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ORIGINAL ARTICLE

Regional Differences in the Clinical Manifestation of Ocular Toxoplasmosis between the Center and Northeast of Argentina

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ABSTRACT

Purpose: To compare the clinical characteristics of patients with active episodes of ocular toxoplasmosis from three provinces, Misiones, Santa Fe, and Buenos Aires, Argentina.

Methods: Patients with a diagnosis of ocular toxoplasmosis from three databases of four tertiary referral uveitis centers were reviewed. Collected data included presentation of the retinochoroiditis, location of the active lesions, associated inflammatory ocular signs and complications.

Results: Three hundred thirty-four patients were included in this study. Bilateral involvement of the ocular disease occurred in 26 patients in Misiones (35.14%), 21 patients (12.8%) in Santa Fe, and 9 patients in Buenos Aires (9.4%) ($p < 0.001$). Extensive retinitis was observed in 49 patients (66.2%) in Misiones, 39 patients (23.8%) in Santa Fe, and 12 patients (12.5%) in Buenos Aires ($p < 0.001$).

Conclusion: The results indicate that there are differences in the clinical characteristics of ocular toxoplasmosis in patients from Misiones, Santa Fe, and Buenos Aires.

Keywords: Clinical manifestations, ocular toxoplasmosis, posterior uveitis, retinitis

Toxoplasmosis is one of the most extended and prevalent zoonoses worldwide.[1] In the immunocompetent human being, the ocular involvement predominates among its clinical manifestations. [2] Ocular toxoplasmosis is the most frequent posterior uveitis.[2] Focal retinitis is usually the typical lesion that characterizes this ocular inflammatory entity.[2]

Clinical features of ocular toxoplasmosis seem to differ from one region to another.[3–5] The reason for this may be due to the genotype of the parasite as well as the dietary habits, socioeconomic conditions, and genetic predisposition of the affected individuals.[6–8] The age and immunological status of the patient may also influence the severity of the ocular disease.[2,8]

To our knowledge, there are three studies that report patients with toxoplasmosis in Argentina, all of which show data from the northeast part of the Mesopotamia region, which is the most northeastern

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part of the country.[9–11] A high prevalence (20%) of toxoplasmic retinochoroidal scars was observed in the mideastern region of the province of Misiones, comparable to what was seen in the southern region of Brazil.[10] In addition, a brief report from this location presented findings of bilateral active toxoplasmic retinochoroidal lesions in four immunocompetent patients.[11] In the region of Misiones, it was established that there is an association between the frequency of toxoplasmic reactivation and the intensity and duration of the rainfall periods.[9] The purpose of the current study was to assess the clinical manifestations of ocular toxoplasmosis in Argentina by comparing clinical findings in patients from three different Argentine provinces: two from the mideastern part of the country (Santa Fe and Buenos Aires) and one from the northeastern region (Misiones), respectively.

MATERIALS AND METHODS

Three databases from four tertiary referral uveitis centers were reviewed: Consultorio de Uveítis y Glaucoma, Oberá, from April 1, 2009, to May 31, 2014 ("Misiones"), Oftalmología Global Rosario from January 1, 2011, to June 31, 2015 ("Santa Fe"), University of Buenos Aires and Austral University January 1, 2011, to August 31, 2015 ("Buenos Aires").

This study adhered to the tenets of the Declaration of Helsinki. Approval of the Institutional Review Board was obtained from each center as a retrospective study.

Those patients with a diagnosis of ocular toxoplasmosis who had complete clinical data of at least one episode of active retinitis were included. The last episode of active retinitis of each patient (in cases wherein the patient had recorded more than one) was assessed for comparison. The four tertiary referral uveitis centers treat every episode of active ocular toxoplasmosis with antiparasitic therapy according to the clinical criteria of the treating physician.

