Prospective Evaluation of Ocular Syphilis: A Screening-Based Approach

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ABSTRACT

Objective: This study aims to evaluate the prevalence and clinical characteristics of ocular syphilis (OS) through a screening-based approach in syphilis patients, including both symptomatic and asymptomatic cases.

Methods: A total of 46 syphilis patients were included in this prospective study. Patients diagnosed with syphilis were referred for ophthalmologic evaluations regardless of symptoms. Clinical data, including syphilis stage, sexual orientation, and HIV co-infection, rapid plasma reagin (RPR) titer, and ocular findings were recorded.

Results: The mean age was 43.0 ± 11.6 years, and 42 patients (91.3%) were male. Among the patients, 8 (17.4%) had OS, affecting 14 eyes. The majority of OS patients were in the secondary stage of syphilis (87.5%). Six patients with OS exhibited ocular symptoms. The median RPR titer was significantly higher in the OS group ($p< 0.001$). Final diagnoses included interstitial keratitis, syphilitic optic neuropathy, granulomatous anterior uveitis, panuveitis, acute syphilitic posterior placoid chorioretinitis, and syphilis-related acute retinal necrosis. Baseline best-corrected visual acuity (BCVA) in OS patients was 0.81 ± 0.83 logMAR, and the final BCVA improved to 0.14 ± 0.13 logMAR ($p= 0.001$).

Conclusion: This study demonstrates the significant prevalence of OS, particularly in secondary syphilis, and emphasizes the importance of comprehensive ocular screening, even in the absence of visual symptoms. Early detection and treatment can significantly improve visual outcomes. While syphilis stage, and elevated RPR titers were key factors, special attention should be given to HIV-negative patients, who may present with more subtle or asymptomatic manifestations, potentially leading to delayed diagnosis.

Key words: Syphilis, Ocular Syphilis, ASPPC, Syphilitic Optic Neuropathy, Uveitis

INTRODUCTION

Syphilis is a multi-systemic infection caused by Treponema pallidum, affecting a range of organs, including the eyes and central nervous system. Clinical findings are observed during the early (primary and secondary) and late (tertiary) stages of syphilis, whereas in the latent stage, cases are asymptomatic and only syphilis-specific serological tests are positive. Although syphilis is a well-known cause of ocular involvement, it remains frequently underdiagnosed due to its diverse clinical presentation.[1,2]

Ocular syphilis (OS) encompasses a range of inflammatory eye conditions resulting from syphilis, including episcleritis, interstitial keratitis, uveitis, retinal vasculitis, and optic neuropathies.[3,4]. Among these, uveitis and optic neuropathies are the most commonly observed ocular manifestations. These conditions can occur at any stage of the disease and may affect any part of the eye.[4,5] The visual prognosis is generally favorable when diagnosed and treated promptly.[6] However, OS may occasionally be the sole clinical manifestation, mimicking other ophthalmic

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conditions such as non-infectious uveitis. Misdiagnosis and inappropriate treatment—especially the use of steroids—can significantly worsen the condition, potentially leading to irreversible visual loss.[1]

To prevent diagnostic errors and ensure timely intervention, this study aims to evaluate the prevalence of ocular syphilis. By employing a prospective screening approach, we aim to identify ocular findings that may be more common than initially anticipated. Our goal is to underline the importance of comprehensive ocular screening in syphilis patients, facilitating early detection and treatment of ocular syphilis.

METHODS

This prospective study aims to evaluate syphilis-related ocular complications in patients diagnosed with syphilis. The study was conducted at Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey, in collaboration with the Departments of Ophthalmology and Infectious Diseases and Clinical Microbiology. Institutional review board approval was obtained (IRB Number: 2023-03.103), and the study adhered to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Patient Selection and Syphilis Diagnosis

Between June 2024 and May 2025, a total of 64 patients were diagnosed with syphilis. Diagnosis was based on clinical signs and confirmed through serological testing, including rapid plasma reagin (RPR) and Treponema pallidum hemagglutination assay (TPHA). RPR was used as a non-treponemal test, while TPHA served as a treponemal confirmatory test. Detailed demographic and clinical data, including age, gender, sexual orientation, Human Immunodeficiency Virus (HIV) coinfection and syphilis stage, were collected. Only patients with a new diagnosis of syphilis were included in the study, while those who had previously received treatment or declined participation were excluded.

