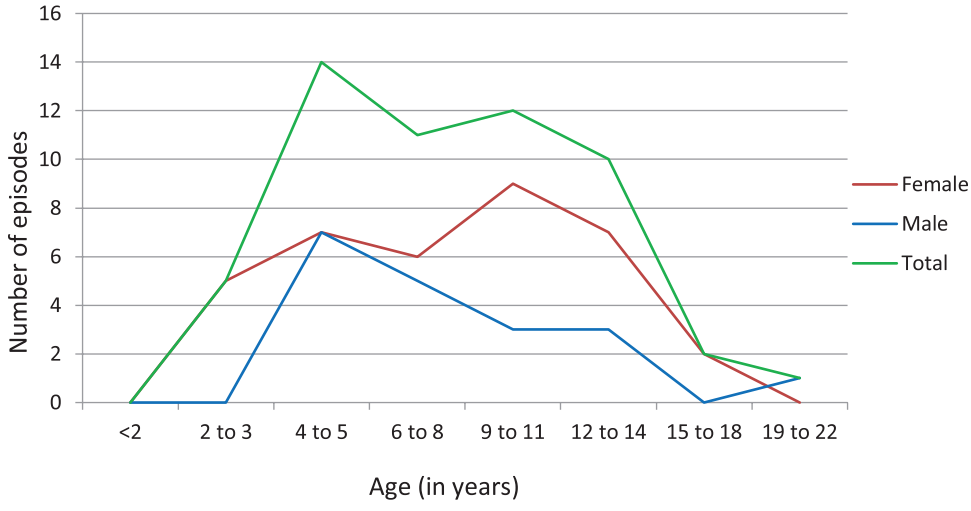

FIGURE 1. Age at development of retinochoroidal lesions (first episode or relapse) after the first year of life: 55 episodes in 29 patients with congenital toxoplasmosis.

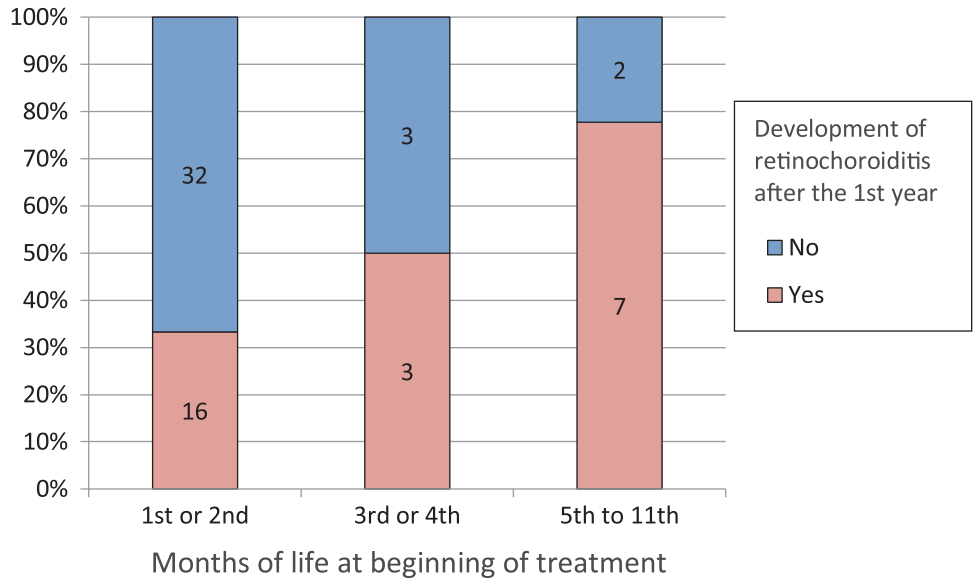

FIGURE 2. Development of episodes of retinochoroiditis after the first year of life according to the age at which treatment for congenital toxoplasmosis was initiated, in 63 patients treated within the first year and followed up at least until the fifth year of life. * First group versus third group (treatment initiated before 2 months versus after the fourth month): RR = 0.42, 95% CI: 0.25–0.72, *P* = 0.01. Sum of the first 2 groups versus third group (treatment initiated before 4 months versus after the fourth month): RR = 0.45, 95% CI: 0.27–0.75, *P* = 0.02. Statistics: Fisher's exact test. CI indicates confidence interval; RR, relative risk.

of age (relative risk = 0.42, 95% confidence intervals: 0.25–0.72, *P* = 0.01) (Fig. 2).