Active ocular toxoplasmosis was defined as (1) the presence of a lesion of retinochoroiditis, associated or not to a previous retinochoroidal scar, with presence of serum antibodies against *Toxoplasma gondii*; or (2) positive polymerase chain reaction findings for toxoplasma deoxyribonucleic acid in the aqueous humor.[2,12] Retinochoroiditis was defined as the presence of a yellow-white lesion with indistinct borders, accompanied by vitreous inflammatory cells.[2] Those patients without complete clinical data of an episode of active ocular toxoplasmosis and/or those with an equivocal diagnosis according to the clinical data were excluded from the present study.

Collected data from clinical records included best-corrected visual acuity findings at presentation and at the end of the active episode, chronic or acute infection, acquisition of the infection (acquired, congenital, or undetermined), primary or recurrent retinal lesion, typical or atypical retinal lesion, presentation of active retinochoroiditis (focal, multifocal, extensive, bilateral, neuroretinitis), location of the active lesion (posterior pole, juxtapapillary, peripheral), associated ocular signs at the beginning of the active episode, complications, time of duration of the active episode, and number of recurrences.

Acute infection was defined as the presence of positive immunoglobulin (Ig)M antibodies for toxoplasma in the serum. [12] Chronic infection was defined as the presence of positive IgG antibodies with negative IgM antibodies for toxoplasma in the serum.[12]

Acquisition of the infection was regarded as congenital when a positive IgM antibody was detected in an infant, a history of maternal seroconversion for toxoplasma was recorded during pregnancy, or toxoplasmic retinochoroidal lesions were detected before the age of 2 years.[12,13] Acquisition of the infection was considered as acquired if the patient had positive IgM antibodies for toxoplasma.[12,13] Lastly, acquisition of the infection was regarded as undetermined when the patient did not satisfy the criteria for either acquired or congenital toxoplasmosis.[12,13]

Time of duration of the active episode was measured from the initial visit for the active episode until the visit at which the retinochoroidal lesions were regarded to be inactive. Retinochoroidal lesions were considered inactive when their borders become discrete and retinochoroidal atrophy and/or pigmentation occurred.[2]

Primary ocular toxoplasmosis was defined as an active retinitis lesion in the absence of a previous retinochoroidal scar in either eye.[12] Recurrent ocular toxoplasmosis was defined as an active retinitis lesion associated with a previous retinochoroidal scar in either eye.[12]

Neuroretinitis was defined as the inflammation of the optic disk, associated with a stellate macular exudation, and with juxtapapillary active retinitis.[14,15]

Extensive retinochoroiditis was defined as an active retinal lesion with an extension greater than three disk areas.[12] Bilateral retinochoroiditis was defined as the presence of active retinal lesions in both eyes at the same time.[2]

The typical presentation of ocular toxoplasmosis is a focal active retinochoroiditis, with an extension of less than three disk areas that is associated with a previous scar.[2] Atypical presentation of ocular toxoplasmosis was defined according to the features described by Smith et al.[2]

Regarding laterality, unilateral ocular toxoplasmosis was defined as the presence of an active retinitis lesion and/or retinochoroidal scars in only one eye. Bilateral ocular toxoplasmosis includes in its definition both cases with bilateral activity and cases with bilateral involvement but with unilateral activity.

The recorded associated ocular signs in the involved patients included anterior chamber inflammatory cells,

presence and type of keratic precipitates, iris nodules, ocular hypertension at presentation of the active episode, vitreous haze, retinal vasculitis, papillitis, and serous detachment of the neurosensory retina. Term definitions of the ocular inflammatory signs were in agreement with those established by the Standardization of Uveitis Nomenclature Working Group.[16]

Consigned ocular complications at the end of the active episode included macular edema, epiretinal membrane, choroidal neovascularization, macular hole, macular ischemia, tractional, rhegmatogenous, exudative retinal detachment, choroidal detachment, optic atrophy, ocular hypertension, glaucoma, cataract, phthisis bulbi, posterior synechia, branch venous occlusion, and branch arterial occlusion.

Ocular hypertension was defined as an intraocular pressure greater than 21 mmHg, measured with Goldmann tonometry. Ocular hypertension secondary to a permanent structural damage caused by the uveitis or originated by corticosteroid treatment was included within complications.

