

# Exploratory Analysis of Ocular Syphilis Epidemiology in a Tertiary Center

## Sífilis Ocular: O Ressurgimento de uma Doença Antiga, Experiência de um Centro Terciário em Portugal

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### ABSTRACT

**INTRODUCTION:** Syphilis incidence has been increasing and, consequently, so has ocular syphilis (OS), an uncommon cause of ocular inflammation with many disease phenotypes. We aimed to estimate the number of OS cases diagnosed in a tertiary centre in Portugal, to correlate with the increase in syphilis diagnosis and characterize the OS population.

**METHODS:** We conducted a retrospective, observational, single-center study that included patients with OS, from 2015 to 2023 at Centro Hospitalar e Universitário de Coimbra (CHUC). Demographic data were collected and a complete ophthalmological examination was performed with multimodal imaging acquisition. Data on syphilis incidence from the European Center for Disease Prevention and Control (ECDC) and Portuguese National Healthcare Service (NHS), correlated with OS data.

**RESULTS:** In total, 49 patients with OS were observed. The mean age of  $54.29 \pm 14.84$  years, 36 (73.47%) were male and 16 (44.44%) were men who have sex with men. Considering syphilis diagnosis at our institution, the proportion of ocular syphilis in these patients per year ranged from 0% to 7.14%. Twelve patients (24.49%) were co-infected with HIV. Forty-five patients (91.84%) complained of decreased visual acuity. Ocular pain, hyperemia, photophobia, photopsias and floaters were also reported. Nineteen patients (38.78%) had systemic findings (mostly skin rash). In 33 cases (67.35%), the presentation was bilateral and 24 (48.98%) presented with anterior segment involvement. Forty-two patients (85.71%) had posterior segment involvement and the most common phenotypical presentation was posterior placoid chorioretinitis (21%-50.0%). Nineteen patients (38.78%) had optic nerve involvement.

All patients were admitted and underwent 2-week treatment with endovenous penicillin. Visual acuity improved from logMAR 0.71 to logMAR 0.25 ( $p < 0.001$ ).

Syphilis incidence gradually increased in the years considered and a peak of disease diagnoses was registered in 2022, after the COVID-19 pandemic.

**CONCLUSION:** Syphilis is a public health challenge. OS is a heterogeneous disease with a wide range of presentations. The incidence is on the rise and must be considered in every patient with uveitis or optic neuritis.

**KEYWORDS:** Eye Infections, Bacterial/diagnosis; Eye Infections, Bacterial/epidemiology; Syphilis/diagnosis; Syphilis/epidemiology; Uveitis.

## RESUMO

**INTRODUÇÃO:** A incidência da sífilis tem aumentado, tal como, consequentemente, a sífilis ocular (SO), uma causa incomum de inflamação ocular com vários fenótipos de doença. Pretendemos estimar o número de casos de SO diagnosticados num centro terciário em Portugal, correlacionar com o aumento do diagnóstico de sífilis e caracterizar a população de SO.

**MÉTODOS:** Realizámos um estudo retrospectivo, observacional, unicêntrico que incluiu doentes com SO, de 2015 a 2023 no Centro Hospitalar e Universitário de Coimbra (CHUC). Foram colhidos dados demográficos e realizado um exame oftalmológico completo com aquisição de imagiologia multimodal. Os dados sobre a incidência da sífilis do Centro Europeu de Prevenção e Controlo das Doenças (ECDC) e do Serviço Nacional de Saúde (SNS) foram correlacionados com os dados da SO.

**RESULTADOS:** No total, foram observados 49 doentes com SO. A média de idades foi de 54,29±14,84 anos, 36 (73,47%) eram do sexo masculino e 16 (44,44%) eram homens que fazem sexo com homens. Considerando o diagnóstico de sífilis na nossa instituição, a proporção de sífilis ocular nesses doentes por ano variou de 0% a 7,14%. Doze doentes (24,49%) estavam co-infetados pelo VIH. Quarenta e cinco doentes (91,84%) queixaram-se de diminuição da acuidade visual. Dor ocular, hiperemia, fotofobia, ftopias e miodesópsias também foram relatadas. Dezanove doentes (38,78%) apresentaram sintomatologia sistémica (principalmente rash cutâneo). Em 33 casos (67,35%) a apresentação foi bilateral e 24 (48,98%) apresentaram envolvimento do segmento anterior. Quarenta e dois doentes (85,71%) apresentaram envolvimento do segmento posterior e a apresentação fenotípica mais comum foi a coriorretinite placóide posterior (21%-50,0%). Dezanove doentes (38,78%) tiveram envolvimento do nervo óptico.

