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INFLAMMATORY DISORDERS

Monitoring of visual field over 6 months after active ocular toxoplasmosis

J. Blot[1,2] · F. Aptel[1,2,3] · B. F. F. Chumpitazi[4,5] · P. Gain[6] · C. Vasseneix[7] · O. Savy[8] · L. Bouillet[9,10] · H. Pelloux[4,5] · Christophe Chiquet[1,2,3]

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Abstract

Purpose To prospectively report the perimetric defects during a 6-month follow-up (FU) in patients with initially active ocular toxoplasmosis (OT).

Methods Twenty-four patients were studied, including 11 eyes with chorioretinal toxoplasmosis proven with a positive aqueous humor sample and 13 eyes with a biologically unproven, chorioretinal lesion. Automated 24-2 SITA-Standard visual fields were performed at baseline, at the first, and sixth months of FU. A composite clinical severity score was calculated from visual acuity (VA), severity of vitreitis, chorioretinal lesion size, location of the lesion in zone 1, the presence of an initial macular or papillary edema, and long-term scarring. This provided a relative cutoff level of severity. Nine eyes out of the 24 eyes were considered severe (3 unproven and 6 proven OT).

Results Initial and final visual field parameters (mean deviation [MD] and pattern standard deviation [PSD]) were significantly correlated ($r = 0.873$; $p < 0.001$, and $r = 0.890$; $p < 0.001$, respectively). During FU, only foveal threshold [FT] was correlated with VA at baseline ($r = 0.48$; $p = 0.01$) and at the 6-month FU visit ($r = 0.547$; $p = 0.004$). The MD initial predictive value of clinical severity was 0.739 according to the ROC curve. At baseline, severe and nonsevere OT exhibited no significant difference in term of MD ($p = 0.06$) and PSD ($p = 0.1$). During the FU, taking into account all the data, MD, PSD, visual function index [VFI], and FT were associated with the severity of toxoplasmosis ($p = 0.018$, 0.05, 0.016, and 0.02, respectively): the unproven group had a faster recovery of MD during FU ($p = 0.05$).

Conclusion Visual field parameters better reflected the chorioretinal destruction related to the toxoplasmosis lesion and the functional repercussions than VA alone. Interestingly, MD at presentation could be a discriminating factor of severity in active OT, and each visual field parameter follow-up could be a support to manage patients with active OT, especially in the severe group.

Keywords Ocular toxoplasmosis · Visual acuity · Scotoma · Visual field

✉ Christophe Chiquet
christophe.chiquet@inserm.fr

[1] Department of Ophthalmology, University Hospital of Grenoble, Grenoble Alpes University, Cs10217, 38043 Grenoble cedex 09, France

[2] Grenoble Alpes University, F-38041 Grenoble, France

[3] INSERM U1042 Lab Hypoxia and Physiopathology HP2, Grenoble, France

[4] Department of Parasitology, University Hospital, Grenoble, France

[5] INSERM U1209 Institute for Advanced Biosciences UMR CNRS-UGA 5309, Grenoble, France

[6] Department of Ophthalmology, University Hospital, Saint Etienne, France

[7] Department of Ophthalmology, General Hospital, Valence, France

[8] Department of Ophthalmology, General Hospital, Chambéry, France

[9] Department of Internal Medicine, University Hospital, Grenoble, France

[10] INSERM-UGA-CEA-CNRS U1036 Institute for Biosciences, Grenoble, France

Introduction

Ocular toxoplasmosis (OT) is a frequent infectious disease caused by an intracellular protozoan parasite, *Toxoplasma gondii* (*T. gondii*), which infects one-third of the world's population [1–3]. Toxoplasmic retinochoroiditis is the commonest form of posterior uveitis in immunocompetent patients and can lead to severe visual deficiency, accepted as a cause of legal blindness worldwide [4–6].