Glaucoma was defined by the presence of ocular hypertension associated with visual field defects or by the presence of a reduced thickness of the retinal nerve fiber layer measured by optical coherence tomography.

Definitions were discussed between all the authors of this study in order to exclude misunderstandings previous to the statistical analysis.

To compare proportions, Fisher's exact test or χ^2 were used as needed. When comparing visual outcomes, the right eye was chosen in case of bilateral active retinochoroiditis. To compare numerical variables, analysis of variance (ANOVA) or Student's t test were used as appropriate. A multinomial logistic regression analysis was used to assess relationships between several variables. p values were calculated for every analysis and $p < 0.05$ was considered significant. Statistical analysis was done with SPSS software version 15.0 (SPSS, Inc, Chicago, IL).

RESULTS

Three hundred thirty-four patients were included (159 female and 175 male); of these, 74 were from Misiones (40 female and 34 male), 164 were from Santa Fe (64 female and 100 male), and 96 were from Buenos Aires (55 female and 41 male). No patient was excluded from the analysis. The proportions of gender were different in the three provinces ($p < 0.01$). The average age and the proportion of patients with documented acquired infection showed no statistically significant differences upon comparing among the three provinces (Table 1). There was a difference in the proportion of patients with documented congenital infection ($p < 0.001$) (Table 1). Bilateral involvement of disease was different among the three provinces (χ^2 test; $p < 0.001$) (Table 1).

There was no difference in the proportion of immunocompetent patients ($p = 0.08$) (Table 1). Also, 8 patients were treated with immunosuppressive therapy (5 from Santa Fe and 3 from Buenos Aires); 10 patients had malignancies (3 from Misiones, 6 from Santa Fe, and 1 from Buenos Aires); 6 patients had diabetes (3 from Misiones and 3 from Santa Fe); 60 patients had an age >50 years (10 from Misiones, 34 from Santa Fe, and 16 from Buenos Aires); and 17 patients had HIV infection (16 from Santa Fe and 1 from Buenos Aires, $p < 0.001$). More than one cause of immunodeficiency coexisted in some patients.

Primary lesion occurrence differed when comparing the three provinces (χ^2 test; $p < 0.001$). Duration of the episode was unknown in 3 of the 96 patients from Buenos Aires and in 16 of the 164 patients from Santa Fe, but in none of the 74 patients from Misiones. The means of episode duration for the three provinces were different ($p < 0.001$) (Table 1).

Regarding the type of presentation, the proportion of patients with atypical lesions as well as focal, extensive, multifocal, and bilateral active retinochoroiditis showed a difference between the three provinces (Table 1). However, the occurrence of neuroretinitis was not different among the three regions (Table 1). In some cases, the patient had more than one type of coexisting presentation (e.g., focal and neuroretinitis; bilateral, extensive, and multifocal retinochoroiditis) (Table 1).

Regarding the location of the active lesion (Table 1), posterior pole and peripheral involvement showed no differences between the three provinces. Notwithstanding, juxtapapillary involvement occurrence was dissimilar between the three regions. In some cases, the lesions involved more than one location, particularly in patients with extensive and multifocal lesions (Table 1).

There was a difference in the proportion of patients with present anterior chamber cells between the three provinces. The occurrence of 2+ anterior chamber cells, ocular hypertension at presentation, keratic precipitates, iris nodules, retinal vasculitis, serous detachment of the neurosensory retina, and vitreous haze ≥2+ showed differences between the three groups (Table 2).

Best-corrected visual acuity at the end of the episode was <20/60 in 23% of the eyes from Misiones, in 25.6% of the eyes from Santa Fe, and in 21.9% of the eyes from Buenos Aires, respectively (χ^2 test; $p = 0.77$) (Table 2).

Complications were observed in 34 patients from Misiones (41.9%), in 78 patients from Santa Fe (47.6%), and in 41 patients (42.7%) from Buenos Aires (χ^2 test; $p = 0.64$).

Details of the total observed complications in each of the three patient samples can be seen in Table 3.

TABLE 1. Demographics characteristics and clinical data of patients with ocular toxoplasmosis of the total sample of patients, and comparison between the three provinces.

