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Etude clinique et angiographique lors de la Syphilis Oculaire

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par

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Résumé

Une recrudescence des cas de syphilis a été observée ces dernières années. Son diagnostic clinique reste particulièrement difficile en l'absence de signe pathognomonique. Sur le plan oculaire elle présente un vaste spectre de manifestations diverses lui ayant valu le surnom de « la grande imitatrice ». Sa rareté et son hétérogénéité ont empêché l'identification et la vérification statistique des facteurs liés à un pronostic défavorable. Le but de cette étude a été d'explorer les paramètres cliniques et para-cliniques déterminant la sévérité et influençant l'évolution de la maladie.

Ce travail comprend deux volets, la première partie intitulée : «Analysis of significant factors influencing visual acuity in ocular syphilis» publiée dans le British Journal of Ophthalmology a démontré qu'une mauvaise acuité visuelle initiale est associée de façon statistiquement significative à la sévérité de l'amputation du champ visuel, à la présence d'un œdème maculaire ou d'une neuropathie optique. Une amélioration de l'acuité visuelle grâce au traitement antibiotique est associée à la présence d'une vasculite (visible à l'angiographie fluorescéinique), d'une neurosyphilis ou d'une uvéite antérieure. Une récidive inflammatoire est fortement associée à une durée prolongée des symptômes avant l'introduction du traitement et à la présence de douleur comme signe d'appel. L'utilité clinique principale de ces résultats statistiques permet de conclure que les formes inflammatoires sévères associées à la triade (vasculite, neurosyphilis et uvéite antérieure) constituent un phénomène réversible pour autant qu'un traitement précoce et adéquat ait été introduit.

Le deuxième volet de l'étude analyse les manifestations angiographiques (à la fluorescéine (AF) et au vert d'indocyanine (AICG)) de la syphilis oculaire et a été publié dans le journal du Graefes Archives of Clinical and Experimental Ophthalmology sous le titre suivant : "Fluorescein and indocyanine-green angiography in ocular syphilis: an exploratory study". Des associations faibles ont été démontrées entre la présence d'une vasculite lors de AF et d'une uvéite antérieure, d'une hyalite et d'un âge plus jeune. Une association forte est identifiée entre la présence des «dark dots» sur l'AICG et d'une uvéite antérieure ainsi qu'entre la présence des «hot spots» sur l'AICG et d'une durée prolongée des symptômes. Les conclusions d'importance clinique significative lors de la syphilis oculaire sont que les « dark dots » ou hypofluorescences en AICG évoquent la présence d'une atteinte inflammatoire oculaire sévère et que les « hot spots » ou hyperfluorescences en AICG sont significatifs d'une atteinte chronique.

Cette étude contribue à modifier les attitudes cliniques lors de la syphilis oculaire surtout en ce qui concerne l'urgence à traiter afin d'assurer une récupération optimale. Elle aide aussi à redéfinir le rôle de l'angiographie dans la syphilis oculaire pour déterminer la sévérité, la durée de la maladie ainsi que le pronostic visuel.

Synthetic Report of the Thesis

Introduction

Syphilis constitutes a rare cause of ocular inflammation accounting for 0.1% of patients evaluated in a general ophthalmology clinic and 2.5% of patients in a referral practice [1, 2]. It has been described as the "great imitator" reflecting its vast range of clinical manifestations and the lack of any pathognomonic ocular signs that could lead to its diagnosis. The increased prevalence of this ocular affliction in recent years, which has been associated with the emergence of HIV infection [3, 4], has led to renewed interest in research aiming at its earlier diagnosis and effective treatment. Controversy exists regarding the applicability of the traditional classification of syphilis in the context of ocular inflammation [5]. Other grey areas in the management of ocular syphilis include indications for performing lumbar puncture, the efficacy of alternative treatment regimens and the role of angiography [6].

Objectives

Main objective of this research project was providing answers to specific questions regarding diagnosis and management of ocular syphilis.
More specifically we attempted to identify statistical associations between demographic, clinical and laboratory parameters at the moment of initial diagnosis of the disease; to determine the sensitivity of lumbar puncture for the diagnosis of neurosyphilis in the context of ocular inflammation[7]; to assess the efficacy of a classic treatment regimen of intravenous penicillin for ocular syphilis and to compare it with an alternative regimen of ceftriaxone[8]; to clarify the role of corticosteroids and immunosuppressors in the management of ocular syphilis; to describe patterns of visual field alterations associated with ocular syphilis; and to identify potential risk factors for a recurrence of the disease after adequate treatment.
A particular focus of the study concerned the identification of angiographic patterns specific to ocular syphilis both on fluoresceine (FA) and on indocyanine green angiography (ICGA). The role of indocyanine green angiography in the diagnosis and

assessment of response to treatment of other types of granulomatous uveitis have been studied in the past [9-11]. However its usefulness in revealing the extent of choroidal inflammation in ocular syphilis has not been thoroughly evaluated, possibly reflecting the rarity of the disease. There is only one study in the literature based on a small number of cases attempting to elucidate the characteristic findings of ocular syphilis on indocyanine green angiography [12]. In our study we attempted to describe the angiographic patterns observed on indocyanine green angiography in ocular syphilis, compare them with the corresponding fluoresceine angiography findings and assess their evolution after treatment. Furthermore, we aimed at exploring any meaningful statistical associations between specific angiographic manifestation and severity of disease presentation, as well as disease evolution after treatment.

Material and Methods

26 patients with ocular syphilis were followed in the context of a referral practice for ocular immunology and infection between 1999 and 2009. The diagnosis of ocular syphilis was based on at least one positive treponemal serologic test and the exclusion of other conditions that could account for the ophthalmic manifestations. Patient follow-up was performed with great homogeneity, by the same ophthalmologist and in accordance with international criteria (IUS6 and the 2005 classification). 23 of the patients underwent dual fluorescein and indocyanine green angiography, using a standard angiographic protocol for ocular inflammation [13]. At least one lumbar puncture was performed at 20 of the patients. All patients received antibiotic treatment for neurosyphilis, either with a standard regimen of intravenous penicillin or with an alternative regimen of ceftriaxone, in accordance with international recommendations. For several patients with persistent ocular inflammation the administration of systemic corticosteroid or immunosuppressive treatment was deemed necessary. Most patients were evaluated over a prolonged period of time in consecutive follow-up visits.

The data for the study were collected retrospectively from the files kept at the "Hôpital Ophtalmique Jules Gonin" and the "Centre Hospitalier Universitaire Vaudois". A cross-sectional analysis was performed for demographic, clinical, laboratory and angiographic findings at the moment of first diagnosis, in search of

statistically significant correlations between these parameters. Statistical associations were also investigated between initial parameters and response to treatment, recurrence of ocular inflammation and evolution of angiographic findings. The pattern and prevalence of angiographic findings was particularly studied, attempting to determine the extent of retinal and choroidal involvement in the ocular inflammation.

Results and published articles

Faced with a wealth of meaningful associations we opted for dividing the work in two stages, one focusing on whether statistical associations can be demonstrated in ocular syphilis between baseline clinical and laboratory parameters with visual acuity at presentation and with any change in visual acuity after treatment and the other aiming at describing angiographic patterns encountered in the context of ocular syphilis, and exploring any statistical associations between the angiographic manifestations and baseline parameters as well as evolution after treatment. The former section of the research resulted in the publication of the article entitled "Analysis of significant factors influencing visual acuity in ocular syphilis" in the British Journal of Ophthalmology. Out of several associations observed, the following factors were associated with worse initial visual acuity in patients with ocular syphilis: severity of visual field impairment at presentation ($p=0.012$), macular oedema ($p=0.004$) and optic neuropathy ($p=0.031$). There was a borderline association with the presence of vasculitis on fluroangiography ($p=0.072$). Improvement in best corrected visual acuity after treatment was significantly associated with the presence of vasculitis on fluroangiography ($p=0.005$), neurosyphilis, according to lumbar puncture findings ($p=0.037$) and marginally with anterior uveitis ($p=0.070$). Inflammation relapse was associated with the coexistence of pain as presenting sign ($p<0.001$) and with a longer duration of symptoms prior to the initial visit ($p=0.023$). The latter stage of the research focusing on angiographic findings in ocular syphilis resulted in the publication of the article entitled "Fluorescein and indocyanine-green angiography in ocular syphilis: an exploratory study" in the journal Graefes Archives of Clinical and Experimental Ophthalmology. The features most frequently observed in fluorescein angiography were retinal staining of focal punctate retinal lesions (43.5%), followed by staining of retinal vessels, mainly veins (30.4%) and disc hyperfluorescence

(30.4%). Indocyanine-Green Angiography features could be classified into three main patterns. The first pattern consisted of hypofluorescent choroidal lesions, visible from the early and intermediate phases of the angiogram onwards, which either became isofluorescent in the late phases, or remained hypofluorescent (dark dots) and were observed in 13 patients (59.1%) The second pattern corresponded to scattered hyperfluorescent spots (hot spots) appearing in the late phases of the angiogram, in the mid-periphery and/or the posterior pole present in 11 patients (50%). The third pattern was fuzzy choroidal vessels with leakage from the intermediate phase of the angiogram onwards in five patients (14.7%). As regards observed statistical associations, the presence of any dark dots in ICGA was significantly associated with anterior uveitis ($p=0.031$). The presence of hot spots in ICGA was significantly associated with longer duration of symptoms prior to initial visit ($p=0.032$) and with male gender ($p=0.012$). Weak non-significant trends were found associating vascular staining in FA with anterior uveitis ($p=0.066$), vitritis ($p=0.069$), and younger age ($p=0.061$), as well as disc hyperfluorescence in FA with seropositivity for HIV ($p=0.089$) and macular edema in FA with longer disease duration ($p=0.061$). The presence of any dark dots in ICGA exhibited a weak trend of association with anterior uveitis and/or vitritis ($p=0.079$).