Visual field defects, or scotomas, are frequent in toxoplasmic retinochoroiditis and are explained by loss of retinal nerve fibers resulting from a transmural destruction of tissue in OT [7] and/or the retinal scar (with retinal atrophy associated with some degree of retinal pigment hyperplasia/hypertrophy) following the focus of active retinitis [8]. Other causes of visual loss are the severity of vitreitis and retinal vasculitis (sometimes with retinal ischemia) and occurrence of complications (cataract, macular edema, serous retinal detachment, epiretinal membranes, retinal detachment, persistent vitreous opacities, choroidal neovascularization, optic disc atrophy). Therefore, in most patients, measurement of visual acuity (VA) may not reflect the seriousness and its functional consequences of OT after recovery of inflammation and infection.

A few previous publications, mostly from transversal studies, reported the perimetric involvements of OT [9–12]. These studies showed that considerable visual field losses were associated with chorioretinal scars close to the optic nerve [9, 11], and moderate to severe functional impairment was noted in 65% of patients compared to 27% for VA [12]. At this time, the monitoring of consecutive visual fields after the acute phase of OT has not been explored. A longitudinal study may help to describe the course of visual field changes under treatment, and to identify potential prognostic factors which may have an impact on visual field (VF) changes.

The aim of this prospective longitudinal study was to report visual field monitoring during a 6-month follow-up in patients with initially active OT.

Materials and methods

This prospective study was conducted in accordance with the ethical principles of the Declaration of Helsinki on medical research in patients. This study was approved by the institutional review board (IRB 2009-A00877-50), and patients were included after they provided written and oral informed consent.

The population consisted of 41 consecutive patients suspected of OT, with a recent acute decreasing VA [13, 14]. Seventeen patients (nine proven OT and eight unproven OT) were excluded from the analysis since they had at least one unreliable visual field (see the visual field procedure below).

We studied 11 patients with biologically proven OT (median age, 49 years) and 13 patients with clinical OT and negative biological diagnosis (median age, 47.5 years). These patients were aged between 21 and 84 years (median, 48.25 years). One patient with a clinical OT was immunosuppressed (Crohn's Disease treated by azathioprine).

The OT biological diagnosis was based on detection of intraocular production of *Toxoplasma*-specific antibody with an aqueous humor sample [15], performed approximately 3 weeks after the first clinical symptoms [16]. Local synthesis of *Toxoplasma*-specific immunoglobulin G was detected with an immunoblotting method and quantified by calculating the Goldmann-Witmer coefficient (GWC), defined as the following ratio: (anti-*Toxoplasma* IgG in aqueous humor/total IgG in aqueous humor)/(anti-*Toxoplasma* IgG in serum/total IgG in serum); a value higher than 2 was considered evidence of intraocular antibody synthesis [17]. *T. gondii* DNA was detected by PCR amplification for immunocompromised patients [18, 19].

Patients were treated by a combination of pyrimethamine (100 mg loading dose orally followed by 50 mg/day) plus sulfadiazine (2–4 g/day divided 4 times daily) or trimethoprim (10 mg/kg/day) sulfamethoxazole (50 mg/kg/day) at least 6 weeks. Oral steroids (during 1 month) were considered according the severity of vitreitis ($\geq$ 3+) and the location (close to the macula or the optic nerve).

The following data were reported at baseline (M0), at the 1-month (M1), and at the 6-month (M6) visit: medical and surgical history, ocular and general treatments, complete ophthalmologic examination with VA measurement (converted in logMAR), Goldmann applanation tonometry for intraocular pressure measurement, and slit lamp and fundus examination. Color fundus images were taken using a Topcon TRC-50IX fundus camera (Topcon, Saint Denis, France). The initial lesion size was calculated according to the optic disc size (IMAGEnet i-base, Topcon, Saint Denis, France) and its location was classified in zone 1, 2, or 3 [20]. Macular spectral-domain optical coherence tomography (SD-OCT), fluorescein angiography (FA), and indocyanine green angiography (ICG) (HRA Spectralis, Heidelberg Engineering, Heidelberg, Germany) were performed at baseline.