Posttreatment Serologic Rebound versus Development or Recurrence of Retinochoroiditis After the First Year of Life

Anti-*T. gondii* IgG was assessed after discontinuation of first treatment in 64 children. Of these, all had posttreatment serologic rebound—IgG concentration reached >1000 IU/mL in 57 (89%), >3000 IU/mL in 42 (65.6%), and >6000 IU/mL in 26 patients (40.6%). The mean time during which IgG levels remained above 1000 IU/mL was 22 ± 19 months, minimum of 4 months and maximum of 7 years.

Throughout the follow-up period, there was no association between anti-*T. gondii* IgG concentrations or length of serologic rebound and the later development of new retinochoroidal lesions. However, no new lesions were observed during the second year of life, when serologic rebound was at its peak; and among 57 patients with IgG levels greater than 1000 IU/mL, only 1 developed a new retinochoroidal lesion (in the fourth year of life).

Visual Quality, Neurodevelopment, and School Performance

Visual quality was assessed in 50 of 55 patients with retinochoroiditis. Sixteen patients (32.0%) were considered to have normal vision, 19 (38.0%) had unilateral or bilateral mild or undetermined visual loss, 10 (20.0%) had poor vision in the worst eye, 4 (8.0%) had poor vision in both eyes, and 1 (2.0%) had bilateral blindness. The last 5 cases (10%), classified as severe visual loss, also had abnormal findings on physical examination immediately after birth (4 with microcephaly, 1 with macrocephaly, and 3 with microphthalmos) and 4 had severe motor and intellectual impairment.

Visual acuity could be determined in 20 patients, 4–25 years of age. By cross-checking the description of retinal lesions with the visual acuity in the 40 eyes, there was a large variation in those eyes with central lesions. In 8 eyes with macular lesions, visual acuity ranged from 10% to 40%; in 10 eyes with paramacular lesions, acuity ranged from 5% to 70%, except in 1 with 100%. In 15 eyes with peripheral lesions only, visual acuity reached 100%, except in 1 with 50% (this eye had more than 10 peripheral lesions). In 7 eyes without lesions, acuity was 100%.

Thirty-four patients with retinochoroiditis were followed up to 10 years of age or older; school performance was poor in 6 (17.6%) and adequate in 28 (82.4%). In the latter, 12 patients (42.9%) did not have visual impairment and 9 (32.1%) had unilateral visual impairment; 7 (25.0%) had bilateral visual impairment, but over the years they improved their visual quality, being able to read and keep up with the school activities. Three infants with macular retinochoroiditis, 2 of whom with nystagmus, showed abnormal head positioning while gazing, which normalized during treatment with visual stimulation.

In 6 patients with retinochoroiditis the age at the end of follow-up was 18 years or older. Three had central lesions in the right eye, and 3 had bilateral central lesions. Visual level ranged between 70% and normal in the best eye and between 10% and peripheral vision in the worst eye. Four of these patients were college students, and 2 had already entered the job market.

DISCUSSION

To the best of our knowledge, this is the first Brazilian study to describe long-term follow-up of a large sample of patients with congenital toxoplasmosis, predominantly identified during routine screening. The importance of early treatment and its maintenance during the first year of life was corroborated, as treatment initiated within the first 4 months of life, especially within the first 2 months, was a protective factor against later development or recurrence of retinochoroiditis. Moreover, this study underscored the importance of both prenatal and newborn screenings: considering only those mothers who had an adequate number of prenatal visits, less than 50% were diagnosed with toxoplasmosis during

pregnancy. Newborn screening allowed detecting infected infants before development of symptoms. The more favorable outcome of patients treated in the first year of life is in line with the findings of other studies[5,16,17] and, for ethical reasons, can only be compared with historical controls of older cohorts when no specific treatment was performed.[18–20]

Despite the positive effect of treatment during the first year of life, a relevant number of children and adolescents developed new ocular lesions, thus highlighting the importance of regular follow-up of patients with congenital toxoplasmosis. The rise in the rate of retinochoroiditis between the end of the first year of life and the end of the study period demonstrates that prevalence of retinochoroiditis in congenital toxoplasmosis may increase as the follow-up is extended, which was previously seen in other populations.[3,21–25]