Conclusions

The foremost conclusion of the article relating to baseline parameters and initial disease severity with significant clinical significance was that the triad of neurosyphilis, anterior uveitis and vasculitis on fluroangiography appears to be associated with improvement in visual acuity after treatment. Interpreting this striking finding we argue that severe ocular inflammation in the context of ocular syphilis, as indicated by the presence of anterior uveitis, vasculitis or vitritis, does not have permanent visual repercussions when appropriately treated. Our findings suggest that in the context of ocular syphilis, vasculitis, anterior uveitis and neurosyphilis are indicative of active, albeit reversible inflammation that responds to proper treatment, thus explaining the improvement observed in visual acuity. On the other hand, irreversible loss in BCVA in the present study occurred in patients with long-standing serous retinal detachment involving the macula and in patients with optic atrophy following syphilitic optic neuropathy. Another clinically relevant conclusion of this

research was that although early treatment of ocular syphilis will lead to a good visual prognosis, a delay in therapy may result in severe ocular complications. Consistent with this statement, the group of patients with inflammation recurrence in our series presented considerably later than the rest in a statistically significant manner, reflecting either an inappropriate initial management or chronic neglect. In our series, there was no statistically significant difference in visual outcome according to the treatment between the two groups of patients, one treated with a classic regimen of intravenous penicillin and the other with a regimen of intravenous ceftriaxone signifying that the latter may be a reasonable alternative to penicillin in the treatment of ocular syphilis.

As regards the second arm of the research relating to angiographic manifestations in ocular syphilis and their clinical significance, we highlighted several trends of association between vascular staining in FA and worse visual acuity at presentation, improvement in visual acuity after treatment, anterior uveitis, vitritis and younger age at presentation. The findings implicating vascular staining may point to a close association between these markers of active inflammation, indicating that eyes with vascular staining are more severely inflamed, which in turn may account for the weak trend towards worse BCVA at baseline in these patients. The high rate of disappearance of vascular staining in FA performed after treatment indicates that vasculitis in ocular syphilis is not accompanied by permanent visual repercussions when properly treated. As far as ICGA manifestations are concerned, we concluded that similar patterns in ICGA to those observed in our series have been described in other forms of granulomatous posterior uveitis, such as sarcoidosis and tuberculosis. Our study revealed a significant association between presence of dark dots in ICGA and anterior uveitis, and a weak trend of association with presence of anterior uveitis and/or vitritis. We suggest that the presence of dark dots, excluding those associated with atrophy, may signify active granulomatous posterior choroidal inflammation. With regards to hot spots in ICGA, the lack of association between hot spots and any ocular manifestation with important functional repercussions, such as macular edema, optic neuropathy, or anterior uveitis, may reveal an exclusively choroidal origin of these angiographic features. On the other hand, the identified association between presence of hot spots and a longer duration of symptoms prior to the first visit may render this angiographic finding indicative of long-standing disease.

Future perspectives

The meaningful contribution of this work on clinical attitudes towards ocular syphilis resides in the realisation of the reversible nature of the condition provided that adequate and timely treatment is administered. This conclusion may help increase the level of clinical suspicion for ocular syphilis in the face of granulomatous ocular inflammation and introduce a sense of urgency for appropriately treating this disease and thus ensuring the best possible outcome for patients. Prompt treatment enables a good visual prognosis, while any delay in therapy increases the risk of subsequent relapse and this principle should guide therapeutic decisions. Our work on angiographic manifestations of ocular syphilis led to the conclusion that both fluorescein and indocyanine-green angiography can offer valuable information concerning disease severity and duration, and can even contribute some clues to disease prognosis and therefore constitute useful tools in the hands of the ocular inflammation specialists. As in any clinical research and especially in the context of a condition characterised by significant rarity and heterogeneity further corroborative studies would serve to confirm the findings presented in this project.

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Analysis of significant factors influencing visual acuity in ocular syphilis

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ABSTRACT

Background The aim of this study is to determine whether statistical associations can be demonstrated in ocular syphilis between baseline clinical and laboratory parameters with visual acuity at presentation and with any change in visual acuity after treatment.

Methods Charts of 26 patients (42 eyes) with ocular syphilis presenting to the Uveitis clinic of the Jules-Gonin Eye Hospital were reviewed. A baseline cross-sectional analysis was performed in order to identify any association between visual acuity at presentation and demographic, clinical or laboratory parameters. After treatment, any analogy between these parameters and a change in visual acuity was subsequently assessed in a series of univariate comparisons.

Results The following factors were associated with worse initial visual acuity: severity of visual field impairment at presentation ($p=0.012$), macular oedema ($p=0.004$) and optic neuropathy ($p=0.031$). There was a borderline association with the presence of vasculitis on fluroangiography ($p=0.072$). Improvement in best corrected visual acuity after treatment was significantly associated with the presence of vasculitis on fluroangiography ($p=0.005$), neurosyphilis, according to lumbar puncture findings ($p=0.037$) and marginally with anterior uveitis ($p=0.070$). Inflammation relapse was associated with the coexistence of pain as presenting sign ($p<0.001$) and with a longer duration of symptoms prior to the initial visit ($p=0.023$).

Conclusions Severe ocular inflammation associated with vasculitis, vitritis or anterior uveitis in ocular syphilis would appear to be a reversible phenomenon that responds well to appropriate antibiotic treatment, resulting in improvement in visual acuity. Prompt treatment enables a good visual prognosis, while any delay in therapy increases the risk of subsequent relapse.

INTRODUCTION

Ocular syphilis accounts for approximately 0.1% of patients presenting to a general ophthalmology clinic and 2.5% of all uveitis cases reported in a reference practice for ocular inflammation.[1 2] There being no typical clinical presentation, ocular syphilis may be included in the differential diagnosis of any form of ocular inflammation, justifying its inclusion among the so-called masquerade syndromes.[3 4]

The re-emergence of ocular syphilis in recent years has excited renewed interest for this ancient disease.[5–7] Previous investigators have described several ocular manifestations of syphilis, including optic neuritis, anterior uveitis, vitritis, chorioretinitis, vasculitis and serous retinal detachment[8] and emphasised the relative frequency of such manifestations. Other key issues in the relevant literature include the role of lumbar puncture in ocular syphilis and the superiority of a classic treatment regimen for neurosyphilis with intravenous penicillin G.[9]

To date there has been no comprehensive statistical approach aiming to identify factors determinant in the severity of the initial presentation of ocular syphilis, nor has there been any attempt to associate baseline parameters with clinical evolution.

The purpose of this paper is to analyse statistical associations between visual acuity at presentation and demographic, ocular and laboratory parameters at baseline, as well as to identify baseline factors significantly associated with changes in visual acuity after treatment. Descriptive statistics drawn from collected data are also presented.

METHODS

A retrospective review was carried out on the charts of 34 consecutive patients presenting, between January 1999 and December 2009 at the uveitis clinic of the Jules-Gonin Eye Hospital, with ocular inflammation and a positive treponemal serological test for syphilis. Inclusion criteria for this study were signs of uveitis compatible with ocular syphilis on clinical evaluation, together with a positive treponema pallidum haemagglutination assay (TPHA) or fluorescent treponemal antibody absorbed (FTA-Abs) test. Medical history and serology for each patient were discussed with an infectious disease specialist (SG). In early syphilis, venereal disease research laboratory (VDRL) test was considered as truly positive in the absence of any other disease that could be at the origin of false-positive results (systemic lupus erythematosus, rheumatoid arthritis, Lyme disease) and was completed by TPHA and FTA-Abs serology. In late syphilis, a positive TPHA or FTA-Abs was considered sufficient to make the diagnosis. False-positive serology due to cross-reactivity in the context of Lyme disease was excluded by a negative ELISA test for Borreliosis and a negative western blot test. None of the patients included in the study had a prior history of ocular inflammation, thus it was assumed that the presenting episode constituted the first in their history of ocular syphilis. The presence of other ocular morbidities in eight patients led to their exclusion from further study.

All patients were followed by the same uveitis specialist (YGC) and according to official recommendations laid down for the management of ocular syphilis.[10] Initial evaluations for all patients

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included fluorescein angiography and indocyanine green angiography, according to a standard protocol for posterior uveitis,[11] octopus static perimetry, treponemal and non-treponemal serology for syphilis and lumbar puncture to identify neurosyphilis. Diagnosis of neurosyphilis was defined as the presence of a positive VDRL (>1) and/or 5 or more white blood cells per ml or increased protein in cerebrospinal fluid ((CSF) normal range 15–45 mg/dl), each supporting the diagnosis of neurosyphilis.

Treatment consisted of either a standard regimen of intravenous penicillin for neurosyphilis at a dose of 6×4 MU per day for 14 days, or an alternative regimen of intravenous ceftriaxone at a dose of 2 g per day for 14 days. At the end of treatment, the same laboratory and angiographic evaluations as those performed at baseline were repeated.

Eye-based statistical analysis was preferred, given that the main factor (logarithmic minimal angle resolution (logMAR)) pertained to each eye. Because of the weak correlation of best corrected visual acuity (BCVA) between right and left eyes in cases of bilateral involvement, as calculated by Spearman's rank correlation coefficient, no adjustment for inter-eye correlation was performed (see the section on Results).

After calculating descriptive statistics, we performed a cross-sectional analysis at baseline. BCVA (logMAR scale) was set as the main factor for the cross-sectional analysis that is, the association between visual acuity, and all demographic, clinical or laboratory parameters were evaluated.

In order to determine the factors associated with disease evolution, two outcomes were assessed: first concerning visual acuity, an ordinal variable was created to describe changes in visual acuity after the completion of treatment (0: deterioration, 1: stability, 2: improvement). Second, concerning relapse after treatment, any recurrence of inflammation was recorded. The associations between each outcome and all registered demographic, clinical or laboratory parameters were assessed in a series of univariate comparisons. Associations were also sought between the individual clinical parameters at baseline.

Concerning visual field impairment, the scale of severity was attributed on the basis of mean deviation (MD) values. Visual field loss was accordingly classified as normal ($MD \geq -2$ decibels [dB]), mild ($-6\ dB < MD < -2\ dB$), moderate ($-12\ dB < MD < -6$ dB), severe ($-18\ dB < MD < -12$ dB) and very severe ($MD \leq -18$ dB). For purposes of statistical analysis, a post hoc merging of categories was subsequently performed; data were presented as severe/very severe versus normal/mild/moderate impairment.