Because all included eyes had a chorioretinal lesion localized in the 24° of visual field, Humphrey automated visual field with 24-2 SITA-standard strategy was performed at each visit (Zeiss Meditech, Dublin, CA, USA). The healthy eye was tested first. All healthy eyes' visual fields were reliable. Mean deviation (MD), pattern standard deviation (PSD), visual function index (VFI), and foveal threshold (FT) were collected for each eye. The reliability indices of the European Glaucoma Society [21] were used: fixation loss lower than 20%, and false-positive errors lower than 33%, and false-negative errors lower than 33% were considered as reliable.

A composite clinical severity score was calculated and based on initial and final VA > 0.5 logMAR (low vision according to the World Health Organization), severity of vitreitis (≥ 3+ considering the number of vitreous cells visualized in 3 mm × 1 mm slit beam, according to the Standardization of Uveitis Nomenclature (SUN) grading system) [22], initial chorioretinal lesion size greater than one papillary diameter (from the color fundus image), location of the chorioretinal lesion in zone 1 [20], an initial macular edema with a central macular thickness more than 310 μm as measured by SD-OCT [23–25], the presence of papillary edema in FA [26, 27], and/or scarring time longer than the median (14 weeks) [28]. The presence of each clinical sign had a value of 1 and the absence zero. We defined a relative cutoff level of OT severity as having higher values than the median severity score ($n = 9/24$).

Statistical analysis

Nonparametric statistical tests were performed for mean comparisons: Mann–Whitney U test and Wilcoxon rank sum test. The correlation coefficient was calculated using the Z test (StatView® 5.0 software by SAS Institute Inc., Abacus Corporation). The receiver operating characteristic (ROC) curve was used to evaluate the predictive value of the initial MD visual field parameter to distinguish severe from nonsevere OT. A statistically significant difference was considered with p values < 0.05.

Results

Comparison between initial and final visual field parameters

Figure 1 illustrates examples of visual field stabilization, worsening, or improvement during the monitoring of patients with active proven OT.

A positive correlation was noted between initial and final MD ($r = 0.873$; $p < 0.001$) and between initial and final PSD ($r = 0.890$; $p < 0.001$) (Fig. 2). Final MD at M6 was significantly higher than initial MD ($p = 0.01$, Table 1). Initial and final PSD values were not significantly different during follow-up (FU). MD and PSD were not significantly correlated with VA ($p = 0.24$) at baseline, nor at M6 ($p = 0.35$). The final FT was significantly higher than the initial FT ($p = 0.02$). There was a positive correlation between FT and VA at baseline ($r = 0.48$; $p = 0.01$) and at the 6-month FU visit ($r = 0.547$; $p = 0.004$).

Comparison between severe OT and nonsevere OT

At baseline, severe and nonsevere OT exhibited no significant difference in term of MD ($p = 0.06$) and PSD ($p = 0.1$).

MD improvement was noted during FU in nonsevere OT (median (initial MD − final MD) = − 0.69 dB) and in severe OT (− 1.2 dB) (Fig. 3). During the FU, MD, PSD, visual function index [VFI], and FT were independently associated with the severity of toxoplasmosis ($p = 0.018$, 0.05, 0.016, and 0.02, respectively). The unproven group had a faster recovery of MD during FU ($p = 0.05$).