	Total (n = 334)	Misiones (n = 74)	Santa Fe (n = 164)	Buenos Aires (n = 96)	p Value
Female gender, n (%)	159 (47.6)	40 (54.05)	64 (39.02)	55 (57.29)	0.008[a]
Age, mean ± SD (years)	33.7 ± 17.5	32.9 ± 16.9	32.1 ± 16	33.6 ± 17.4	0.92[b]
Duration of episodes, mean ± SD (weeks)[d]	6.6 ± 5.6	10 ± 6.4	5.35 ± 3.5	7.1 ± 3.84	< 0.001[b]
Acquired infection, n (%)	33 (9.9)	5 (6.8)	22 (13.4)	6 (6.25)	0.10[a]
Congenital infection, n (%)	18 (5.4)	11 (14.8)	2 (1.2)	5 (5.2)	< 0.001[c]
Bilaterality, n (%)	56 (16.8)	26 (35.1)	20 (12.1)	9 (9.4)	< 0.001[a]
Primary lesions, n (%)	130 (38.9)	10 (13.5)	87 (53)	33 (34.4)	< 0.001[a]
Recurrent lesions, n (%)	204 (61.1)	64 (86.5)	77 (47)	63 (65.6)	< 0.001[a]
Immunocompetent patients, n (%)	254 (76)	60 (81.1)	116 (70.7)	78 (81.3)	0.08[a]
HIV+	17 (5.1)	–	16 (9.76)	1 (1)	< 0.001[c]
Atypical lesions, n (%)	166 (49.7)	56 (75.7)	85 (51.8)	24 (25)	< 0.001[a]
Focal lesions, n (%)	200 (59.9)	19 (25.7)	106 (64.6)	75 (78)	< 0.001[a]
Extensive lesions, n (%)	100 (29.9)	49 (66.2)	39 (23.8)	12 (12.5)	< 0.001[a]
Multifocal lesions, n (%)	64 (19.2)	31 (41.9)	22 (13.4)	11 (11.4)	< 0.001[a]
Bilateral lesions, n (%)	9 (2.69)	7 (9.5)	2 (1.2)	–	0.001[c]
Neuroretinitis, n (%)	9 (2.69)	3 (4.1)	5 (3)	1 (1)	0.405[c]
Macular location, n (%)	107 (32)	30 (40.5)	47 (28.7)	30 (31.3)	0.19[a]
Juxtapapillary location, n (%)	60 (18)	24 (32.4)	25 (15.2)	11 (11.5)	0.001[a]
Peripheral location, n (%)	224 (67.1)	55 (74.3)	107 (65.2)	62 (64.6)	0.32[a]

[a]χ^2 test.
[b]One-way ANOVA.
[c]Fisher's exact test.
[d]Duration of the episode is unknown for 19 cases: 16 from Santa Fe and 3 from Buenos Aires.

TABLE 2. Associated ocular signs at presentation of the total number of patients, and comparison between the three provinces.

	Total (n = 334) n (%)	Misiones (n = 74) n (%)	Santa Fe (n = 164) n (%)	Buenos Aires (n = 96) n (%)	p Value
≥0.5+ anterior chamber cell	283 (84.7)	70 (94.6)	138 (84.1)	75 (78.1)	0.012[a]
≥2+ anterior chamber cell	113 (33.8)	28 (37.8)	51 (31.1)	50 (52.4)	0.004[a]
Hypertension	76 (22.8)	26 (35.1)	22 (13.4)	28 (29.2)	<0.001[a]
Keratic precipitates	220 (65.9)	54 (73)	118 (72)	48 (50)	0.001[a]
Iris nodules	28 (8.4)	16 (21.6)	3 (1.8)	9 (9.4)	<0.001[b]
Retinal vasculitis	170 (50.9)	30 (40.5)	105 (64)	35 (36.5)	<0.001[a]
Serous neuroepithelial detachment	50 (15)	4 (5.4)	18 (9.4)	28 (29.2)	<0.02[b]
Papillitis	121 (36.2)	54 (73)	53 (32.3)	14 (14.6)	<0.001[a]
≥2+ vitreous haze	196 (58.7)	59 (79.7)	84 (51.2)	53 (55.2)	<0.001[a]
Initial BCVA ≤ 20/60	156 (46.7)	37 (50)	68 (41.5)	51 (53.1)	0.16[a]
Final BCVA ≤ 20/60	80 (23.9)	17 (23)	42 (25.6)	21 (21.9)	0.77[a]

[a]χ^2 test.
[b]Fisher's exact test.