Pearson's χ^2, Fisher's exact test and Mann-Whitney-Wilcoxon (MWW) test for independent samples were appropriately applied. The performance of non-parametric statistics regarding BCVA (logMAR scale) was necessitated due to a marked deviation from normality, as evidenced from Kolmogorov–Smirnov and Shapiro–Wilk tests. The level of statistical significance was set to $p<0.05$. However, results of borderline significance ($0.10<p<0.05$) were also provided, given that they may become significant in the context of a larger sample.[12] Taking into account the small sample size, no multivariate analysis was performed. Statistical analysis was performed with STATA 8.0 statistical software (Stata Corporation, College Station, Texas,USA).

Institutional Review Board /Ethics Committee approval of the University of Lausanne was obtained. Described research adhered to the tenets of the Declaration of Helsinki.

RESULTS

Patient-based features of the study sample are presented in table 1. The 26 patients included in the study had a median age of 45 years. There were 18 men and 8 women. Four patients were African, 1 was Asian and 21 Caucasian. Sixteen patients had bilateral ocular involvement and 10 unilateral. Seven patients recalled the presence of a chancre at some point in the past, eight reported a history of systemic signs of syphilis consisting of a cutaneous eruption of the palms and trunk and four had systemic signs of syphilis at presentation (one patient had a cutaneous eruption, two had central nervous system involvement and one suffered from syphilitic aortitis). Of the 10 patients who had a diagnosis of syphilis in the past, 6 reported having been treated with an indeterminate number of intramuscular injections of penicillin.

Table 1 Demographic, clinical and laboratory features of the study sample. Patient-based descriptive statistics (n=26)

Continuous variables	Median (range)
Age (years)	45 (33–80)
Duration of symptoms before the first visit (days)	60 (0 to more than 10 years)
Follow-up (months)	10 (0–68)
Categorical and ordinal variables	**n (%)**
Male sex	18 (69.2)
Calling sign-related parameters	
Bilateral ophthalmic syphilis	16 (61.5)
Calling sign	
Sudden drop in visual acuity	12 (46.2)
Progressive drop in visual acuity	5 (19.2)
Drop in visual acuity (not specified)	2 (7.7)
Myodesopsias	2 (7.7)
Pain as only symptom	1 (3.8)
Symptoms of uveitis evolving chronically	2 (7.7)
Argyll-Robertson pupils	1 (3.8)
Asymptomatic	1 (3.8)
Coexistence of pain as a calling sign	10 (38.5)
Syphilis and HIV history	
History of systemic signs of syphilis	8 (30.8)
Known syphilis	10 (38.5)
Recall of chancre	7 (26.9)
HIV infection	2 (7.7)
Primary syphilis	0 (0.0)
Secondary syphilis	3 (11.5)
Tertiary syphilis	23 (88.5)
Neurosyphilis	15 (57.7)
Findings of lumbar puncture	
Positive VDRL (total n=18)	1 (5.5)
Positive TPHA (total n=19)	11 (57.9)
Positive FTA-IgG (total n=8)	2 (25.0)
Treatment-related parameters	
Type of antibiotic (total n=23)	
Intravenous penicillin G	15 (65.0)
Ceftriaxone	8 (35.0)
Administration of systemic corticoids (total n=23)	11 (48.0)
Administration of immunosuppressive agents (total n=23)	2 (8.7)
Relapse after treatment (total n=23)	4 (17.4)
Reaction Jarisch–Herxheimer (total n=23)	2 (8.7)

FTA, fluorescent treponemal antibody; TPHA, treponema pallidum haemagglutination assay; VDRL, venereal disease research laboratory test.

Fifteen patients had a diagnosis of neurosyphilis by lumbar puncture findings. VDRL analysis in CSF was positive only in one patient, CSF cell count ranged between 0 and 153, with a median of 12, whereas CSF protein ranged from 30 to 1000 mg/dl with a median of 464 mg/dl. Fourteen patients (53.8%) had a positive VDRL (>1) in the serum, ranging up to 2048, while all patients had positive TPHA and FTA-Abs.

The most frequent ocular manifestations are presented in table 2. Mean BCVA at presentation (logMAR) was 0.62±0.78.

Table 2 Clinical manifestations of ophthalmic syphilis in the study sample. Eye-based statistics (n=42)

Continuous variables	Mean±SD
BCVA at presentation (logMAR)	0.62±0.78*
BCVA at the end of follow-up (logMAR)	0.29±0.57*
Categorical and ordinal variables	**n (%)**
RAPD	3 (7.1)
Optic neuropathy	13 (31.0)
Anterior uveitis	19 (45.2)
Vitritis	21 (50.0)
Retinitis	29 (69.1)
Macular oedema	8 (19.1)
Vasculitic signs	11 (26.2)
Retinal haemorrhage	4 (9.5)
Serous retinal detachment	4 (9.5)
Scleritis	2 (4.8)

*At the end of follow-up, a statistically significant improvement in BCVA was achieved (p=0.001, Wilcoxon matched-pairs signed ranks test).
BCVA, best corrected visual acuity; logMAR, logarithmic minimal angle resolution; RAPD, relative afferent pupillary defect.

BCVA at presentation below the threshold for legal blindness (≥1 on the logMAR scale) was observed in 28.6% of the involved eyes (12 of 42). Of the cases with posterior involvement, 45.2% had concomitant anterior chamber inflammation, but no case of isolated anterior uveitis was observed. One patient had a diagnosis of unilateral choroidal neovascularisation; one presented with unilateral peripheral temporal retinal neovascularisation; there was one case of bilateral giant retinal tears and consequent retinal detachment following a Jarisch–Herxheimer reaction to treatment with penicillin; one patient developed unilateral central retinal vein occlusion.

Fifteen patients underwent treatment with a regimen of penicillin and eight with a regimen of ceftriaxone within 1 month of initial presentation. Administration of systemic steroids was deemed necessary in 11 patients, at an initial dose of 1 mg/kg/day and consequent adaptation according to the response. Of these patients, six had persistent vitritis, three had cystoid macular oedema, one had extensive vasculitis and one had persistent papillitis. Mean BCVA at the end of follow-up was 0.29±0.57. Improvement in BCVA after treatment was statistically significant (p=0.001). Of the 22 eyes that exhibited improvement in BCVA after treatment, 13 gained more than three lines (each line on the standardised visual acuity chart increasing by 0.1 log units), nine of these gained more than four lines. Deterioration in BCVA after treatment was observed in 15.8% of the involved eyes (6 of 38), with one presenting a loss of more than two lines. In all these cases, BCVA remained below the threshold for legal blindness. Of the six eyes concerned, three had optic neuropathy, two had serous retinal detachment involving the macula and one had central retinal vein occlusion. Four patients, after an initial favourable response to treatment, presented with a recurrence of ocular inflammation between 3 months and 1 year after the end of treatment. We were able to exclude the possibility of a re-infection or a poor response to treatment in these four patients by monitoring VDRL; this remained negative in three cases and exhibited a fourfold decrease in titre in one case. Of these patients, three presented with a relapse of vitritis and chorioretinitis and one exhibited a recurrence of anterior uveitis with hypopyon. All four patients received a new treatment cycle with oral prednisone.

In patients with bilateral impairment in visual acuity, the correlation between BCVA of the right and left eyes was weak and far from reaching formal statistical significance (r=0.367, p=0.240). Consequently, eye-based statistical analyses were not controlled for inter-eye relationships in patients with bilateral ocular involvement.

The factors significantly associated with visual acuity at baseline are presented in table 3. Statistically significant associations were demonstrated between poor visual acuity and the following: female gender (p=0.03); severity of visual field impairment at presentation (p=0.012); macular oedema (p=0.004); optic neuropathy (p=0.031) and a borderline association with the presence of vasculitis on fluroangiography (p=0.072, difference: 0.28, 95% CI: −0.31 to 0.86). Worthy of note, severity of visual field impairment was marginally associated with vitritis (p=0.053, MWW, yielding difference: 0.57, 95% CI: 0.15 to 2.51).

Factors significantly associated with modification in BCVA after treatment are presented in table 4. Improvement in BCVA was associated with the presence of vasculitis on fluroangiography (p=0.005) and neurosyphilis, according to lumbar puncture findings (p=0.037); there was a borderline association with anterior uveitis (p=0.070, difference in percentages: +34.4%, 95% CI: +4.4% to +64.4%). These three parameters were also statistically associated with each other. More specifically, neurosyphilis was associated with vasculitis on fluroangiography (p=0.020, Fisher's exact test) and with anterior uveitis (p=0.025, χ^2 test); vasculitis on fluroangiography was associated with anterior uveitis (p=0.019, Fisher's exact test). Vasculitis on fluroangiography was also associated with vitritis (p=0.003, Fisher's exact test). Presence of macular oedema at baseline did not correlate with either deterioration or improvement in BCVA after treatment (p=0.111, Mann-Whitney-Wilcoxon test). Of the eight eyes with this clinical manifestation, seven exhibited improvement in BCVA after treatment. Change in visual acuity was not associated with the choice of antibiotic treatment (p=0.498, MWW). However, the choice of antibiotic treatment administered was significantly associated with baseline BCVA (p=0.008, MWW).

Table 3 Factors significantly associated with BCVA (logMAR) at presentation. Eye-based analysis (n=42)

	Mean±SD baseline BCVA	p
Sex		0.030[MWW]
Male (n=27)	0.49±0.78	
Female (n=15)	0.85±0.74	
Severity of visual field impairment		
Normal/mild/moderate (n=10)	0.15±0.18	0.012[MWW]
Severe/very severe (n=15)	0.85±0.78	
Vasculitis in fluroangiography		0.072[MWW]
Yes (n=9)	0.83±0.74	
No (n=27)	0.55±0.76	
Macular oedema		0.004[MWW]
Yes (n=8)	1.32±0.89	
No (n=34)	0.45±0.66	
Optic neuropathy or RAPD		0.031[MWW]
Yes (n=14)	0.97±0.81	
No (n=28)	0.44±0.71	
Recall of chancre		0.012[MWW]
Yes (n=11)	0.91±0.74	
No (n=31)	0.51±0.77	
Type of antibiotic treatment subsequently administered		0.008[MWW]
Intravenous penicillin G	0.95±0.84	
Ceftriaxone	0.25±0.38	

[MWW]p value derived from Mann-Whitney-Wilcoxon test for independent samples.
BCVA, best corrected visual acuity; RAPD, relative afferent pupillary defect.