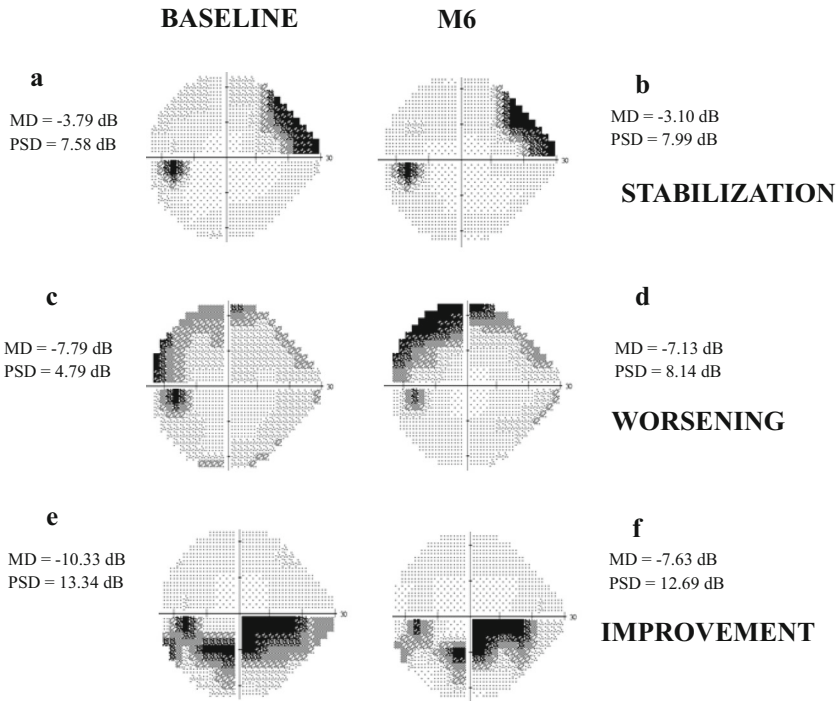

Fig. 1 Examples of visual field progression from three patients with proven ocular toxoplasmosis during the study, between baseline and the 6th month. **a**, **b** (patient 1). Stabilization of a scotoma in the superior nasal quadrant associated with an enlarged blind spot. **c**, **d** (patient 2). Worsening of visual field defects observed mostly in the superior temporal quadrant. **e**, **f** (patient 3). Improvement of visual field of a patient presenting an arcuate scotoma in the inferior hemifield during follow-up