After the first year of life, the first peak incidence of new retinochoroidal lesions (initial and relapses) occurred between 4 and 5 years of age, and the second peak occurred between 9 and 11 years (among girls only). Phan et al[17] described a peak incidence from 5 to 7 years and another one from 15 to 20 years; Wallon et al[23] observed peaks around 7 years of age and between 11 and 13 years, but no difference between sexes was described. Issues about age and sex had never been described in Brazilian children. Gómez-Marin et al,[26] in a Colombian cross-sectional study, found a higher frequency of ocular toxoplasmosis in girls with 13–16 years of age when compared with boys of the same age; and in the United Kingdom, Chapman et al[27] found a higher prevalence of young women in a group of patients with ocular toxoplasmosis compared with a control group. Both hormonal and immunologic factors are likely implicated in the associations of retinochoroiditis with age, puberty, and sex.[27–29]

Retinochoroidal lesions developed after the first year of life, either for the first time or as relapses, were predominantly peripheric, concurring with the findings of other studies on children treated within the first year of life.[3,17,25,30,31] This is quite the opposite of what occurred with patients not treated in the first year of life, in whom most of the new lesions, developing at any time, were described as central,[19,20,32] suggesting the effect of postnatal treatment on the severity of lesions. The literature has demonstrated that severely affected children, especially those with neurologic manifestations, tend to have more severe retinochoroidal lesions,[16,33] which was also observed in the present cohort.

Given the difficulty in performing an ophthalmologic examination in young children, several authors have suggested that peripheral cicatricial retinochoroidal lesions detected later could be already present at birth.[28,34–37] In the present study, nearly 20% of the patients examined in the first 2 months of life, who apparently did not have any ocular involvement, had peripheral lesions on an examination carried out some weeks later. For that reason, retinochoroidal lesions detected until the end of the first year were used as our starting point.

This leads to the recommendation that ophthalmologic examination be repeated every month in the first year of life in newborn infants with a suspected diagnosis of congenital toxoplasmosis whose first examination had normal findings. Sometimes, retinochoroiditis may be the only diagnostic confirmation in an infant with suspected congenital toxoplasmosis. This was observed by Vasconcelos-Santos[37] in 15.7% of newborn infants with positive IgM in the paper-filter technique but negative IgM and IgA in confirmatory tests, in which retinochoroiditis was the only abnormal finding. With regard to monitoring within the first months of life, we underscore the development of clinical signs, such as hepatomegaly and splenomegaly, after the neonatal period, which could also be a warning sign in cases of uncertain diagnosis.

No relapse or development of first lesion was observed in children with 12–24 months of age, most of whom had very high specific IgG levels due to posttreatment serologic rebound. This fact was also noted by Phan et al,[32] who pointed out an increase in antibody levels after treatment discontinuation, but absence of new lesions, suggesting that the parasite could have been reactivated but then suppressed by the child's immune response. This finding leads to the conclusion that in the second year of life, right after the treatment has been discontinued, there is no increased risk of developing retinochoroiditis.

There exists a consensus agreement that the treatment of congenital toxoplasmosis should be initiated as soon as possible, but after the diagnosis is confirmed.[1,4,6,7] Such treatment requires regular blood and urine tests because of possible adverse effects, mainly neutropenia, which was the major cause for treatment discontinuation in this cohort, in line with the literature and twice as frequent according to a study carried out in Minas Gerais.[1,38] However, no severe consequence of neutropenia or other drug-related adverse effects were observed.

Visual acuity varied considerably in eyes with paramacular lesions (5%–70%) and with macular lesions (10%–40%). This has been described in the literature. In the study by Tan et al,[30] ophthalmologists estimated the visual acuity of 25 patients based only on the characteristics of the retina. They correctly identified 10/17 (58,8%) eyes with visual impairment and 28/33 (84,8%) eyes with no visual impairment. Errors occurred mainly in eyes with central lesions. Mets et al[39] were also surprised at the satisfactory visual quality of some patients, even in the presence of apparent foveal involvement, and Peyron et al,[21] assessing adults with congenital toxoplasmosis, observed a better visual acuity than expected from the characteristics of retinal lesions.

Some children of this cohort, who seemed to have severe visual impairment at an early age, developed reading skills with some visual support and managed to keep up with their school activities. In several cases, the child evidently replaced central vision with peripheral vision over time. The main explanation for that is the so-called eccentric fixation, that is, very young patients with bilateral macular lesions develop an adaptive strategy for using the peripheral retina instead of the damaged fovea. This locus is known as preferred retinal locus, showing an association with the abnormal head position adopted by some patients during activities of daily living.[40] Another explanation, according to Mets et al,[39] is that, in some cases of extensive central lesions, an essential part of the macula might have been spared. We concluded that even in the presence of extensive macular lesions in a young child, it is not possible to predict the final visual function.