Table 4 Factors significantly associated with the change in BCVA after treatment. Eye-based analysis (n=38). Percentages are given with 100%, corresponding to each row.

	Deterioration in BCVA Freq (%)	No change in BCVA Freq (%)	Improvement in BCVA Freq (%)	p
Vasculitis in fluroangiography				0.005[MWW]
Yes (n=9)	0 (0.0)	0 (0.0)	9 (100.0)	
No (n=25)	5 (20.0)	9 (36.0)	11 (44.0)	
Neurosyphilis				0.037[MWW]
Yes (n=19)	3 (15.8)	1 (5.3)	15 (79.0)	
No (n=17)	2 (11.8)	9 (52.9)	6 (35.3)	
Anterior uveitis				0.070[MWW]
Yes (n=17)	2 (11.8)	2 (11.8)	13 (76.4)	
No (n=19)	3 (15.8)	8 (42.1)	8 (42.1)	
Retinal participation*				0.097[MWW]
Yes (n=31)	4 (12.9)	7 (22.6)	20 (64.5)	
No (n=5)	1 (20.0)	3 (60.0)	1 (20.0)	
Type of antibiotic treatment				0.498[MWW]
Intravenous penicillin G (n=23)	4 (17.0)	3 (13.0)	16 (70.0)	
Ceftriaxone (n=13)	1 (7.6)	5 (38.4)	7 (54.0)	

[MWW]p value derived from Mann-Whitney-Wilcoxon test for independent samples.
*Defined as any of the following constituents: retinitis, macular oedema, retinal detachment and retinal haemorrhage.
BCVA, best corrected visual acuity.

Recurrence of inflammation after initial remission following proper antibiotic treatment was associated with the coexistence of pain as a presenting sign (p<0.001, Fisher's exact test) and with a longer duration of symptoms prior to the initial visit (p=0.023, MWW). Coexistence of pain as a presenting sign was also associated with anterior uveitis (p=0.023, Fisher's exact test).

DISCUSSION

Baseline factors statistically associated with visual acuity at presentation have not previously been described in the context of ocular syphilis. In our study, poorer visual acuity at presentation was associated with female gender, macular oedema, optic neuropathy and the presence of vasculitis on fluorescein angiography. Furthermore, poor visual acuity was associated with the severity of visual field impairment at presentation.

Associations between baseline parameters and change in visual acuity after treatment have not been previously identified in ocular syphilis. The triad of neurosyphilis, anterior uveitis and vasculitis on fluroangiography appears to be associated with improvement in visual acuity after treatment. These three parameters are closely interrelated with each other, further reinforcing their joint importance in predicting disease evolution. Vasculitis on fluorescein angiography is further associated with vitritis, another marker of active ocular inflammation. We argue that severe ocular inflammation in the context of ocular syphilis, as indicated by the presence of anterior uveitis, vasculitis or vitritis, does not have permanent visual repercussions when appropriately treated. Central nervous system involvement and vasculitis have been identified as negative prognostic indicators for visual acuity in ocular Behçet, revealing the occlusive-ischaemic aspect underlying the pathophysiology of this disease.[13] Our findings, however, suggest that in the context of ocular syphilis, vasculitis, anterior uveitis and neurosyphilis are indicative of active, albeit reversible inflammation that responds to proper treatment, thus explaining the improvement observed in visual acuity. On the other hand, irreversible loss in BCVA in the present study occurred in patients with long-standing serous retinal detachment involving the macula and in patients with optic atrophy following syphilitic optic neuropathy. BCVA in eyes with macular oedema at presentation tented to improve after treatment, though the association did not reach statistical significance.

In accordance with Beck *et al*,[14] we preferred to use an ordinal variable expressing any change in logMAR as primary outcome, instead of creating a binary variable based on whether or not there has been a particular worsening in visual acuity of three or more lines. Given the small study sample, this elaborate approach maximised the information gained from the data and enabled accommodating, instead of overlooking, subtle changes concerning both improvement and deterioration of acuity. We acknowledge that our method does not take into account the magnitude of improvement, which, nevertheless, was in most cases significant, further reinforcing the reliability of the obtained statistical associations.

We considered the resurgence of inflammation after initial remission as a principally immune-mediated reaction, rather than a failure of treatment for syphilitic infection, and we managed it accordingly. Based on the evolution of serum VDRL titres, the possibilities of re-infection or treatment failure were excluded by an infectious disease specialist. Similar cases are reported in the literature, specifically a case of development of cystoid macular oedema after the resolution of inflammation that responded to intravitreal triamcinolone.[15] This was also observed in one patient in the series reported by Browning,[9] cases 4 and 5 in that of Halperin *et al*[16] and in the case reported by Currie *et al*[17] A pattern that arises from the study of such cases is that, although an early treatment of syphilis will lead to a good visual prognosis, a delay in therapy may result in severe ocular complications.[18] Consistent with this statement, the group of patients with inflammation recurrence in our series presented considerably later than the rest in a statistically significant manner, reflecting either an inappropriate initial management or chronic neglect. Another common characteristic that stands out in this group of relapsing patients is the coexistence of pain as a presenting sign, which in turn is associated with the presence of anterior uveitis. This finding, albeit statistically significant, is rather more difficult to interpret, possibly pointing to a more intense, persistent inflammatory response already present at the onset of ocular syphilis.

Our study confirms the less-than universal finding of abnormal CSF in the context of ocular syphilis (57.7%). Given that the ocular involvement in the context of syphilitic infection classifies the disease as neurosyphilis irrespective of compatible CSF findings, the value of performing a lumbar puncture is controversial.[19–21] This is the first time, however, that CSF findings are statistically associated with change in visual acuity in syphilitic eye disease. The presence of neurosyphilis was identified as a factor followed by improvement of BCVA after treatment. It was subsequently associated with the presence of two other factors similarly associated with favourable response to treatment: anterior uveitis and presence of vasculitis on FA. A possible interpretation of these findings resides in the better penetration of antibiotic treatment in the context of a compromised blood–ocular barrier, as is the case in anterior uveitis and a compromised internal blood–retinal barrier, as identified by the presence of vasculitic signs, in the same manner as a compromised blood–cerebral barrier facilitates antibiotic tissue penetration in the context of bacterial meningitis.[22]

In our series, there was no statistically significant difference in visual outcome according to the treatment between the two groups of patients, one treated with a classic regimen of intravenous penicillin and the other with a regimen of intravenous

ceftriaxone. Another interesting finding, which however limits the comparison between the above-mentioned groups, is that the choice of antibiotic treatment was affected by the severity of disease presentation, with a tendency to favour the more convenient regimen of ceftriaxone in cases with better BCVA at baseline. Our results corroborate the study by Marra *et al*[23] for the treatment of neurosyphilis, who concluded that intravenous ceftriaxone may be an alternative to penicillin in the treatment of HIV-infected patients with neurosyphilis.

Limitations of the current study comprise its retrospective design and the small study sample. It should be emphasised that the independence of the associations presented herein may not be warranted, given the inability to perform multivariate analysis. Consequently, the existence of underlying mutual confounding may not be ruled out. However, the emergence of statistically significant associations in this study may well point to their replication in future larger studies with substantial power. A meaningful aspect that should be declared pertains to the fact that generalised estimating questions with appropriate interaction terms could not be applied, given the small number of observations per cell. Specifically, although the association between eyes in bilateral cases was not statistically significant, the inability of the analysis to allow for correlation between eyes remains a limitation of the research.

Other limitations of a retrospective analysis include non-standardised data collection and follow-up assessment at irregular intervals, albeit homogeneous in the current series with a single observer. Three patients were lost to follow-up, further limiting available data regarding change in visual acuity after treatment. However, the rate of loss to follow-up is not excessive, bearing in mind the social stigma still associated with this disease. Given the above-mentioned limitations, mainly stemming from the rarity and heterogeneity of the disease, further corroborative studies are required to confirm our findings.

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Analysis of significant factors influencing visual acuity in ocular syphilis

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INFLAMMATORY DISORDERS

Fluorescein and indocyanine-green angiography in ocular syphilis: an exploratory study

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Abstract
Background Fluorescein (FA) and indocyanine-green angiography (ICGA) may offer valuable information concerning disease severity and prognosis in ocular syphilis. The aim of the present study is to describe angiographic patterns encountered in the context of ocular syphilis, and to explore the associations between specific angiographic manifestations and severity of disease presentation, as well as disease evolution after treatment.
Methods We performed a retrospective institutional study with the inclusion of 23 patients with ocular syphilis presenting to the uveitis clinic of the Jules-Gonin Eye Hospital in a 10-year period. FA and ICGA were performed following a standard protocol for posterior uveitis. Patterns of fluorescence were noted, and statistical associations between each angiographic pattern and any demographic, clinical, or laboratory parameter at baseline and after treatment were sought.
Results The presence of any dark dots in ICGA was significantly associated with anterior uveitis (p=0.031). The presence of hot spots in ICGA was significantly associated with longer duration of symptoms prior to initial visit (p=0.032) and with male gender (p=0.012). Weak non-significant trends were found associating vascular staining in FA with anterior uveitis (p=0.066), vitritis (p=0.069), and younger age (p=0.061), as well as disc hyperfluorescence in FA with seropositivity for HIV (p=0.089) and macular edema in FA with longer disease duration (p=0.061). The presence of any dark dots in ICGA exhibited a weak trend of association with anterior uveitis and/or vitritis (p=0.079).
Conclusions Out of the several associations identified implicating specific angiographic features, we underline the possible role of the presence of dark dots in ICGA for identifying active inflammation, and the role of hot spots in ICGA as markers of long-standing disease. Vascular staining in FA appears to be more common in patients with severe ocular inflammation with presence of anterior uveitis and/or vitritis.