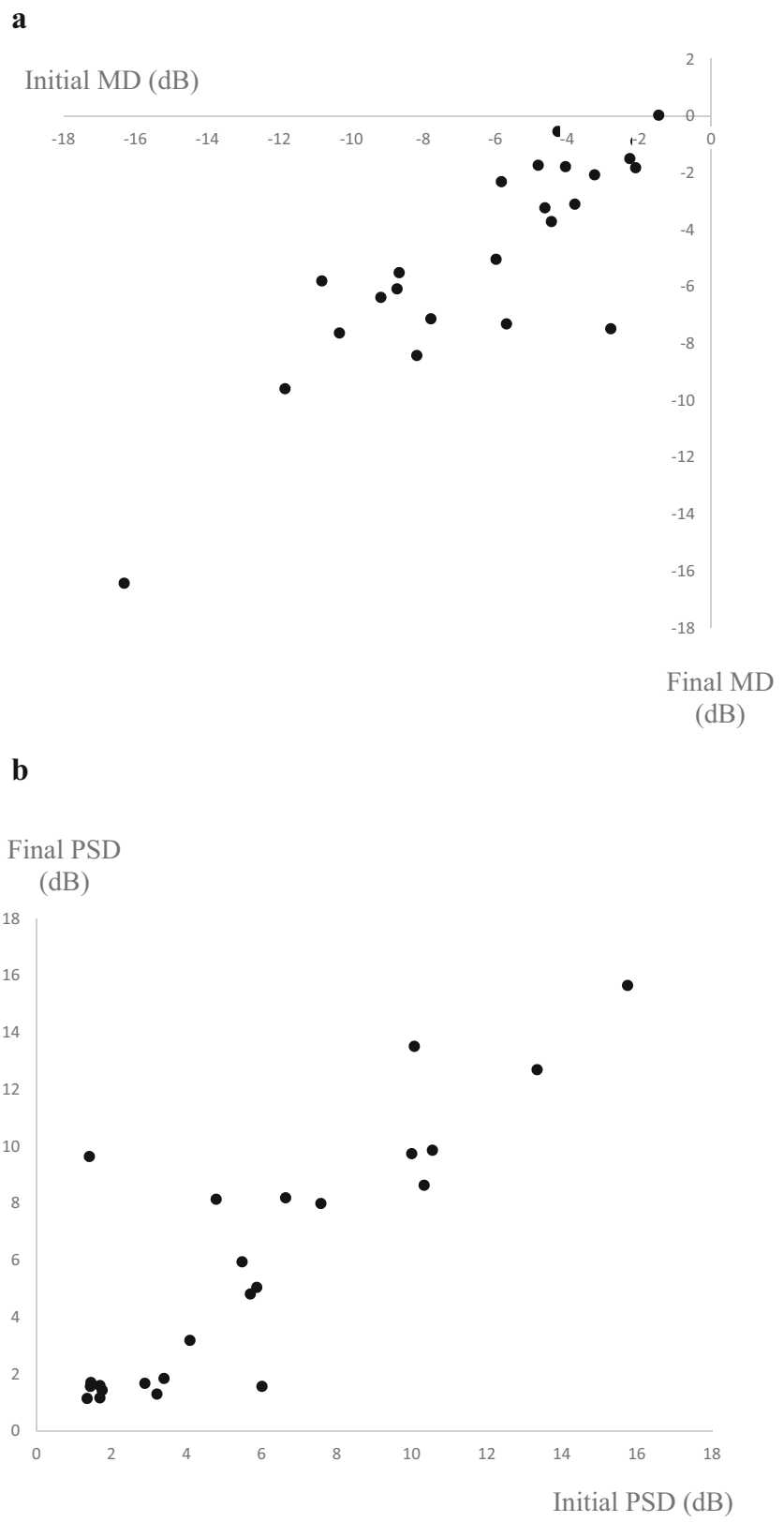

Fig. 2 Graphic comparison between initial and final MD and PSD. **a** Significant *Z* correlation between initial and final MD values ($R = 0.873$, $p < 0.001$). **b** Significant *Z* correlation between initial and final PSD values ($R = 0.890$, $p < 0.0001$).

To evaluate the predictive value of initial MD to distinguish severe from nonsevere OT, the receiver operating characteristic (ROC) curve was used. The area under the curve comprised between 0.7 and 0.8 was considered fair (Fig. 4).

Table 1 Visual field parameters and visual acuity follow-up of ocular toxoplasmosis (OT) cases

	Overall OT		Severe OT		Nonsevere OT		*p* values
	Median	Range	Median	Range	Median	Range	
Baseline							
MD	− 6.49	(− 16.31; − 0.35)	− 8.73	(− 16.31; − 0.46)	− 4.26	(− 10.82; − 0.35)	0.06
PSD	5.39	(1.31; 15.75)	7.58	(1.31; 15.75)	3.21	(1.35; 10.55)	0.20
FT	FT32.5	(20;41)	32	(20; 41)	34	(29; 36)	0.11
VFI	89	(51; 100)	86	(51; 100	96	(81; 100)	1.15
VA	0.15	(0; 1.5)	0.3	(0.1; 1.3)	0.1	(0; 1.5)	*0.02**
M1							
MD	− 5	(− 15.74; − 1.44)	− 7.66	(−15.74; − 4.07)	− 2.34	(− 8.12; − 1.44)	0.32
PSD	5.20	(0.99; 16.61)	7.82	(1.56; 16.61)	2.59	(0.99; 10.19)	0.10
FT	35	(31;39)	34	(31;36)	36	(35;39)	0.06
VFI	91	(51; 100)	86	(51; 98)	96	(86; 100)	0.30
VA	0.1	(0; 1.3)	0.2	(0; 1.3)	0.1	(0; 0.2)	*0.003**
M6							
MD	− 4.60	(− 16.43; 1.55)	−7.13	(− 16.43; 0.47)	− 2.07	(− 8.59; 1.55)	0.11
PSD	4.92	(1.45; 15.65)	8.14	(1.45; 15.65)	2.14	(1.14; 4.86)	0.07
FT	91.4	(52; 100)	85	(52; 100	98	(81; 100)	0.08
VA	0.05	(0; 1)	0.1	(0; 1)	0.1	(0; 0.1)	*0.03**

p values compare severe and nonsevere OT (Mann–Whitney *U* test). Medians are expressed in dB. Intervals are ranges. *p* values < 0.05 are in italic with an asterisk. MD, mean defect; PSD, pattern standard deviation; FT, foveal threshold; VFI, visual function index; VA, visual acuity

Correlation between visual field and lesion size

Initial MD and initial chorioretinal lesion size were significantly correlated ($r = 0.496$; $p = 0.02$) (Fig. 5). Final MD and initial chorioretinal lesion size were not significantly correlated ($p = 0.47$).