Ophthalmologic Evaluation

All patients diagnosed with syphilis, regardless of symptoms, were referred to the ophthalmology clinic for comprehensive ophthalmic evaluations. These assessments were conducted by a specialist in uveitis and retinal diseases (S.C.H.). Ophthalmic examinations included best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, intraocular pressure measurement, dilated fundus examination, optical coherence tomography, and fundus photography. Visual acuity was converted to LogMAR for statistical analysis. Count fingers, hand motion, light perception, and no light perception were assigned LogMAR values of 2.0, 2.3, 2.6, and 2.9, respectively. Anterior chamber cells and vitreous haze were graded according to the Standardization of Uveitis Nomenclature (SUN) criteria.[7,8]

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as median (minimum-maximum) or mean (standard deviation), depending on the normality of the distribution. Categorical variables were analyzed using Pearson's Chi-square or Fisher's exact tests, while non-normally distributed continuous variables were compared using the Mann-Whitney U test. For comparisons among multiple groups, the Kruskal-Wallis test was used. A significance level of $p < 0.05$ was considered, with Bonferroni correction applied for multiple comparisons.

RESULTS

A total of 46 patients were included in the study, with 42 patients (91.3%) being male. The mean age was 43.0 ± 11.6 years. Regarding disease stage, 2 patients (4.3%) were in the primary stage, 12 (26.1%) in the secondary stage, and 32 (69.6%) in the latent stage of syphilis. In terms of sexual orientation, 21 patients (45.7%) identified as heterosexual, 16 (34.8%) as bisexual, and 9 (19.6%) as men who have sex with men. Additionally, 38 patients (82.6%) were HIV-positive (Table 1).

Out of the 46 patients, 8 (17.4%) exhibited OS, affecting a total of 14 eyes. Two patients (25%) had unilateral involvement. No significant correlation was found between HIV status and laterality ($p = 1.000$). Six OS patients had ocular symptoms, with 6 experiencing blurred vision and 4 reporting floaters. One patient had previously visited an external eye doctor, who diagnosed uveitis. After being diagnosed as HIV-positive, the patient was referred to an infectious disease specialist, and syphilis was subsequently diagnosed after further tests at our hospital (patient no.1).

The majority of patients with OS were in the secondary stage, as shown in Table 1. Statistically significant differences were observed between the OS and non-OS

groups regarding disease stage ($p < 0.001$) and symptom presence ($p < 0.001$). The median RPR titer was significantly higher in the OS group ($p < 0.001$) (Figure 1).

Among the OS patients, 6 exhibited granulomatous or microgranulomatous keratic precipitates, 6 had anterior chamber cells, and 3 had vitreous cells. Final diagnoses included one case of interstitial keratitis, one of syphilitic optic neuropathy, three cases of granulomatous anterior uveitis, one case of panuveitis, one case of acute syphilitic posterior placoid chorioretinitis (ASPPC), and one diagnosed with syphilis-related acute retinal necrosis (ARN) (Table 2). The baseline BCVA for eyes with OS was 0.81 ± 0.83 LogMAR. All patients with OS received intravenous crystalline penicillin G (24 million units per day for 14 days, administered as 4 million units every four hours). In cases with optic neuropathy or posterior segment involvement, systemic corticosteroid therapy was initiated after 48 hours of penicillin treatment, in consultation with the infectious disease specialist. Following treatment, the final BCVA improved significantly to 0.14 ± 0.13 logMAR ($p = 0.001$).

While 3 patients refused lumbar puncture (LP), the procedure was performed on 5 OS cases. In 3 of these cases, cerebrospinal fluid (CSF) protein levels were ≥0.45 g/L, and all CSF VDRL tests were negative. Additionally, among the 46 patients referred for syphilis screening, cytomegalovirus retinitis was diagnosed in 4 patients, and HIV-related retinopathy was identified in 3 patients.

Table 1. *Demographic and Clinical Characteristics of Syphilis Patients with and without Ocular Syphilis*

	All Patients (n=46)	OS+ (n= 8)	OS- (n= 38)	p
Age (mean± SD)	43.0 ± 11.6	49.1± 9.3	41.7± 11.7	0.070
Gender (M/F)	42/4	6/2	36/2	0.134
Disease Stage (n, %)				< 0.001
Primary	2 (4.3)	0 (0)	2 (5.3)	
Secondary	12 (26.1)	7 (87.5)	5 (13.2)	
Latent	32 (69.6)	1 (12.5)	31 (81.6)	
HIV Coinfection (n, %)	38 (82.6)	5 (62.5)	33 (86.8)	0.129
Symptom (n, %)	12 (26.1)	6 (75)	5 (13.2)	< 0.001
RPR Titre (median (min-max))	1/16 (1/16-1/256)	1/48 (1/32- 1/128)	1/16 (1/16- 1/256)	< 0.001

OS: Ocular Syphilis, M: Male, F: Female, HIV: Human Immunodeficiency Virus,
RPR: Rapid plasma reagin

Table 2. *Clinical Characteristics and Ocular Findings in Ocular Syphilis Patients*