Keywords Ocular syphilis · Fluorescein angiography · Indocyanine-green angiogrpahy

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Introduction

Ocular involvement in the context of syphilitic infection presents certain particularities stemming from the close anatomic proximity of the eye to the central nervous system. Ocular syphilis is therefore classified as a variant of neurosyphilis, irrespective of compatible findings in the cerebrospinal fluid. The classical description of the clinical course of syphilitic infection in three consecutive stages is less relevant in the presence of ocular involvement, as reflected in the Centers for Disease Control (CDC) guidelines for the management of syphilis that prompt clinicians to treat all

cases of ocular syphilitic infection as neurosyphilis [1]. The value of laboratory investigations in determining disease severity and prognosis in ocular syphilis is limited. Although serum VDRL titers are considered appropriate for evaluating disease activity and response to treatment in syphilis, this is less clear in the context of ocular involvement, which is most common in the secondary, but also in the tertiary stage of the disease, when VDRL serology is almost invariably negative. Active and potentially debilitating ocular disease can therefore be accompanied by negative non-treponemal serology for syphilis [2]. Further laboratory investigations would therefore be needed to offer clues as regards disease severity and prognosis. The role of angiography in determining disease severity and in predicting disease evolution after treatment has not been adequately studied in ocular syphilis.

Fluorescein angiography (FA) has been extensively used for the evaluation of ocular inflammation in the context of posterior uveitis [3–5]. As fluorescein sodium fluoresces in the wavelengths of visible light, its value is mostly limited in revealing pathology of the superficial structures of the fundus [6]. Indocyanine-green (ICG), on the other hand, fluoresces on the infrared spectrum, giving access to the choroidal compartment through the retinal pigment epithelium. ICG leaks unimpaired from fenestrated choriocapillaris, albeit slowly, gradually impregnating choroidal tissue and giving rise to intermediate and late choroidal background fluorescence in the course of the angiogram. This fluorescence and its disturbance from choroidal inflammatory lesions are the main components studied in ICG angiography (ICGA) performed for posterior granulomatous uveitis [7–9].

FA manifestations of ocular syphilis have been reported in previous publications, identifying non-specific patterns of retinal inflammation, such as retinal and vascular staining, capillary leakage, macular edema, and optic disc hyperfluorescence [3–5]. A pattern unique to the disease has been described by Gass [10], corresponding to the entity named syphilitic posterior placoid chorioretinitis. ICGA patterns in ocular syphilis have been described in a case series by Mora et al., emphasizing the presence of late scattered hyperfluorescence as characteristic to the disease [11].

The purpose of the present study is to describe angiographic patterns in ocular syphilis both in fluorescein and ICG angiography, and to look for meaningful associations between specific angiographic findings and any baseline demographic or clinical parameter, as well as disease evolution after treatment and probability for relapse.

Methods

We retrospectively reviewed the charts of 26 patients with ocular inflammation and a positive treponemal serologic test for syphilis presenting to the Uveitis department of the Jules-Gonin Eye Hospital in the period between January 1999 and December 2009. Inclusion criteria for this study were signs of uveitis compatible with ocular syphilis on clinical evaluation, together with a positive TPHA or FTA-Abs test. Medical history and serology for each patient were discussed with an infectious disease specialist (SG), in order to ascertain diagnosis of syphilis and determine stage of disease progression. All patients were followed by the same uveitis specialist (YGC), and according to official recommendations laid down for the management of ocular syphilis [1]. Treatment consisted of either a standard regimen of intravenous penicillin for neurosyphilis at a dose of 6 × 4 MO IU per day for 14 days, or an alternative regimen of intravenous ceftriaxone at a dose of 2 gr per day for 14 days. Inclusion criteria, clinical and laboratory evaluations, and management are extensively discussed in a previous publication. Associations drawn from the same study sample as regards disease severity at baseline and disease evolution after treatment have also been previously reported [12]. Out of the 26 patients, three refused to enter into the proposed follow-up including fluorescein and ICG angiography, lumbar puncture, and visual field assessment. Twenty-three patients underwent dual fluorescein and ICG angiography following a standard protocol for the evaluation of posterior uveitis at the moment of disease diagnosis [13]. The same angiographic evaluation was performed after the completion of a treatment cycle for ocular syphilis in 17 patients.

As angiography constitutes an examination not readily quantifiable in clinical practice, and its interpretation remains to a large extent descriptive, we employed a qualitative approach to the recording of angiographic findings, noting the presence or absence of each characteristic pattern, but not its extent. This was mainly done in order to proceed to a concise, parsimonious statistical analysis of angiographic findings, given the small study sample.

Recorded angiographic patterns in FA included macular edema, disc hyperfluorescence, retinal staining, vascular staining, retinal ischemia, pinpoint leakage, mask effect from preretinal hemorrhage, window defects, and fluorescein leakage from choroidal or retinal neovascularization.

Recorded angiographic patterns in ICGA included: (1) persistent dark dots, defined as diversely sized hypofluorescent areas already present in the early and intermediate phases of the angiogram and remaining hypofluorescent in the late phase, (2) vanishing dark dots, different in that they became isofluorescent in the late phase of the angiogram, and (3) atrophic dark dots, a sub-variant of persistent dark dots remaining unaltered in subsequent angiograms after proper antibiotic treatment. Other noted angiographic features included hot spots, defined as scattered hyperfluorescent foci

in the posterior pole or the mid-periphery in late angiographic frames, and fuzzy choroidal vessels observed in the intermediate phase of the angiogram.

With regard to statistical analysis of observed angiographic patterns, the following angiographic features were set as main factors in a series of univariate comparisons: retinal staining, vascular staining, disc hyperfluorescence, and macular edema in FA, as well as the presence of any dark dots and hot spots in ICGA. More specifically, the associations between the main factors and all registered demographic, clinical or laboratory parameters (ten in total) at baseline were thoroughly assessed. The aforementioned parameters included gender, age at diagnosis, unilateral or bilateral involvement, HIV status, duration of symptoms prior to initial visit, pain as a calling sign, anterior uveitis, vitritis, optic nerve involvement [as evidenced by a relative afferent pupillary defect (RAPD), and/or optic disc swelling], and relapse of inflammation after treatment. A further parameter, constituting an indicator of active ocular inflammation, was examined against all registered angiographic manifestations; the presence of anterior uveitis and/or vitritis vs the absence of both.

Inter-eye correlations implicating specific angiographic manifestations in cases with bilateral disease involvement were calculated in order to identify the degree of symmetry in FA and ICGA of ocular syphilis with bilateral involvement. Associations among the various angiographic manifestations both in FA and in ICGA were also sought.

Pearson's chi-square, Fisher's exact test and the Mann–Whitney–Wilcoxon test for independent samples (MWW) were appropriately applied in the light of deviation from normality (as evidenced from Kolmogorov–Smirnov and Shapiro–Wilk tests). With regard to continuous variables, median values and inter-quartile ranges are reported given the nonparametric statistical approach adopted. The level of statistical significance was set to 5%. A patient-based analysis was performed in order to circumvent the potential inter-eye correlation in cases with bilateral involvement; the presence of any specific angiographic manifestation in any particular patient was only included once in the analysis irrespective of unilateral or bilateral involvement, thus eliminating the effect of inter-eye correlation. In simple terms, at the patient-based analysis, each patient was deemed positive regarding an angiographic manifestation when *one or both* eyes had exhibited the respective manifestation. Nevertheless, an alternative eye-based analysis was also performed, and is thoroughly presented in the Appendix, ensuring a comprehensive approach to available data. Given the exploratory nature of the present study, no adjustment of the significance level to account for multiple statistical comparisons was deemed to be warranted. Taking into account the small sample size, no multivariate analysis was performed. Observed associations may therefore be prone to mutual confounding which cannot be further investigated by multivariate analysis in the context of this study. Statistical analysis was performed with STATA 8.0 statistical software (Stata Corporation, College Station, TX, USA).

Institutional Review Board (IRB)/ Ethics Committee approval of the University of Lausanne was obtained. Described research adhered to the tenets of the Declaration of Helsinki.

Results

Simultaneous fluorescein and ICG angiography were performed in 23 patients (39 eyes) at presentation, following a standard angiographic protocol for the evaluation of posterior uveitis. The most frequent patterns of fluorescence in FA and ICGA are presented in Table 1. The features most frequently observed in FA were retinal staining of focal punctate retinal lesions (43.5%), followed by staining of retinal vessels, mainly veins (30.4%) and disc hyperfluorescence (30.4%) (Fig. 1). Four patients presented a particular angiographic pattern consisting of hypofluorescent foci corresponding to the presence of chorioretinal scars, surrounded by hyperfluorescent areas in the late phase, an aspect compatible with syphilitic posterior placoid chorioretinitis. ICGA features could be classified into three main patterns. The first pattern consisted of hypofluorescent choroidal lesions, visible from the early and intermediate phases of the angiogram onwards, which either became isofluorescent in the late phases, or remained hypofluorescent. These lesions, also referred to as dark dots, varied considerably in size, number and localisation, sharing the common characteristic of being invisible in fluorescein angiography or

Table 1 Findings in fluorescein and indocyanine-green angiography (n=23 and 22 patients respectively)

	N (%)
Findings in fluoroangiography (n=23)	
Disc hyperfluorescence	7 (30.4)
Macular edema	4 (17.4)
Vascular staining	7 (30.4)
Retinal staining and/or capillary leakage	10 (43.5)
Retinal ischemia	2 (8.7)
Normal	2 (8.7)
Findings in ICGA (n=22)	
Dark dots	13 (59.1)
Persistent dark dots exclusively	3 (13.6)
Persistent and vanishing dark dots	10 (45.5)
Hot spots	11 (50.0)
Fuzzy choroidal vessels	5 (14.7)
Normal	3 (8.8)