Comparison between proven OT and unproven OT

The median slope determined by linear regression of MD during FU 0.82 dB/year (coefficient of determination R^2, 0.54) for proven OT and 2 dB/year (coefficient of determination R^2, 0.4028) for unproven OT. There was a difference between MD slope from the proven and unproven OT groups: unproven OT had a faster MD recovery ($p = 0.05$).

Discussion

This prospective study of perimetric defect change in patients with initially active OT showed that initial and final MD and PSD were strongly correlated, whereas MD decreased significantly from baseline to the 6-month visit. Visual field parameters were not correlated with VA at baseline and during the FU. Whereas visual field parameters were similar at baseline between severe and nonsevere OT, a significant difference between severe and nonsevere OT was observed for each visual field parameter during the longitudinal FU ($p \leq 0.05$).

To date, few cross-sectional studies have evaluated the visual field abnormalities in subjects with OT. This prospective study has an original approach since we studied the relationship between VF data and the biological status of the infection (proven/unproven) and the clinical severity of ocular toxoplasmosis. Two publications [9, 11] reported antibody serological tests, whereas other publications [10, 12] reported diagnoses based on clinical presentation. One strength of our prospective study was to systematically use testing of AH samples, and identify biologically proved toxoplasmosis. We found that proven toxoplasmosis exhibited a slower slope of VF recovery, suggesting that the positivity of AH samples could be considered in the management of patient with active toxoplasmosis. The slope of the MD improvement may appear to be clinically unimportant. However, MD is calculated by averaging the retinal sensitivity of the 52 locations tested during the 24-2 visual examination, whereas most of the scotomas only affected a small part of the visual field. This likely explains that the MD, a global parameter of the visual field, shows few changes, whereas substantial improvements in retinal sensitivity of the particular location of the visual field can be observed, directly corresponding to the choroid–retinal lesions.

Given the absence of a previous standard score of severity, we used a composite severity clinical score, which was