When assessing the three groups together, an association was observed between the presence of 2+ or more anterior chamber cells and ocular hypertension at presentation (χ^2 test; $p < 0.001$).

Regarding the whole sample, an association was found between the presence of extensive retinochoroiditis lesions and a duration ≥10 weeks (χ^2 test; $p < 0.001$). In addition, an association was found between the presence of extensive retinochoroiditis and an age of 50 years or more (χ^2 test; $p < 0.001$). An association between the presence of cells and extensive lesions was also found (χ^2 test; $p < 0.001$). Moreover, there was an association between the presence of extensive lesions and the presence of vitreous haze ≥2+ (χ^2 test; $p < 0.001$). An association was also found between the location of the lesions in the periphery and the presence of vitreous haze ≥ 2+ ($p < 0.001$). The association between posterior pole location and a presence of vitreous haze ≥2+ was also studied; however, an association was not found (χ^2 test; $p = 0.28$).

TABLE 3. Ocular complications of the total number of patients, and comparison between the three provinces.

	Total (n = 334) n (%)	Misiones (n = 74) n (%)	Santa Fe (n = 164) n (%)	Buenos Aires (n = 96) n (%)
Macular edema	42 (12.5)	9 (12.2)	26 (15.9)	7 (7.3)
Epiretinal membrane	62 (18.6)	8 (10.8)	42 (25.6)	12 (12.5)
Choroidal neovascularization	8 (2.4)	0	8 (4.9)	0
Macular hole	1 (0.3)	0	1 (0.6)	0
Macular ischemia	2 (0.6)	0	1 (0.6)	1 (1)
Tractional retinal detachment	6 (1.8)	0	3 (1.8)	3 (3.1)
Rhegmatogenous retinal detachment	14 (4.2)	0	11 (6.7)	3 (3.1)
Exudative retinal detachment	4 (1.2)	0	3 (1.8)	1 (1)
Choroidal detachment	1 (0.3)	0	0	1 (1)
Optic nerve atrophy	6 (1.8)	0	5 (3)	1 (1)
Ocular hypertension	10 (3)	4 (5.4)	1 (0.6)	5 (5.2)
Glaucoma	9 (2.7)	4 (5.4)	4 (2.4)	1 (1)
Cataract	20 (6)	7 (9.4)	8 (4.9)	5 (5.2)
Phthisis bulbi	1 (0.3)	0	0	1 (1)
Posterior synechia	12 (3.6)	2 (2.7)	6 (3.7)	4 (4.2)
Branch retinal vein occlusion	3 (0.9)	2 (2.7)	0	1 (1)
Branch retinal artery occlusion	3 (0.9)	0	2 (1.2)	1 (1)
Subretinal fibrosis	7 (2.1)	3 (4.1)	4 (2.4)	0
Nistagmus	4 (1.2)	3 (4.1)	1 (0.6)	0
Retinal tear	9 (2.7)	1 (1.4)	7 (4.3)	1 (1)

In multinomial logistic regression analysis, associations were found between the presence of vitreous haze ≥2+ and peripheral location, extensive lesions, and duration of the episode ≥10 weeks of retinal lesion presence. However, age equal to 50 years or more was not associated with vitreous haze ≥2+ (Table 4).

DISCUSSION

This study presents data related to the clinical characteristics of ocular toxoplasmosis in patients from three different locations in Argentina. The three samples had neither a significant difference in patient age nor a significant difference in the prevalence of immunocompromised patients, which could affect the clinical features of this ocular ailment. The proportion of cases with congenital origin was shown to have statistically significant differences between the three provinces. Notwithstanding, the number of congenital cases in the whole sample was low, and this finding was considered of little influence in the comparison of clinical features between the three groups.