In eyes with peripheral lesions only, visual acuity could be more easily predicted; all eyes showed 100% of acuity, except one with multiple lesions. However, visual quality may eventually be affected in the presence of peripheral lesions, as they can cause macular traction and lead to retinal detachment.[39,41] Other ocular manifestations than retinochoroiditis may affect visual acuity, such as strabismus, cataract, glaucoma, and optic neuritis. Some of these lesions are treatable and may remit. Just as in this study, the literature describes strabismus as the second most frequent ocular manifestation after retinochoroiditis and, quite often, this is the sign that alerts to an ocular lesion in a child without previous diagnosis of toxoplasmosis.[30,36,41] Antunes-Foschini et al[40] underscore the importance of rehabilitation and of rigorous follow-up since childhood, and the importance of stimulation of both eyes, as one cannot know which eye will be the dominant one when the visual system is fully developed.

T. gondii can circulate in the bloodstream of immunocompetent individuals, and parasitemia can be associated with retinochoroiditis reactivation. This explains the development of lesions at distant sites from the primary lesions and in eyes that had not been

previously affected.[42] This finding strengthens the recommendation for drug treatment of active retinochoroiditis, regardless of location, especially in South America, where *T. gondii* strains are more aggressive. In addition, treatment at any age is associated with quick resolution and healing of the lesions, preventing additional visual damage.[1,2,32,36,39,43]

The fact that children younger than 7 years did not report visual symptoms is clinically relevant and justifies ophthalmologic assessments at intervals shorter than 6 months in this age group. On the other hand, older children and adolescents often, although not always, reported visual symptoms related to reactivation of retinochoroiditis. Parents should be warned about the possible development of these symptoms so that ophthalmologic examination can be anticipated and treatment initiated, but this warning should be given carefully to prevent undermining the self-confidence of parents or patients themselves.[44] In some cases of chronic retinochoroiditis, even in the presence of lesions that could cause scotoma, the "perceptual filling-in" (a response from the visual cortex in which blind spots are filled in by preserved surrounding or contralateral areas) may eliminate the symptom.[45]

This study demonstrated that the prognosis of the patients without neurologic involvement was generally good, in spite of the indisputable negative aspects of visual impairment. In over 80% of the patients followed up for 10 years or more, school performance was appropriate, even in those with bilateral visual impairment. Wallon et al[3] and Peyron et al[21] also described normal school performance and good quality of life in adolescents and adults with congenital toxoplasmosis treated during the first year of life. Roizen et al[46] conducted intelligence tests in children with visual impairment caused by congenital toxoplasmosis. Children with monocular visual impairment had intelligence quotients within normal ranges but below the means obtained by children without deficit; the scores were lower in tests that require discriminating thin intersection lines, indicating that visual involvement might affect some aspects of the cognitive test. The authors comment that intervention strategies may be useful, facilitating the learning and performance of these children, and they recommend the development of instruments for measuring cognitive functions regardless of visual impairment.[46]

Limitations of this study include its retrospective nature so that ophthalmologic assessments were performed in not entirely uniform periods by several ophthalmologists. Nevertheless, the examinations were made by experienced ophthalmologists using appropriate techniques. Another limitation was the small number of patients who had their visual acuity assessed, in addition to the lack of a standardized acuity measurement and of perimetry examination, since visual field defects are described in most individuals with ocular toxoplasmosis.[30,47,48]

The sample, which comprised almost exclusively patients treated in the first year of life, did not have statistical power to assess the effect of presence of treatment. Also, it was not possible to assess the effect of prenatal treatment given the small number of treated mothers. Previous studies have shown beneficial effects of prenatal treatment, reducing the rate of new retinochoroidal lesions, decreasing vertical transmission rates, and improving the general prognosis of congenital toxoplasmosis.[8,17,24,49,50]

Failure to identify *T. gondii* strains was also a limitation. It is known that the parasite genetics is a determining factor for the outcome of toxoplasmosis, which is different between continents.[9,11,49,51–53] Several *T. gondii* genotypes can be found even within the same region, including in human newborn infants with congenital toxoplasmosis. Moreover, genetic characteristics of the host also influence the clinical presentation of infection.[52,54] Thus, other factors, not assessed in this study, could be involved in the outcomes.