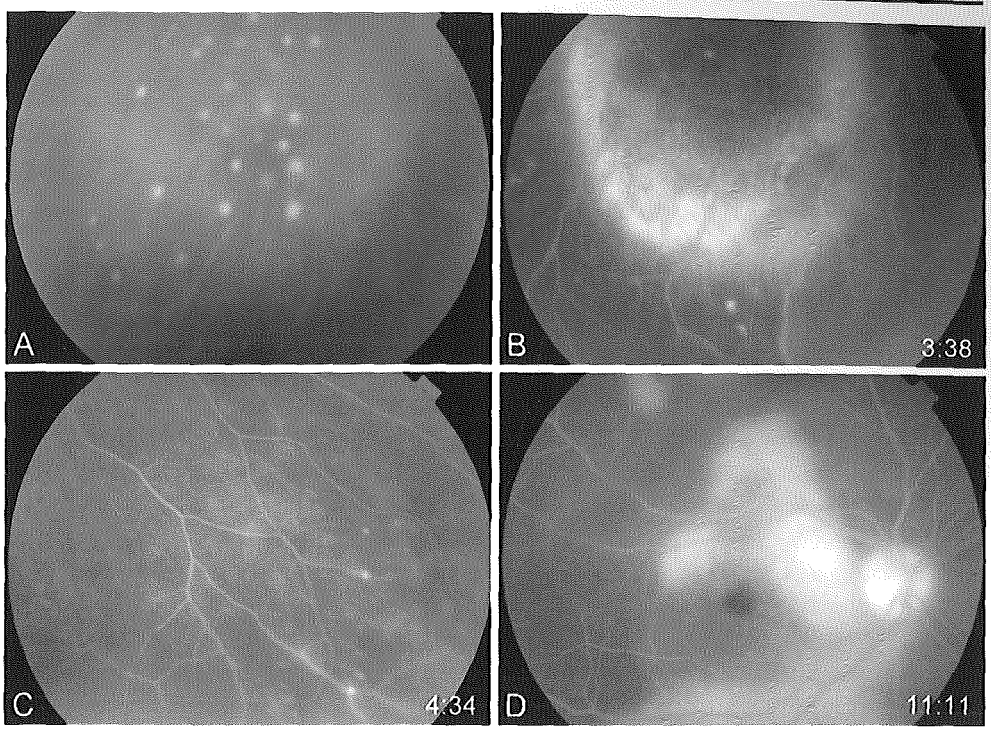

Fig. 1 **a** Fundus photograph depicting snowballs in the vitreous. **b, d** Extensive central and peripheral retinal staining and/or capillary leakage in FA. **c** Foci of peripheral retinal vascular staining in FA

fundoscopy, and were observed in 13 patients (59.1%) (Fig. 2). The second pattern corresponded to scattered hyperfluorescent spots (hot spots) appearing in the late phases of the angiogram, in the mid-periphery and/or the posterior pole present in 11 patients (50%). The third pattern was fuzzy choroidal vessels with leakage from the intermediate phase of the angiogram onwards in five patients (14.7%). In 13.6% of patients, the persistent variant of dark dots that remained unaltered in the late frames of the angiogram was observed, while 45.5% of patients presented both persistent and vanishing dark dots, the latter becoming isofluorescent in late frames. Seventeen patients were submitted to the same angiographic investigations after the completion of an antibiotic treatment regimen for neurosyphilis. Where comparison was possible, in FA vascular staining disappeared after treatment in five out of seven cases (71.4%), disc hyperfluorescence in five out of seven cases (71.4%), and retinal staining in four out of ten cases (40%). In ICGA, three cases of persistent dark dots remaining unaltered in size after treatment, corresponding to chorioretinal scars, were identified. Hot spots disappeared in almost every case after treatment (9 out of 11 patients, 82%) (Fig. 3).

Out of the 23 patients, 13 had inflammatory signs evidenced by the presence of anterior uveitis and/or vitritis, whereas ten did not. Out of the latter patients, six had concomitant optic nerve involvement, two had posterior placoid chorioretinitis, three had retinal staining in FA, and only one had vascular staining, whereas no patient without anterior uveitis and/or vitritis presented with macular edema. With regard to dark dots, which were more common in eyes with anterior uveitis and/or vitritis though not in a statistically significant way, they were present in all four cases that presented relapse of inflammation after proper antibiotic treatment.

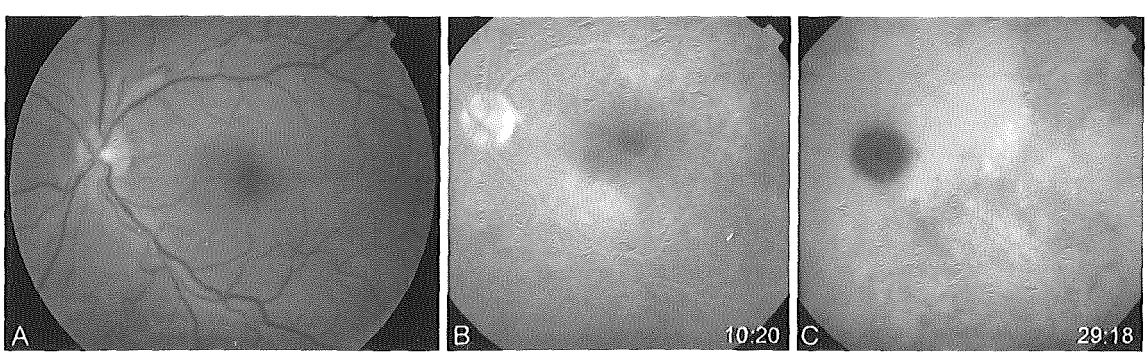

Fig. 2 **a** Fundus photograph depicting normal retina. **b** FA of the same case revealing minimal retinal staining. **c** ICGA of the same case revealing extensive dark dots and some hot spots, invisible on both fundus photograph and FA

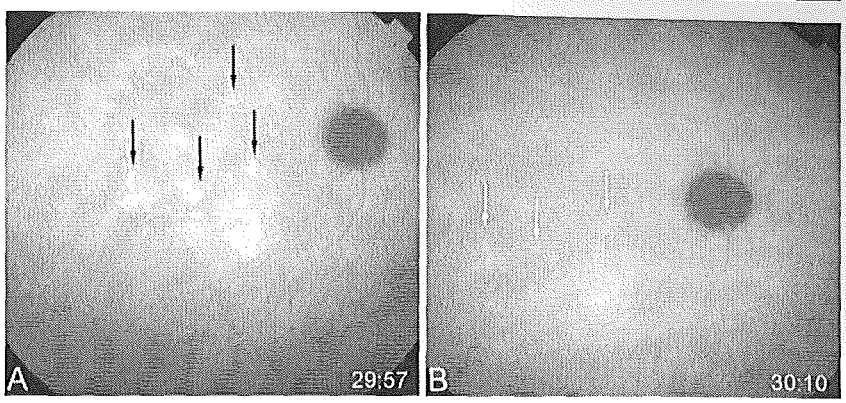

Fig. 3 **a** ICGA revealing hot spots. **b** Disappearance of hot spots after treatment

Associations among the various angiographic manifestations in FA and ICGA are presented in the triangular Table 2. It is obvious that no significant associations could be identified, other than a weak trend implicating vascular staining and macular edema in FA (p=0.067, Fisher's exact test), though not reaching statistical significance.

Associations between the two most frequent angiographic manifestations in FA, retinal staining and vascular staining, and all registered baseline factors are presented in Tables 3 and 4 respectively. With regard to associations implicating specific angiographic features, vascular staining in FA exhibited a weak trend of association with vitritis (6/12 patients with vitritis also exhibited vascular staining in FA, whereas only 1/11 patients without vitritis exhibited vascular staining, p=0.069, Fisher's exact test), anterior uveitis (5/9 patients with anterior uveitis presented with vascular staining vs 2/14 patients without anterior uveitis, p=0.066, Fisher's exact test) and younger age at presentation [39.0 years (inter-quartile range (IQR) 9.2] for patients with vascular staining vs 47.8 (IQR 14.8) for those without, p=0.061, Mann–Whitney–Wilcoxon test), though none of the associations reached statistical significance. A strong association between presence of anterior uveitis and presence of vitritis was also identified (p=0.015, Fisher's exact test). The association between vascular staining in fluorescein angiography with worse visual acuity at baseline did not reach formal statistical significance (p=0.072, MWW), though there was a significant association with improvement in visual acuity after treatment (p=0.005), as exhaustively described in a previous publication [12]. There was a weak trend of association between disc hyperfluorescence in FA and seropositivity for HIV infection (2/2 patients with HIV also exhibited disc hyperfluorescence vs only 5/21 patients without HIV infection, p=0.083, Fisher's exact test) as well as between macular edema in FA and longer disease duration prior to initial presentation [225 days (IQR 122) for patients with macular edema vs 12 (IQR 23) for patients without macular edema, p=0.061, MWW], though the associations did not reach statistical significance. As expected, disc hyperfluorescence was significantly associated with optic nerve involvement (p<0.001). All other associations implicating specific FA manifestations were non-significant.

Associations between the presence of any dark dots in ICGA and any other parameter are presented in Table 5. The presence of any dark dots was significantly associated with anterior uveitis (p=0.031, Fisher's), while dark dots were more common in patients with anterior uveitis and/or vitritis (p=0.079, Fisher's). The presence of any hot spots in ICGA was associated with male gender (p=0.012, Fisher's) and longer duration of symptoms prior to initial visit (p=0.032, MWW), as can be seen in Table 6. The former association remained significant even after the exclusion of patients positive for HIV infection (p=0.008, Fisher's). There was, however, no association between hot spots and any sign of active ocular inflammation.