In spite of the fact that there was no significant difference in the proportion of immunocompetent patients between the three provinces, the number of patients with HIV infection was higher in the group from the province of Santa Fe. Notwithstanding, the number of HIV-positive patients in the total patient cohort was low, and it was considered of little influence in the comparison between the three groups.

Bosch-Driessen et al. found bilateral involvement of ocular toxoplasmosis in 32% of their patients, with 8% being congenital cases.[12] In the current study, bilateral involvement occurred in 16.8% of our 334 total patients, though the group from Misiones had a proportion of bilateral occurrence of the disease that was closer to that seen in the Dutch series (35.1%). In Misiones, there was a prevalence of 14.8% being congenital cases, which may explain the similarity of the proportion of cases between this group and the series studied by Bosch-Driessen et al.[12] Moreover, bilateral active retinochoroiditis in immunocompetent patients from Misiones is not unusual and points out the retinal tropism of the infecting *T. gondii* strains present in this humid subtropical region of Argentina.[11] Interestingly, a cross-sectional study comparing the clinical characteristics between Colombian and French patients with ocular toxoplasmosis showed that bilateral involvement of the disease was significantly more prevalent in the first group.[5]

It is noteworthy that significant differences between the three locations were observable with respect to the prevalence of atypical lesions, the presentation of active lesions, and the presence of vitreous haze ≥2+. A greater frequency of extensive, bilateral, or multifocal lesions in the Misiones patient group suggests a greater aggressiveness of the clinical picture, which may be understood as a more extensive invasion and higher parasitic proliferation.[5] Additionally, a greater prevalence of patients with significant vitritis and a larger mean duration of the episodes in this location, as we have shown in the statistical analysis, may be related to a more frequent occurrence of aggressive cases. Notably, those variables were not influenced by the presence or absence of treatment because all the patients were treated with antiparasitic therapy.

TABLE 4. Relationships between vitreous haze ≥2+ at baseline examination of the active episode and characteristics of the lesions, duration of the episode, and patients age for the whole sample.

	Odds ratio	95% CI	Significance
Age 50 years or older	0.715	0.358–1.428	0.342
Extensive lesions	5.569	2.866–10.823	<0.001
Peripheral lesions	2.323	1.372–3.934	0.002
Duration of the episode ≥ 10 weeks	2.435	1.011–5.866	0.047

CI: confidence interval.

Associations between variables were assessed by means of multinomial logistic regression analysis.

Interestingly, differences in the clinical manifestations between the three patient groups had little influence on the location of retinal lesions. There was no significant variation between the three patient groups in terms of lesion location except with regards to the juxtapapillary location, which was more frequently seen in patients from Misiones. In the comparative Colombian–French study mentioned above, the macular location of the lesions was significantly more prevalent in Colombian patients.[5] In the present study, in spite of the fact that the macular location was more frequently seen in patients from Misiones, this difference did not reach statistical significance.

A higher prevalence of patients with 1+ or more anterior chamber cells in Misiones was also observed, which can be linked to the demonstration in this study of a statistically significant association between the presence of 1+ or more anterior chamber cells and the observation of extensive retinitis lesions. An association between 1+ anterior chamber cells and extensive retinal lesions has also been shown by other authors.[3]

Differences in the clinical characteristics of ocular toxoplasmosis between the three geographic locations had no impact on the visual outcomes of each of the three series. The difference in the rate of a final best-corrected visual acuity of <20/60 between the three locations was not statistically significant. Furthermore, there were no statistically significant differences in the number of patients with ocular complications due to active episodes between the three locations. The latter finding may explain in part why we did not find significant differences in visual outcomes. It would be important to assess whether this fact would change or not when studying larger samples.

Regional differences in the clinical manifestations of ocular toxoplasmosis between the three provinces may be multifactorial in origin, comprising eating habits, sources of infection, and parasite genotypes as well as ethnic, social, geographic, and climatic causes.