In spite of these limitations, it may be concluded that retinochoroidal lesions that arose after treatment were mainly peripheral and were less frequent in those cases in which treatment was initiated within the first 4 months of life, especially within the first 2 months. There were no new lesions in the second year of life during posttreatment serologic rebound, but from the third-year new lesions were common, with a peak incidence in preschool years and another one in early puberty, the latter only among girls. Patients with central retinochoroidal lesions had a better outcome than expected in terms of visual quality and not necessarily hindered intellectual development. The most severe ocular involvement was observed in association with severe central nervous system manifestations already present at birth. Despite the favorable prognosis for most patients, the high morbidity of congenital toxoplasmosis in Brazil was confirmed.

These findings, which contribute to the knowledge on the outcome of congenital ocular toxoplasmosis, may apply to populations other than the Brazilian one, even those in which the parasite and the host have different characteristics. Guidelines for the management of both gestational and congenital toxoplasmosis should underscore the importance of detecting suspected cases using a sensitive method, establishing the diagnosis quickly, initiating treatment as soon as possible, allowing the maintenance of treatment during the first year of life, and ensuring the long-term follow-up of patients.

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REFERENCES

1. Peyron F, Wallon M, Kieffer F. Toxoplasmosis. In: Wilson C, Nizet V, Maldonado YA, et al, eds. *Remington and Klein's Infectious Diseases of the Fetus and Newborn Infant*. 8th edn. Philadelphia, PA: Elsevier/Saunders; 2016.
2. McLeod R, Lykins J, Gwendolyn-Noble A, et al. Management of congenital toxoplasmosis. *Curr Pediatr Rep*. 2014;2:166–194.
3. Wallon M, Garweg JG, Abrahamowicz M, et al. Ophthalmic outcomes of congenital toxoplasmosis followed until adolescence. *Pediatrics*. 2014;133:e601–e608.
4. Moncada PA, Montoya JG. Toxoplasmosis in the fetus and newborn: an update on prevalence, diagnosis and treatment. *Expert Rev Anti Infect Ther*. 2012;10:815–828.
5. McLeod R, Boyer K, Karrison T, et al; Toxoplasmosis Study Group. Outcome of treatment for congenital toxoplasmosis, 1981-2004: the National Collaborative Chicago-Based, Congenital Toxoplasmosis Study. *Clin Infect Dis*. 2006;42:1383–1394.
6. Peyron F, L'ollivier C, Mandelbrot L, et al. Maternal and congenital toxoplasmosis: diagnosis and treatment recommendations of a french multidisciplinary working group. *Pathogens*. 2019;8:E24.
7. Maldonado YA, Read JS; Committee on Infectious Diseases. Diagnosis, treatment, and prevention of congenital toxoplasmosis in the United States. *Pediatrics*. 2017;139:e20163860.
8. Wallon M, Peyron F. Effect of antenatal treatment on the severity of congenital toxoplasmosis. *Clin Infect Dis*. 2016;62:811–812.
9. Gilbert RE, Freeman K, Lago EG, et al; European Multicentre Study on Congenital Toxoplasmosis (EMSCOT). Ocular sequelae of congenital toxoplasmosis in Brazil compared with Europe. *PLoS Negl Trop Dis*. 2008;2:e277.
10. Cañón-Franco WA, López-Orozco N, Gómez-Marín JE, et al. An overview of seventy years of research (1944-2014) on toxoplasmosis in Colombia, South America. *Parasit Vectors*. 2014;7:427.
11. Dubey JP, Lago EG, Gennari SM, et al. Toxoplasmosis in humans and animals in Brazil: high prevalence, high burden of disease, and epidemiology. *Parasitology*. 2012;139:1375–1424.