In cases with bilateral disease, angiographic manifestations strongly correlated between fellow eyes as follows: retinal staining (rho=0.854, p=0.005), vascular staining

Table 2 Associations between the various angiographic manifestations in FA and ICGA

	Retinal staining	Vascular staining	Disc hyperfluorescence	Macular edema	Dark dots	Hot spots
Retinal staining	—					
Vascular staining	0.405	—				
Disc hyperfluorescence	0.405	>0.999	—			
Macular edema	0.104	0.067	0.557	—		
Dark dots	0.674	0.648	0.648	0.616	—	
Hot spots	>0.999	>0.999	>0.999	>0.999	>0.999	—

Table 3 Variables associated with retinal staining (patient-based analysis). Percentages are given with 100% corresponding to each row

	Retinal staining	No retinal staining	
Categorical variables	Freq (%)	Freq (%)	*P*
Gender			>0.999[F]
Male (*n*=16)	7 (43.8)	9 (56.3)	
Female (*n*=7)	3 (42.9)	4 (57.1)	
Involvement			0.402[F]
Unilateral (*n*=10)	3 (30.0)	7 (70.0)	
Bilateral (*n*=13)	7 (53.9)	6 (46.2)	
HIV status			0.486[F]
Positive (*n*=2)	0 (0.0)	2 (100.0)	
Negative (n=21)	10 (47.6)	11 (52.4)	
Pain as a calling sign			0.074[F]
Yes (*n*=8)	1 (12.5)	7 (87.5)	
No (*n*=15)	9 (60.0)	6 (40.0)	
Optic neuropathy			> 0.999[F]
Yes (*n*=9)	4 (44.4)	5 (55.6)	
No (*n*=14)	6 (42.9)	8 (57.1)	
Anterior uveitis			>0.999[F]
Yes (*n*=9)	4 (44.4)	5 (55.6)	
No (*n*=14)	6 (42.9)	8 (57.1)	
Vitritis			0.214[F]
Yes (*n*=12)	7 (58.3)	5 (41.7)	
No (*n*=11)	3 (27.3)	8 (72.7)	
Anterior uveitis and/or vitritis**			0.402[F]
Yes (*n*=13)	7 (53.9)	6 (46.1)	
No (*n*=10)	3 (30.0)	6 (70.0)	
Relapse after treatment			0.582[F]
Yes (*n*=4)	1 (25.0)	3 (75.0)	
No (*n*=15)	8 (53.3)	7 (46.7)	
Continuous variables	Median (IQR)	Median (IQR)	*P*
Age (years)	43.0 (11.5)	47.6 (11.8)	0.385[MWW]
Duration of symptoms prior to initial visit (days)	36 (87)	90 (146)	0.755[MWW]

[F] Fisher's exact test

[MWW] Mann–Whitney–Wilcoxon test

Table 4 Variables associated with vascular staining (patient-based analysis). Percentages are given with 100% corresponding to each row

	Vascular staining	No vascular staining	
Categorical variables	Freq (%)	Freq (%)	*P*
Gender			>0.999[F]
Male (*n*=16)	5 (31.2)	11 (68.8)	
Female (*n*=7)	2 (28.6)	5 (71.4)	
Involvement			0.650[F]
Unilateral (*n*=10)	4 (40.0)	6 (60.0)	
Bilateral (*n*=13)	3 (23.1)	10 (76.9)	
HIV status			0.526[F]
Positive (*n*=2)	1 (50.0)	1 (50.0)	
Negative (*n*=21)	6 (28.6)	15 (71.4)	
Pain as a calling sign			0.182[F]
Yes (*n*=8)	4 (50.0)	4 (50.0)	
No (*n*=15)	3 (20.0)	12 (80.0)	
Optic neuropathy			> 0.999[F]
Yes (*n*=9)	3 (33.3)	6 (66.7)	
No (*n*=14)	4 (28.6)	10 (71.4)	
Anterior uveitis			0.066[F]
Yes (*n*=9)	5 (55.6)	4 (44.4)	
No (*n*=14)	2 (14.3)	12 (85.7)	
Vitritis			0.069[F]
Yes (*n*=12)	6 (50.0)	6 (50.0)	
No (*n*=11)	1 (9.1)	10 (90.9)	
Anterior uveitis and/or vitritis**			0.089[F]
Yes (*n*=13)	6 (46.1)	7 (53.9)	
No (*n*=10)	1 (10.0)	9 (90.0)	
Relapse after treatment			0.557[F]
Yes (*n*=4)	2 (50.0)	2 (50.0)	
No (*n*= 15)	4 (26.7)	11 (73.3)	
Continuous variables	Median (IQR)	Median (IQR)	*P*
Age (years)	39.0 (9.2)	47.8 (14.8)	0.061[MWW]
Duration of symptoms prior to initial visit (days)	7 (147)	75 (115.5)	0.946[MWW]

[F] Fisher's exact test

[MWW] Mann–Whitney–Wilcoxon test

(rho=0.779, p=0.038), macular edema (rho=0.779, p=0.038), dark dots (rho=0.810, p=0.024),and hot spots (rho=0.837, p=0.010). Disc hyperfluorescence did not exhibit a significant correlation in cases with bilateral disease (rho=0.426, p=0.203), with rho values corresponding to Pearson's correlation coefficient and p-values deriving from Fisher's exact test. In the eye-based analysis, a shift was observed of some statistically non-significant results towards statistical significance, as is thoroughly presented in the Appendix.

Discussion

We conducted this exploratory study in search of associations between specific angiographic manifestations and several baseline demographic, clinical, or laboratory parameters. As regards the associations implicating specific angiographic manifestations in FA, only the one between vascular staining and improvement in visual acuity after treatment reached formal statistical significance. Several weak trends of association were, however, highlighted in this analysis, specifically

Table 5 Variables associated with dark dots (patient-based analysis). Percentages are given with 100% corresponding to each row

	Dark dots	No dark dots	
Categorical variables	Freq (%)	Freq (%)	*P*
Gender			>0.999[F]
Male (*n*= 16)	9 (56.3)	7 (43.7)	
Female (*n*=6)	4 (66.7)	2 (33.3)	
Involvement			0.192[F]
Unilateral (*n*= 10)	4 (40.0)	6 (60.0)	
Bilateral (*n*= 12)	9 (75.0)	3 (25.0)	
HIV status			>0.999[F]
Positive (*n*= 2)	1 (50.0)	1 (50.0)	
Negative (*n*=20)	12 (60.0)	8 (40.0)	
Pain as a calling sign			>0.999[F]
Yes (*n*=8)	5 (62.5)	3 (37.5)	
No (*n*=14)	8 (57.1)	6 (42.9)	
Optic neuropathy			0.674[F]
Yes (*n*=9)	6 (66.7)	3 (33.3)	
No (*n*=13)	7 (53.9)	6 (46.1)	
Anterior uveitis			0.031[F]
Yes (*n*=9)	8 (88.9)	1 (11.1)	
No (*n*=13)	5 (38.5)	8 (61.5)	
Vitritis			0.192[F]
Yes (*n*=12)	9 (75.0)	3 (25.0)	
No (*n*=10)	4 (40.0)	6 (60.0)	
Anterior uveitis and/or vitritis**			0.079[F]
Yes (*n*= 13)	10 (76.9)	3 (23.1)	
No (*n*=9)	3 (33.3)	6 (66.7)	
Relapse after treatment			0.245[F]
Yes (*n*=4)	4 (100.0)	0 (0.0)	
No (*n*=15)	8 (53.3)	7 (46.7)	
Continuous variables	Median (IQR)	Median (IQR)	*P*
Age (years)	45.1 (9.1)	42.2 (11.8)	0.867[MWW]
Duration of symptoms prior to initial visit (days)	12 (147)	90 (83)	0.867[MWW]

[F] Fisher's exact test

[MWW] Mann–Whitney–Wilcoxon test

Table 6 Variables associated with hot spots (patient-based analysis). Percentages are given with 100% corresponding to each row

	Hot Spots	No Hot Spots	
Categorical variables	Freq(%)	Freq(%)	p
Gender*			0.012[F]
Male (*n*=16)	11 (68.8)	5 (31.2)	
Female (*n*=6)	0 (0.0)	6 (100.0)	
Involvement			0.670[F]
Unilateral (*n*=10)	6 (60.0)	4 (40.0)	
Bilateral (*n*=12)	5 (41.7)	7 (58.3)	
HIV status			0.476[F]
Positive (*n*=2)	0 (0.0)	2 (100.0)	
Negative (*n*=20)	11 (55.0)	9 (45.0)	
Pain as a calling sign			0.659[F]
Yes (*n*=8)	3 (37.5)	5 (62.5)	
No (*n*=14)	8 (57.1)	6 (42.9)	
Optic neuropathy			> 0.999[F]
Yes (*n*=9)	4 (44.4)	5 (55.6)	
No (*n*=13)	7 (53.9)	6 (46.1)	
Anterior uveitis			>0.999[F]
Yes (*n*=9)	4 (44.4)	5 (55.6)	
No (*n*=13)	7 (53.9)	6 (46.1)	
Vitritis			0.670[F]
Yes (*n*=12)	7 (58.3)	5 (41.7)	
No (*n*=10)	4 (40.0)	6 (60.0)	
Anterior uveitis and/or vitritis**			0.387[F]
Yes (n=13)	8 (61.5)	5 (38.5)	
No (n=9)	3 (33.3)	6 (66.7)	
Relapse after treatment			0.582[F]
Yes (*n*=4)	1 (25.0)	3 (75.0)	
No (*n*=15)	8 (53.3)	7 (46.7)	
Continuous variables	Median (IQR)	Median (IQR)	*P*
Age (years)	39.0 (18.4)	45.1 (8.9)	0.376[MWW]
Duration of symptoms prior to initial visit (days)	90 (210)	7 (59)	0.032[MWW]

* After the exclusion of patients with HIV infection, the association persists (11/15 males vs 0/5 females exhibit hot spots in ICG, $p=0.008$)

[F] Fisher's exact test

[MWW] Mann–Whitney–Wilcoxon test

between vascular staining and anterior uveitis, vitritis, anterior uveitis and/or vitritis, worse visual acuity at presentation, and younger age at presentation, as well as between disc hyperfluorescence and seropositivity for HIV and between macular edema and longer disease duration prior to the initial visit. The findings implicating vascular staining may point to a close association between these markers of active inflammation, indicating that eyes with vascular staining are more severely inflamed, which in turn may account for the weak trend towards worse BCVA at baseline in these patients. As evidenced in our previous study, improvement in visual acuity after treatment was significantly associated with presence of vascular staining in FA, underlining the reversible nature of this type of ocular inflammatory reaction in the context of ocular syphilis [12]. The high rate of disappearance of vascular staining in FA performed after treatment points to the same conclusion, indicating that vasculitis is not accompanied by permanent visual repercussions in ocular syphilis, when properly treated. The fact that all patients with HIV seropositivity

exhibited disc hyperfluorescence in FA, illustrates a probable previously unrecognised site of preferential posterior involvement of ocular syphilis in the context of HIV co-infection. The potential increased prevalence of macular edema in patients with longer duration of intra-ocular inflammation has been suspected in uveitis [14], and may point to a deleterious effect of persistent inflammatory stimuli, leading to gradual accumulation of intraretinal fluid in the macular area. The aspect of "leopard spots" in fluorescein angiography described by Gass [10] in the context of syphilitic posterior placoid chorioretinitis as being highly indicative of syphilitic infection was also observed in four patients in our series. Interestingly, patients without anterior uveitis and/or vitritis mainly presented with optic nerve involvement, and to a lesser extent posterior placoid chorioretinitis and retinal staining, though only one such patient exhibited vascular staining, and none had macular edema.