No	Age	Sex	Disease Stage	HIV+	Affected Eye	Ocular Manifestation	Baseline BCVA	AC Cells	Final BCVA	Vitritis	Previous Ocular History
1	28	M	S	+	OU	ARN	HM/ HM	+/+	0.8/0.8	+/+	Strabismus, ambliopia
2	51	M	S	+	OU	ASPPC	0.3/ 0.4	+/+	0.7/0.7	+/+	CMV retinitis
3	50	M	L	+	OS	Interstitial keratitis	0.1	-	0.3	-	-
4	55	F	S	-	OU	Anterior uveitis	0.9/8 0.6	+/+	1.0/1.0	-/-	-
5	50	M	S	+	OU	Panuveitis	HM/ 0.2	+/+	0.4/0.7	+/+	-
6	41	M	S	+	OU	Optic neuropathy	0.5/ 0.6	-/-	1.0/1.0	-/-	-
7	57	F	S	-	OU	Anterior uveitis	0.2/ 0.4	+/+	0.8/0.6	-	Left exotropia, amblyopia
8	57	M	S	-	OS	Anterior uveitis	0.2	+	0.5	-	-

M: Male, F: Female, S: Secondary, L: Latent, OU: Both Eyes, OS: Left Eye, ARN: Acute Retinal Necrosis, ASPPC: Acute Syphilitic Posterior Placoid Chorioretinitis, BCVA: Best-Corrected Visual Acuity, HM: Hand Motion, AC cells: Anterior Chamber Cells, CMV: Cytomegalovirus

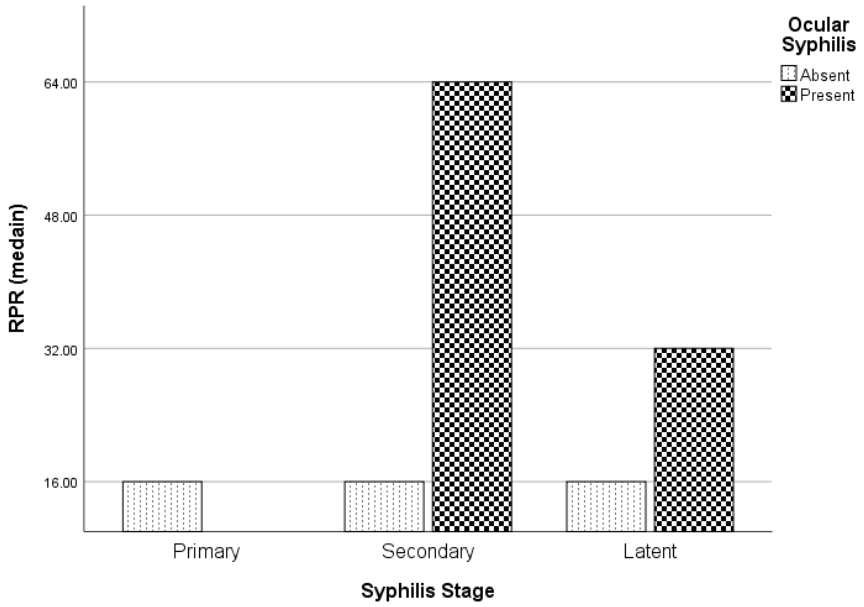

Figure 1. *Distribution of RPR Titers in Ocular Syphilis Patients by Disease Stage and Ocular Involvement*

DISCUSSION

Since the early 2000s, reported syphilis infection rates have increased.[9,10] This rise in syphilis cases has been accompanied by a corresponding increase in OS, albeit at lower rates.[11,12] Several studies have reported follow-up outcomes for OS patients, primarily focusing on those with diagnosed OS.[1,6,12,13] However, our study differs by adopting a screening-based methodology, targeting both symptomatic and asymptomatic syphilis patients before any treatment.

In our study, patients were referred to the ophthalmology department without specific inquiry about visual symptoms, and 17.4% of patients were found to have OS. This rate is notably higher compared to the 2.6% found by Gu et al., which may be attributed to methodological differences.[1] While Gu et al. conducted a retrospective study, our study used a prospective screening approach. Patients with ocular symptoms may have been more likely to participate, which could have further contributed to the higher detection rate in our study. Similarly, Klein et al. screened 93 syphilis patients and detected ocular involvement in 24.7% of cases.[5] Moreover, Du et al. carried out a screening study with 577 syphilis patients and identified 32 cases of syphilitic uveitis and 32 cases of syphilitic optic neuropathy, emphasizing the value of screening for OS.[14]

In Klein et al.'s study, most patients with OS (60.9%) were in the secondary stage, with optic nerve involvement also being predominant in this stage.[5] In the current study, similar to Klein et al.'s findings, a large proportion of patients with OS (87.5%) were in the secondary stage. These finding suggests that the secondary stage plays a significant role in OS, including optic nerve involvement, which may highlight the importance of early identification and treatment of syphilis in this stage to prevent further ocular complications.