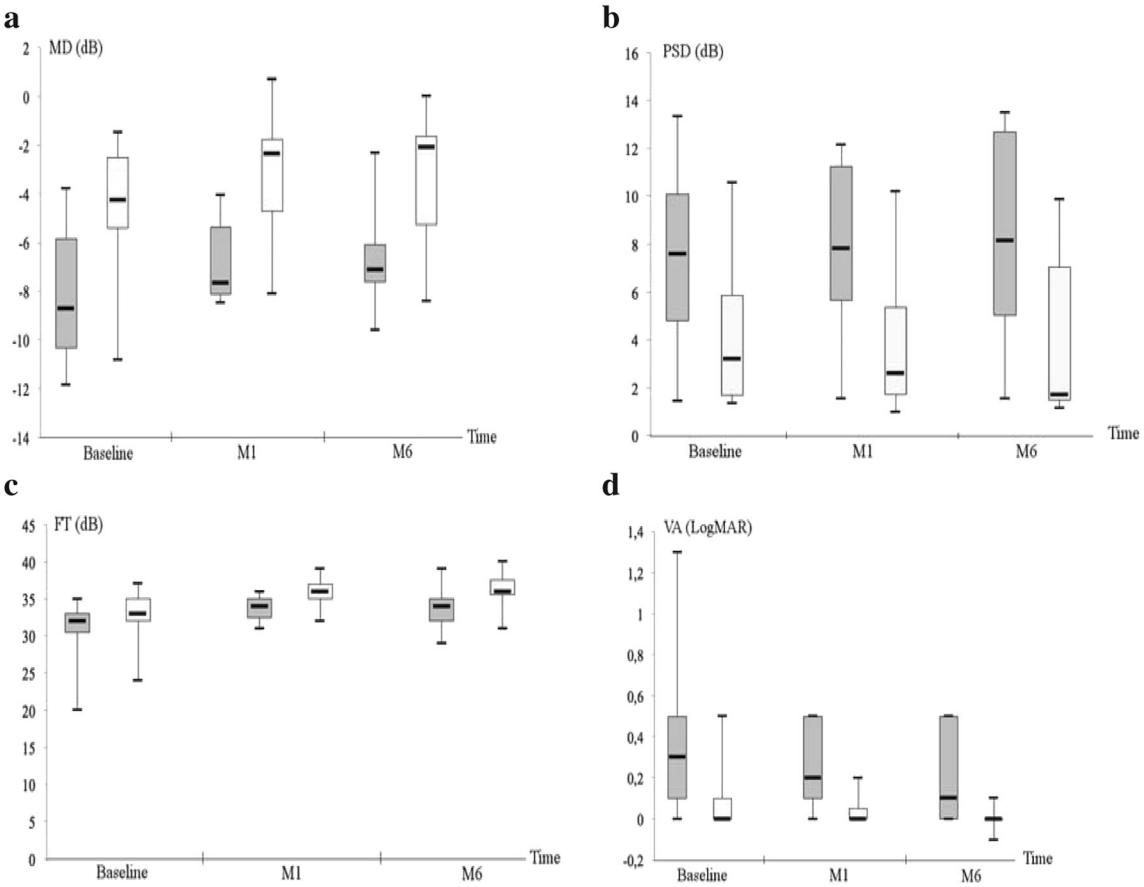

Fig. 3 Comparison and follow-up from baseline to the first month (M1) and the 6th month (M6) with boxplots between severe (in gray) and nonsevere (in white) OT. **a** MD improvement in two groups during the study. **b** Stabilization of PSD in the two groups. **c**: Foveal threshold improvement first and then stabilization in the two groups. **d** Visual acuity recovery in severe OT

calculated using well-known factors of severity such as VA, severity of vitritis [4], a chorioretinal lesion size more than one papillary diameter [4, 8, 29], location of the chorioretinal lesion in zone 1 [20], a macular edema, the presence of papillary edema in FA at baseline [26, 27], and the scarring time [28]. We acknowledge that it did not include other recognized factors such as age, parasite genotypes, patient immune status, number of lesions, and complications [4, 8, 29]. In our series, two patients were older than 65; one was immunosuppressed and had severe OT. None of our patients developed serious complications such as retinal detachment, vascular occlusion, or choroidal neovascularization. Only one patient developed an epiretinal membrane, and three others had a macular edema (one with unproven OT and two with proven OT). We did not

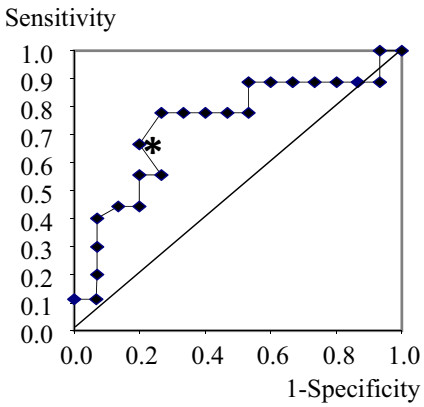

Fig. 4 Receiver operating characteristic (ROC) for initial MD and composite OT severity clinical score evaluated during the study. Area under the curve (AUC) is 0.739

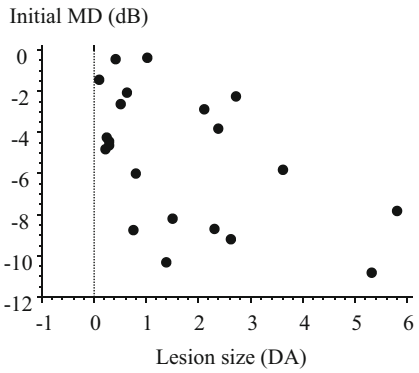

Fig. 5 Significant relationship between initial MD and initial lesion size (DA = disc area), $R = 0.496$ ($p = 0.02$)

find differences in VF at baseline between the severe OT and nonsevere OT but non severe OT at baseline had a faster recovery during the follow-up.