Todos os doentes foram internados e submetidos a tratamento de 2 semanas com penicilina endovenosa. A acuidade visual melhorou de logMAR 0,71 para logMAR 0,25 ( $p<0,001$ ).

A incidência de sífilis aumentou gradualmente nos anos considerados e registou-se um pico de diagnósticos da doença em 2022, após a pandemia de COVID-19.

**CONCLUSÃO:** A sífilis constitui um desafio de saúde pública. A SO é uma doença heterogénea com uma ampla gama de apresentações. A incidência está a aumentar e deve ser considerada em todos os doentes com uveíte ou neuropatia óptica.

**PALAVRAS-CHAVE:** Infecções Oculares Bacterianas/diagnóstico; Infecções Oculares Bacterianas/epidemiologia; Sífilis/diagnóstico; Sífilis/epidemiologia; Uveíte.

## INTRODUCTION

Syphilis is a sexually transmitted disease (STD) caused by *Treponema pallidum*. Syphilis has been on the rise globally over the past decade.<sup>1</sup> According to the European Centre for Disease Prevention and Control (ECDC),<sup>2</sup> the incidence of syphilis (all stages) has gradually increased from 2010, where 18 829 cases were reported, which represents a notification rate of 4.2 cases per 100 000 population, to 2019, where 35 528 cases were reported, which represents a notification rate of 7.4 cases per 100 000 population. Since then, there is no European official surveillance report available. However, according to the Surveillance Atlas of Infectious Diseases of the ECDC,<sup>3</sup> in 2020, 23 487 cases were reported, which represents a notification rate of 5.63 per 100 000 population, and in 2021, 25 270 cases were reported, which represents a notification rate of 7.02 per 100 000 population.

The COVID-19 pandemic has introduced uncertainty and difficulty in interpreting the 2020 data,<sup>4</sup> and epidemiologic data since 2020 must be interpreted with caution. In Portugal, the last official data available is from the National Statistics Institute (INE)<sup>5</sup> and from the Transparency portal<sup>6</sup> and report to 2018.

On the other hand, as a consequence of the increasing incidence of syphilis in the last years, ocular syphilis (OS) has also been increasing. OS is an uncommon cause of ocular inflammation with many disease phenotypes, ranging from uveitis, which accounts for the majority of cases of ocular syphilis,<sup>7</sup> to phenotypes like scleritis and interstitial keratitis.<sup>8</sup> Although ocular involvement may occur at any stage, manifestations are more prevalent in the secondary and tertiary stages,<sup>9</sup> and range from 0.6% to 2% of all patients with syphilis at any stage of disease.<sup>8</sup> Eyelid or conjunctival chancres may occur in primary syphilis, while in

later stages, any part of the eye may become involved.<sup>10</sup> The most common presentation is uveitis, with chorioretinitis commonly occurring in the secondary stage and having a wide range of clinical presentations. The optic nerve may be involved in the form of optic disc edema, optic neuritis, perineuritis or papilledema.<sup>10</sup>

We aimed to estimate the number of OS cases diagnosed in our Centre from 2015 to 2023, and to correlate them with regional and national public health official registries. Additionally, we sought to characterize the OS population presenting to a tertiary center in Portugal, and to report the diverse phenotypic presentations and findings by multimodal imaging.

## MATERIAL AND METHODS

We conducted a retrospective, observational, single-center study which included consecutive newly diagnosed ocular syphilis patients with serologic confirmation, from January 2015 to May 2023 at Centro Hospitalar e Universitário de Coimbra (CHUC). Informed consent was obtained for every included subject. The study was approved by the local Ethics Committee and followed the tenets of the Declaration of Helsinki for biomedical research.