12. Sáfadi MA, Berezin EN, Farhat CK, et al. Clinical presentation and follow up of children with congenital toxoplasmosis in Brazil. *Braz J Infect Dis*. 2003;7:325–331.
13. Bischoff AR, Friedrich L, Cattan JM, et al. Incidence of symptomatic congenital toxoplasmosis during ten years in a Brazilian hospital. *Pediatr Infect Dis J*. 2016;35:1313–1316.
14. Soares JA, Násser LS, Carvalho SF, et al. Achados oculares em crianças com toxoplasmose congênita. *Arq Bras Oftalmol*. 2011;74:255–257.
15. International Council of Ophthalmology. Visual standards: Aspects and ranges of vision loss. 2002. Sydney, Australia. Available at: http://www.icoph.org/downloads/visualstandardsreport.pdf. Accessed June 2019.
16. McAuley J, Boyer KM, Patel D, et al. Early and longitudinal evaluations of treated infants and children and untreated historical patients with congenital toxoplasmosis: the Chicago Collaborative Treatment Trial. *Clin Infect Dis*. 1994;18:38–72.
17. Phan L, Kasza K, Jalbrzikowski J, et al; Toxoplasmosis Study Group. Longitudinal study of new eye lesions in treated congenital toxoplasmosis. *Ophthalmology*. 2008;115:553–559.e8.
18. Alford CA Jr, Stagno S, Reynolds DW. Congenital toxoplasmosis: clinical, laboratory, and therapeutic considerations, with special reference to subclinical disease. *Bull N Y Acad Med*. 1974;50:160–181.
19. Wilson CB, Remington JS, Stagno S, et al. Development of adverse sequelae in children born with subclinical congenital Toxoplasma infection. *Pediatrics*. 1980;66:767–774.
20. Koppe JG, Loewer-Sieger DH, de Roever-Bonnet H. Results of 20-year follow-up of congenital toxoplasmosis. *Lancet*. 1986;1:254–256.
21. Peyron F, Garweg JG, Wallon M, et al. Long-term impact of treated congenital toxoplasmosis on quality of life and visual performance. *Pediatr Infect Dis J*. 2011;30:597–600.
22. Freeman K, Tan HK, Prusa A, et al; European Multicentre Study on Congenital Toxoplasmosis. Predictors of retinochoroiditis in children with congenital toxoplasmosis: European, prospective cohort study. *Pediatrics*. 2008;121:e1215–e1222.
23. Wallon M, Kodjikian L, Binquet C, et al. Long-term ocular prognosis in 327 children with congenital toxoplasmosis. *Pediatrics*. 2004;113:1567–1572.
24. Berrébi A, Assouline C, Bessières MH, et al. Long-term outcome of children with congenital toxoplasmosis. *Am J Obstet Gynecol*. 2010;203:552.e1–552.e6.
25. Faucher B, Garcia-Meric P, Franck J, et al. Long-term ocular outcome in congenital toxoplasmosis: a prospective cohort of treated children. *J Infect*. 2012;64:104–109.
26. Gómez Marín JE, Pinon JM, Bonhomme A, et al. Does human toxoplasmosis involve an imbalance in T1/T2 cytokines? *Med Hypotheses*. 1997;48:161–169.
27. Chapman DJ, Ashburn D, Ogston SA, et al. The relationship between ocular toxoplasmosis and levels of specific toxoplasma antibodies. *Epidemiol Infect*. 1999;122:299–303.
28. Binquet C, Wallon M, Quantin C, et al. Prognostic factors for the long-term development of ocular lesions in 327 children with congenital toxoplasmosis. *Epidemiol Infect*. 2003;131:1157–1168.
29. Holland GN. Ocular toxoplasmosis: the influence of patient age. *Mem Inst Oswaldo Cruz*. 2009;104:351–357.
30. Tan HK, Schmidt D, Stanford M, et al; European Multicentre Study on Congenital Toxoplasmosis (EMSCOT). Risk of visual impairment in children with congenital toxoplasmic retinochoroiditis. *Am J Ophthalmol*. 2007;144:648–653.
31. Kodjikian L, Wallon M, Fleury J, et al. Ocular manifestations in congenital toxoplasmosis. *Graefes Arch Clin Exp Ophthalmol*. 2006;244:14–21.
32. Phan L, Kasza K, Jalbrzikowski J, et al; Toxoplasmosis Study Group. Longitudinal study of new eye lesions in children with toxoplasmosis who were not treated during the first year of life. *Am J Ophthalmol*. 2008;146:375–384.
33. Olariu TR, Remington JS, McLeod R, et al. Severe congenital toxoplasmosis in the United States: clinical and serologic findings in untreated infants. *Pediatr Infect Dis J*. 2011;30:1056–1061.