In a study that assessed the relationship between the reactivation of ocular toxoplasmosis and patient ethnicity in Misiones, Rudzinski et al. showed that Germanic and Slavic patients had a higher risk for reactivation than did Hispanics.[17] Hispanic migration to Argentina started in the 16th century and continued until the first half of the 20th century.[17] Admixture events between Hispanics and Native Americans occurred during this period at such a level that Argentine individuals who have Spanish surnames can carry as much as 80% Native American genetic ancestry.[17] Although there is no accurate data about the proportion of German or Slavic descendants in the populations of Misiones, Santa Fe, and Buenos Aires, it is known that an important part of the population from Misiones is descended from Slavic or German immigrants who arrived in the first half of the 20th century.[17] Regarding this data, Rudzinski et al. hypothesize that European individuals are poorly adapted to the atypical strains found in Misiones and so for that reason are more susceptible to ocular toxoplasmosis.[17] Notably, the aboriginal populations of the three provinces considered in the present study differ somewhat: 1.2% of Misiones' population is of aboriginal origin, while 1.5% of Santa Fe's population and 2% of Buenos Aires' population are of aboriginal origin, respectively.[18] The different composition of the population between the three locations may have had an impact on the susceptibility of suffering ocular involvement.

There are some social differences between the patients of Misiones, Santa Fe, and Buenos Aires. Based on data of the National Statistical Institute of Argentina, a significant part of the population from Misiones are rural dwellers (26.24%), while most of the patients from Buenos Aires live and work in cities (only 2.78% are rural dwellers).[18] Moreover, based on questionnaire data, 67.85% of the patients attending the ophthalmological center in Misiones live or had live in rural areas.[17] In Santa Fe, the situation is in between those of Misiones and Buenos Aires: 9.14% of the population lives in rural areas.[18] Rural dwellers have a higher prevalence of ocular toxoplasmosis, likely related to more frequent contact with sources of infection, mainly with oocysts in soil[19] or water.[20]

An eating habit that is common in patients from Misiones is the consumption of homemade raw or poorly cooked meat sausages, a common German and Eastern European tradition.[10] This habit was considered in several studies as a risk factor for *T. gondii* transmission.[10,19,21] Untreated water is another reported source of toxoplasmic infection both in Buenos Aires[22] and in Misiones.[10] In spite of the fact that social factors, eating habits, and sources of infection are primarily associated with the risk of occurrence of toxoplasmosis, the difference in clinical manifestations between the regions of Argentina

included in the current study may also be related to local variations in these parameters.

Misiones borders the Brazilian states of Parana and Rio Grande do Sul. The greater severity of the clinical manifestations of ocular toxoplasmosis in Brazil compared with in other regions in the world has been demonstrated by Dodds et al.[3] Predominant toxoplasma genotypes found in Brazil have also been shown to be different from other geographic regions.[23,24] This has also been noted in studies carried out with strains of toxoplasma from Colombia.[5] In both regions, greater predominances of atypical strains and, to a lesser extent, of genotype I of this parasite, were revealed.[5,23] In a recent study conducted in Misiones, *T. gondii* was isolated via the inoculation of mice with samples from the brains of chickens belonging to farms of patients with toxoplasmic retinochoroidal lesions. The parasites obtained from these mice were genotyped, being observed in all of these samples as atypical or noncanonical markers with alleles III and I.[25] The strains found in this study had similarities with strains from Brazil. The isolated strain TgCK11-9 from two different and distant farms in the mideastern region of Misiones[25] is similar to the isolated strain TgCKBrPr#5 from Paraná.[26] That strain is similar to the Toxoplasma Genomics Resource database genotype #19.[25] In Misiones, other two isolated strains from free-range chickens were found to be similar to the Toxoplasma Genomics Resource database genotypes #116 and #14/138,[25] not reported in the isolations from Vieira et al.,[26] but isolated from free-range chickens from Brazil.[27] Potentially, all of these isolated parasites may be involved in the severe cases of ocular toxoplasmosis reported in Misiones.[10] These genotypes contrast with those observed in sentinel and free-range chickens from the province of Buenos Aires, where different combinations of alleles and/or the clonal type II were observed.[25,28] Clonal type II is found principally in Europe and the United States, where the clinical manifestations of ocular toxoplasmosis are less severe.[29] Clinical manifestations in ocular toxoplasmosis are also typically less severe in Buenos Aires as was shown in the present study. Therefore, it is reasonable to suspect that these isolated parasites found in Buenos Aires may cause this less severe ocular disease in this location. Genotyping of the infecting parasites in our patients is lacking. Notwithstanding, these observations about the genotypes in these different regions of Argentina are in correlation with the differences observed in the clinical characteristics of ocular toxoplasmosis in Misiones and Buenos Aires.