Similar patterns in ICGA to those observed in our series have been described in other forms of granulomatous posterior uveitis, such as sarcoidosis and tuberculosis [15, 16], and are not unique to ocular syphilis. Probable interpretations for the above mentioned patterns are atrophy, fibrosis, or full-thickness granuloma for persistent dark dots, partial thickness granuloma or delayed perfusion of choriocapillaris for vanishing dark dots, and choroidal vasculitis for fuzzy choroidal vessels. Dark dots have also been described in ocular sarcoidosis and ocular tuberculosis, the latter allegedly being associated with more extensive and more confluent lesions [17]. Our study revealed a significant association between presence of dark dots and anterior uveitis, and a weak trend of association with presence of anterior uveitis and/or vitritis. It should be emphasized that there was a strong association between the presence of anterior uveitis and the presence of vitritis, prompting us to introduce a combined parameter implicating both inflammatory indicators and to test all baseline factors against this parameter as well. Dark dots were present in all four patients that exhibited relapse of inflammation after initial remission following proper antibiotic treatment, though no statistically significant association could be drawn from such small numbers. We suggest that the presence of dark dots, excluding those associated with atrophy, may signify active granulomatous posterior choroidal inflammation. Due to the small sample, however, we were unable to identify the specific characteristics of dark dots, for instance size, number, and localisation, which are more evocative of active inflammation.

With regard to hot spots, although they have been observed in other granulomatous uveitis, their high prevalence in ocular syphilis could be characteristic to the disease. These features have been described in the article by Mora et al. [11], and probable proposed interpretations include fixing of ICG molecules on active granuloma or staining of leucocytes. These manifestations have also been alleged to indicate active disease or long-standing disease. The former assumption was not, however, statistically confirmed in the present study. On the contrary, the lack of association between hot spots and any ocular manifestation with important functional repercussions, such as macular edema, optic neuropathy, or anterior uveitis, may reveal an exclusively choroidal origin of these angiographic features. On the other hand, the identified association between the presence of hot spots and a longer duration of symptoms prior to the first visit may render this angiographic finding indicative of long-standing disease. Hot spots appeared to be significantly more common in male patients. This association, though persisting even after the exclusion of patients with HIV co-infection, was rather more difficult to interpret.

Surprisingly, no association could be identified between various angiographic manifestations both in FA and ICGA, other than a weak positive trend implicating vascular staining and macular edema. Although both vascular staining in FA and dark dots in ICGA appear to be more common in eyes with anterior uveitis and/or vitritis, they do not seem to coexist in the same eye. This observation, in conjunction with the absence of any other association between ICGA findings and any clinical parameter indicative of retinal inflammation such as retinal staining or macular edema, could justify the speculation of two morphologically and angiographically distinct patterns of syphilitic eye disease, namely a predominantly choroidal versus a predominantly retinal variant.

Inter-eye correlation of angiographic manifestations in case of bilateral disease involvement appears significant and strong as regards all main factors apart from disc hyperfluorescence. This analysis makes it possible to provide useful insight into the degree of correlation of angiographic findings between fellow eyes in bilateral ocular syphilis, which has not so far been reported. Given the high degree of inter-eye correlation of angiographic manifestations identified, the use of a patient-based analysis becomes even more appropriate in the context of the present study.

This study has certain limitations stemming mainly from its retrospective design and the small study sample. A further shortcoming lies in the loss of six patients to follow-up with regard to angiographic evaluation after treatment, further limiting our ability to assess the effect of treatment on observed angiographic patterns. It should also be emphasized that given the small study sample, multivariate analysis could not be performed so as to avoid over-interpretation of available data. Observed associations may therefore be prone to mutual confounding, and their independence may not be warranted.

We conclude, based on our findings, that angiographic investigation in ocular syphilis can offer valuable information concerning disease severity and duration, and can even contribute some clues to disease prognosis. Vascular staining in FA and dark dots in ICGA appear to be more common in more severely inflamed eyes with anterior uveitis and/or vitritis, whereas hot spots are more often present in patients with long-standing disease without other signs of severe

inflammation. Two variants of the disease, one with predominantly choroidal involvement and one predominantly retinal, could be hypothesized. In view, however, of the exploratory nature of the current study and the above-mentioned limitations, further corroborative studies are required to confirm our findings. Nevertheless, some earlier arbitrary hypotheses concerning the significance of specific angiographic features in granulomatous posterior uveitis were for the first time statistically investigated in the present study.

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We particularly thank Catherine Guex-Crosier for her valuable contribution to data collection and management.

Appendix

An eye-based analysis of registered data was performed in the service of comprehensiveness and in an attempt to exploit all available data. Angiographic manifestations encountered in FA and ICGA on an eye basis are presented in Table 7. With regard to associations implicating specific angiographic features, vascular staining in FA exhibited a statistically significant association with vitritis (8/19 eyes with vitritis also exhibited vascular staining in FA, whereas only 1/17 eyes without vitritis exhibited vascular staining, $p=0.020$), anterior uveitis (7/15 eyes with anterior uveitis presented with vascular staining vs 2/21 eyes without anterior uveitis, $p=0.019$) and a weak trend implicating macular edema (4/8 eyes with macular oedema vs 5/28 eyes without macular edema exhibited vascular staining, $p=0.086$), with p-values derived from Fisher's exact test. The association between vascular staining in fluorescein angiography with worse visual acuity at baseline did not reach formal statistical significance ($p=0.072$, MWW), though there was a significant association with improvement in visual acuity after treatment ($p=0.005$), as exhaustively described in a previous publication [12]. Disc hyperfluorescence in FA was significantly associated with seropositivity for HIV infection (3/3 eyes with HIV also exhibited disc hyperfluorescence vs only 6/33 eyes without HIV infection, $p=0.012$, Fisher's exact test).

Associations between the presence of any dark dots in ICGA and any other parameter are presented in Table 8. The presence of any dark dots was significantly associated with

Table 7 Findings in fluorescein and indocyanine-green angiography ($n=39$ eyes)

	N (%)
Findings in fluoroangiography ($n=36$)	
Disc hyperfluorescence	9 (25.0)
Macular edema	5 (13.9)
Vascular staining	9 (25.0)
Retinal staining and/or capillary leakage	15 (41.7)
Retinal ischemia	3 (6.5)
Normal	3 (6.5)
Findings in ICGA ($n=34$)	
Dark dots	21 (61.8)
Persistent dark dots	4 (11.8)
Persistent and vanishing dark dots	17 (50.0)
Hot spots	15 (44.1)
Fuzzy choroidal vessels	5 (14.7)
Normal	3 (8.8)

Table 8 Variables associated with dark dots (eye-based analysis). Percentages are given with 100% corresponding to each row

	Dark dots	No dark dots	
Categorical variables	Freq(%)	Freq(%)	*P*
Anterior uveitis			0.013^{F}
Yes ($n=15$)	13 (86.7)	2 (13.3)	
No ($n=19$)	8 (42.1)	11 (57.9)	
Vitritis			0.034^{F}
Yes ($n=19$)	15 (79.0)	4 (21.0)	
No ($n=15$)	6 (40.0)	9 (60.0)	
Vascular staining in FA			0.427^{F}
Yes ($n=9$)	7 (77.8)	2 (22.2)	
No ($n=25$)	14 (56.0)	11 (44.0)	
Relapse after treatment			0.066^{F}
Yes ($n=7$)	7 (100.0)	0 (0.0)	
No ($n=24$)	14 (58.3)	10 (41.7)	

^{F}p-value derived from Fisher's exact test

Table 9 Variables associated with hot spots (eye-based analysis). Percentages are given with 100% corresponding to each row

	Hot spots	No hot spots	
Categorical variables	Freq (%)	Freq (%)	P
Gender			$<0.001^{F}$
Male ($n=23$)	15 (65.2)	8 (34.8)	
Female ($n=11$)	0 (0.0)	11 (100.0)	
Relapse			0.201^{F}
Yes ($n=7$)	1 (14.3)	6 (85.7)	
No ($n=24$)	11 (45.8)	13 (54.2)	
Continuous variables	Median (IQR)	Median (IQR)	*P*
Duration of symptoms prior to initial visit (days)	7 (149)	120 (210)	0.007^{MWW}

^{F}p-value derived from Fisher's exact test; ^{MWW}p-value derived from Mann–Whitney–Wilcoxon test for independent samples; IQR: interquartile range

anterior uveitis (p=0.013), vitritis (p=0.034), while dark dots were observed in all seven eyes with relapse of inflammation after proper antibiotic treatment (p=0.066). The presence of any hot spots in ICGA was associated with male gender (p<0.001) and longer duration of symptoms prior to initial visit (p=0.007), as can be seen in Table 9. There was, however, no association with relapse of inflammation after treatment (p=0.201).

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