34. Couvreur J, Desmonts G, Aron-Rosa D. Le prognostic oculaire de la toxoplasmose congénitale: rôle du traitement. *Ann Pediatr*. 1984;31:855–858.
35. Kieffer F, Wallon M, Garcia P, et al. Risk factors for retinochoroiditis during the first 2 years of life in infants with treated congenital toxoplasmosis. *Pediatr Infect Dis J*. 2008;27:27–32.
36. Melamed J, Eckert GU, Spadoni VS, et al. Ocular manifestations of congenital toxoplasmosis. *Eye (Lond)*. 2010;24:528–534.
37. Vasconcelos-Santos DV, Machado Azevedo DO, Campos WR, et al; UFMG Congenital Toxoplasmosis Brazilian Group. Congenital toxoplasmosis in southeastern Brazil: results of early ophthalmologic examination of a large cohort of neonates. *Ophthalmology*. 2009;116:2199–205.e1.
38. Carellos EVM, de Andrade JQ, Romanelli RMC, et al; UFMG Congenital Toxoplasmosis Brazilian Group (UFMG-CTBG). High frequency of bone marrow depression during congenital toxoplasmosis therapy in a cohort of children identified by neonatal screening in Minas Gerais, Brazil. *Pediatr Infect Dis J*. 2017;36:1169–1176.
39. Mets MB, Holfels E, Boyer KM, et al. Eye manifestations of congenital toxoplasmosis. *Am J Ophthalmol*. 1996;122:309–324.
40. Antunes-Foschini RMS, Ho W, Messias A. Eccentric fixation patterns, clinical findings, and reading speed in patients with bilateral toxoplasmic macular retinochoroiditis. *Arq Bras Oftalmol*. 2018;81:401–407.
41. Meenken C, Assies J, van Nieuwenhuizen O, et al. Long term ocular and neurological involvement in severe congenital toxoplasmosis. *Br J Ophthalmol*. 1995;79:581–584.
42. Silveira C, Vallochi AL, Rodrigues da Silva U, et al. Toxoplasma gondii in the peripheral blood of patients with acute and chronic toxoplasmosis. *Br J Ophthalmol*. 2011;95:396–400.
43. de-la-Torre A, Stanford M, Curi A, et al. Therapy for ocular toxoplasmosis. *Ocul Immunol Inflamm*. 2011;19:314–320.
44. Brézin AP, Thulliez P, Couvreur J, et al. Ophthalmic outcomes after prenatal and postnatal treatment of congenital toxoplasmosis. *Am J Ophthalmol*. 2003;135:779–784.
45. Alvarenga DP, Couto MF, Pessoa VF. Perceptual visual filling-in of toxoplasmic retinochoroiditis scotomas. *Neuroreport*. 2007;18:1679–1681.
46. Roizen N, Kasza K, Karrison T, et al. Impact of visual impairment on measures of cognitive function for children with congenital toxoplasmosis: implications for compensatory intervention strategies. *Pediatrics*. 2006;118:e379–e390.
47. Stanford MR, Tomlin EA, Comyn O, et al. The visual field in toxoplasmic retinochoroiditis. *Br J Ophthalmol*. 2005;89:812–814.
48. Scherrer J, Iliev ME, Halberstadt M, et al. Visual function in human ocular toxoplasmosis. *Br J Ophthalmol*. 2007;91:233–236.
49. Thiébaut R, Leproust S, Chene G, et al; The SYROCOT Study Group. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data. *Lancet*. 2007;369:115–122.
50. Cortina-Borja M, Tan HK, Wallon M, et al; European Multicentre Study on Congenital Toxoplasmosis (EMSCOT). Prenatal treatment for serious neurological sequelae of congenital toxoplasmosis: an observational prospective cohort study. *PLoS Med*. 2010;7:e1000351.
51. Peyron F, Lobry JR, Musset K, et al. Serotyping of Toxoplasma gondii in chronically infected pregnant women: predominance of type II in Europe and types I and III in Colombia (South America). *Microbes Infect*. 2006;8:2333–2340.
52. Carneiro AC, Andrade GM, Costa JG, et al. Genetic characterization of Toxoplasma gondii revealed highly diverse genotypes for isolates from newborns with congenital toxoplasmosis in southeastern Brazil. *J Clin Microbiol*. 2013;51:901–907.
53. Ajzenberg D. 1995-2015: it is time to celebrate 20 years of (intensive) genotyping of Toxoplasma gondii strains. *Future Microbiol*. 2015;10:689–691.
54. Shwab EK, Saraf P, Zhu XQ, et al. Human impact on the diversity and virulence of the ubiquitous zoonotic parasite Toxoplasma gondii. *Proc Natl Acad Sci U S A*. 2018;115:E6956–E6963.