The present study confirmed that visual field defect was correlated to the lesion size at presentation. Using Humphrey automated static perimetry, Stanford et al. [11] evaluated the 24-2 Fast-Pac strategy in 69 eyes with an active or inactive retinochoroidal scar consistent with OT and showed that scars within one disc diameter from the optic disc were more likely to be associated with absolute defects breaking out to the periphery. This transversal study did not study the relationship between size of scars and VF parameters. For this reason, our study gives new insight in the relationship between lesion size and the impact on VF due to its longitudinal design. We report that initial lesion size and MD were highly correlated at the early stage of inflammation but not at the healing stage. This is a new finding suggesting that the appropriate scarring of toxoplasmic chorioretinal lesions may improve the functional sensitivity of the retina in these locations.

As previously reported, the monitoring of VA alone does not adequately evaluate the functional damage associated with OT. In a transversal retrospective study including inactive OT, correlation with the clinical location of chorioretinal scars has been reported better for the visual field (70% of the cases) than for VA (27%) [12]. In this previous study, visual field damage was found in 94% of the eyes, whereas only 41% of the eyes had reduced VA. On the other hand, normal VA was found in 59% of the eyes, including 33 eyes with a 20/20 or better VA, while a normal visual field was registered in only four eyes. Only one study [30] reported the evaluation of patients with OT using electroretinography (ERG) and showed that 50% of the patients with a lesion within the central 12° of the visual field had reduced photopic ERG recordings, whereas 50% of the patients with a lesion outside the 12° of the visual field had reduced scotopic ERG recordings.

In summary, our results strongly suggest that patients seen at baseline with a severe clinical presentation and a biologically proven toxoplasmosis have a higher risk of slower VF recovery. These two factors could be taken considered for the therapeutic management of patients, especially for the use of steroid therapy. At the time of the present study, we used oral steroids (during 1 month) according the severity of vitreitis (≥ 3+) and the location of the chorioretinal lesion (close to the macula or the optic nerve). Other clinical parameters, included in the clinical score such as VA, a chorioretinal lesion size more than one papillary diameter, a macular edema, and the presence of papillary edema in FA at baseline could be considered for a more aggressive treatment in order to decrease the worsening of the size of the chorioretinal scar and consecutive visual field scotoma.

Some limitations of this study should be discussed. Firstly, inclusion biases could be due to unreliable visual field or loss of patients to follow-up. At baseline, the visual field exam learning conditions may be difficult due to visual disturbances relative to intraocular inflammation. The second limitation of this evaluation of the visual field progression along the course of active OT occurrence is that we used a 24-2 strategy for the visual field evaluation. This is a rather central part of the complete human visual field, and it is likely that lesions located peripherally could sometimes not affect the 24-2 visual field.

In conclusion, this prospective and longitudinal study of patients with active ocular toxoplasmosis showed that visual field improvement was noted after active ocular toxoplasmosis with a significant increase in MD at 6 months and no significant change in PSD. Nonsevere OT, defined by clinical parameters, was slightly associated with a more rapid visual field recovery. These results suggest that the visual field follow-up is useful for the clinical assessment of patients with OT and should be studied in clinical trials evaluating drugs against ocular toxoplasmosis.

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Other participating investigators:

Guillemot C., MD, Department of Ophthalmology, University Hospital, Saint Etienne, France.

Fricker-Hidalgo H., MD, Department of Parasitology, University Hospital, Grenoble, France.

Brenier-Pinchart M.P., MD, Department of Parasitology, University Hospital, Grenoble, France.

Lesoin A., MD, Department of Ophthalmology, University Hospital, Grenoble, France and Grenoble Alpes University, Grenoble, F-38041, France.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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