Misiones, Santa Fe, and Buenos Aires are connected by the Parana River, which runs from north to south along a path of about 1200 km to Buenos Aires. Misiones, which geologically belongs to the Brazilian Massif, has a subtropical climate without a dry season, with a mean annual temperature of 22°C, and an average precipitation of 1867 mm per year recorded in a period between 1981 and 2010.[30] Approximately 45% of its surface is covered by remnants of the Parana Subtropical or Atlantic Forest.[25] Buenos Aires is located in the central region of Argentina in the Pampas lowlands without forest and with template temperatures (mean annual temperature of 18°C), with annual precipitations of an average of 1233 mm recorded in a period between 1981 and 2010.[30] Santa Fe, also in the Pampas region, due to its latitudinal location between Buenos Aires and Misiones, has a template climate with significant influence of subtropical rains.[31] Lelu et al. showed that, in soil with higher humidity, such as in the rainforests, the survival rate of toxoplasma cysts is higher.[32] In addition, Dubey suggested that toxoplasma oocysts have prolonged survival in mild temperatures.[33] Therefore, of the three locations, Misiones has particularly ideal conditions for oocyst survival and potential infectivity.[32,33] Interestingly, in the province of Santa Fe, which is located north of Buenos Aires, clinical manifestations of the patients studied herein had some characteristics similar to those of the Buenos Aires group and some characteristics similar to those of the Misiones group.

Several studies have shown that elderly patients have extensive retinochoroidal lesions more frequently than younger patients.[3,34,35] When studying the total number of patients from the three samples, a statistically significant association was shown between an age ≥50 years and the occurrence of extensive retinitis. It has been suggested that the decline of the T cell-mediated immune response, as well as nutritional deficiencies, may at least partially explain this fact.[2]

In this study, a relation was found between the severity of the anterior segment inflammation and ocular hypertension at the time of presentation of the active episode. This association was also described in other series.[3] Westfall et al. found a trend associating anterior chamber cells and elevated intraocular pressure, albeit one that was statistically nonsignificant.[36] It is likely that a higher number of anterior chamber cells may be associated with the involvement of other anterior segment structures, such as the trabecular meshwork. The latter has an inflammatory involvement in other hypertensive uveitis conditions including Posner–Schlossman syndrome and herpetic anterior uveitis, among others.[37]

In another study, a statistically significant association was found between a higher level of vitreous haze and peripheral lesions.[3] We observed the same association, even following adjustment for extensive lesions by means of logistic regression.

Limitations of the present study include its retrospective nature and the fact that we did not collect the complete time of follow-up of every patient but rather only the duration of the active episode of the ocular disease. However, we assessed only one episode in every patient, and for the aim of the study, this information was not considered to be relevant. Another

limitation is that we only gathered information from the mideastern and the northeastern regions of the country. Therefore, it is not known what the clinical manifestations of the disease are in the northwestern, midwestern, and southern regions of the territory, and this dearth of information restricts the perspective of what is happening in the whole country.

In conclusion, data from our results indicate that there are statistically significant differences in the clinical manifestations of ocular toxoplasmosis between the provinces of Misiones, Santa Fe, and Buenos Aires. It may be possible that geographic and climatic regional differences as well as dissimilarities in social composition, eating habits, sources of infection, and parasite genotypes have some effect on the observed regional variations in the clinical manifestation of ocular toxoplasmosis.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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