Klein et al. also observed that a significant proportion of OS patients exhibited asymptomatic ocular inflammation.[5] Similarly, for anterior uveitis, 50% of the cases of OS were found to be silent and asymptomatic.[15] In a prospective study by Du et al., it was observed that 40% of eyes with secondary syphilitic optic disc edema were asymptomatic.[14] Likewise, our study found two asymptomatic cases of anterior uveitis, further emphasizing the need for screening programs to detect asymptomatic OS cases early.

Cope et al. reported that HIV-positive syphilis patients are more likely to develop OS, with the condition being more severe in this group.[16] In contrast, our study found no significant difference in the likelihood of developing OS between HIV-positive and HIV-negative syphilis patients. Previous research suggests that inflammation

tends to be more severe in HIV-positive OS patients.[17] In line with this, in our cohort, all patients with significant vitreous involvement or posterior segment pathologies were HIV-positive, while the three HIV-negative patients had isolated granulomatous anterior uveitis, two of whom were asymptomatic. This underscores the importance of paying special attention to HIV-negative patients, as they may present with asymptomatic OS, potentially leading to delayed diagnosis.

Harvey et al. found that panuveitis was the most common manifestation of OS (60%), while isolated anterior uveitis was observed in only 16% of cases.[12] Similarly, Mathew et al. reported panuveitis as the most common diagnosis (41.3%), with isolated anterior uveitis seen in just 9.5% of cases.[13] In contrast, our study found that 37.5% of HIV-negative OS patients (3 out of 8) exhibited isolated anterior uveitis. Posterior segment and optic nerve involvement, were observed less frequently in our cohort compared to previous studies. This discrepancy may be due to the relatively small sample size in our OS group, which could have influenced the statistical analysis and frequency of certain ocular manifestations.

In our study, 62.5% of OS cases were HIV-positive, consistent with the findings of Puech et al.[18] This contrasts with Sun et al., who reported only 2.9% of OS cases in HIV-positive.[19] Sun and colleagues noted that OS is more frequently found in HIV-negative patients in East Asian countries, such as China, compared to western countries. This discrepancy may be influenced by changing social behaviors, including the increased prevalence of men who have sex with men populations, as well as the large urban setting of our study, conducted in Istanbul.

Our study also observed higher RPR titers in the OS group, with a median titer of 1/48 (1/32-1/128), which is consistent with the findings of Sun et al., where 78.6% of OS cases had a RPR titer greater than 1/16 at presentation.[19] Additionally, a large cohort study identified an RPR titer greater than 1/8 as a significant risk factor for OS in multivariate analysis.[1] These findings emphasize the importance of screening for OS in patients with elevated RPR titers, as it may help in detecting asymptomatic cases and potentially preventing vision loss.

Ocular syphilis can present with a wide spectrum of clinical features, including ASPPC and optic nerve involvement. A recent review of 128 publications from 1988 to 2024 reported that the proportion of ASPPC within OS increased from 9.1% in 2001–2010 to 26.3% after 2020, indicating a significant rise in frequency.[20] Visual outcomes in ASPPC were generally favorable, with LogMAR 0.0 or better achieved in 44% of eyes, and 0.3 or better in 85% of eyes. While the review suggested similar outcomes for HIV-positive and HIV-negative patients, we did not perform a formal statistical comparison in our cohort due to small subgroup sizes. Nevertheless, individual patient outcomes in our study indicated that visual acuity improved in both groups, particularly among those with uveitic or optic neuropathic involvement, which is consistent with previous studies reporting favorable visual outcomes.[5,12] These observations underscore the importance of early recognition and timely treatment of OS. Prompt intervention can substantially improve visual prognosis, and raising clinician awareness about its diverse clinical spectrum remains crucial.

This study has several limitations. First, the small sample size of both the overall syphilis cohort and the OS group limits the generalizability of our findings. Furthermore, the study's design, primarily involving patients referred for ocular screening, may have introduced a selection bias as those with ocular symptoms may have been more likely to participate. However, the value of our study lies in the inclusion of asymptomatic cases and their clinical and serological characteristics, which provide valuable insights into the importance of early detection and screening of OS, even in the absence of symptoms.

In conclusion, our study highlights the significant prevalence of ocular syphilis, particularly in patients with secondary stage syphilis. Comprehensive ocular screening is crucial, even for patients without visual symptoms, as it facilitates early diagnosis and treatment, which significantly improve visual outcomes. Furthermore, RPR titers and syphilis stages were found to be significant factors in ocular syphilis, and HIV-negative patients, who may present with more subtle or asymptomatic manifestations, require special attention. This group may be at risk for delayed diagnosis, emphasizing the need for careful monitoring. Further research with larger sample sizes is needed to evaluate the

role of syphilis stages, HIV co-infection, and RPR titers in predicting ocular involvement and to optimize early diagnostic strategies.

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