A detailed review of medical records was performed, and demographic data were collected. Clinical presentation details included the duration of ophthalmic symptoms, laterality, and a complete ophthalmological examination, which included best corrected visual acuity (BCVA), intraocular pressure (IOP), slit lamp biomicroscopy and fundus examination; focus was given to signs of intraocular inflammation, that were specifically noted. Uveitis was classified according to the Standardization of Uveitis Nomenclature (SUN) classification.<sup>11</sup> These data were complemented with multimodal imaging acquisition: Spectral-domain optical coherence tomography (OCT) (SD-OCT, SPECTRALIS, Heidelberg Engineering, Heidelberg, Germany), wide-field fundus photography and fundus autofluorescence (Optos California, Optos GmbH, Germany) and, when warranted, angiography (Heidelberg Spectralis Fluorescein Angiography Module) and standard automated perimetry (Humphrey Field Analyzer HFA 750 II (Carl Zeiss-Humphrey Systems, Dublin, California, USA)).

Serologic confirmation of systemic infection with *T. pallidum* included the reverse algorithm testing protocol,<sup>12</sup> which is routine in our center, and consists of IgG and IgM testing (chemiluminescent microparticle immunoassay - CMIA), and if positive, rapid plasma reagin (RPR) and *Treponema pallidum* particle agglutination (TPPA). Appropriate laboratory investigations in addition to the syphilis screening described above were sought to exclude other uveitic entities that could present similarly.

All patients were admitted and managed in a multidisciplinary team setting that included Ophthalmology and Infectious Diseases, and when warranted, other specialties, such as Neurology, Internal Medicine or Otorhinolaryngology. Clinical data were collected, including systemic manifestations and co-infections screening, with emphasis on HIV, hepatitis C and B and latent tuberculosis. Lumbar

puncture was performed when deemed necessary by the Infectious Diseases specialists.

Data on syphilis incidence from the ECDC and Portuguese National Healthcare Service (NHS), were also collected and correlated with OS data. The Annual Epidemiological Report for 2019 from the ECDC and the Surveillance Atlas of Infectious Diseases of the ECDC available online were consulted to obtain the confirmed syphilis cases and rates per 100 000 population from 2015 to 2021. These data were compared with Portuguese official registries, namely the “Transparency Portal” and the INE statistics, which include data until 2018.

A descriptive analysis was conducted to all study variables. Continuous variables were expressed as mean  $\pm$  standard deviation. BCVA was expressed in logMAR. Demographic and baseline data were described according to each variable type. Statistically significant results were considered for p-values lower than 0.05. For statistical analysis, GraphPad Prism Software for Windows, version 8.4.2 (GraphPad Software Inc, California, USA) was used.

## RESULTS

A total of 49 patients with ocular syphilis were observed at the Department of Ophthalmology between January 2015 and May 2023, distributed as follows: 6 in 2015, 0 in 2016, 1 in 2017, 4 in 2018, 4 in 2019, 5 in 2020, 6 in 2021, 16 in 2022 and 7 in 2023 (until May). Fig. 1 shows the distribution of confirmed OS cases per year parameterized by the number of months per year, in order to fairly compare the different periods, as in 2023 only the first 5 months were considered.

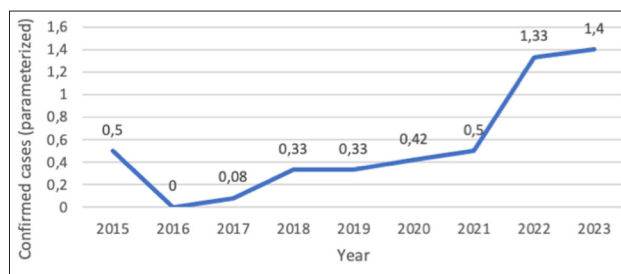


Figure 1. Distribution of confirmed OS cases in CHUC per year parameterized by the number of months per year.

The mean age of OS patients in both genders was 54.29  $\pm$  14.84 years (61.93  $\pm$  13.15 years in females, 49.00  $\pm$  14.37 years in males), from which 36 (73.47%) were male and 16 (44.44%) were men who have sex with men (MSM). Twelve patients (24.49%) were co-infected with HIV. Lumbar puncture (LP) was performed in 25 patients (51.02%) of which 13 had positive cerebrospinal fluid (CSF) serology. Median RPR titer was 1:64 and ranged from 1:1 to 1:512 (Table 1).

Forty-five patients (91.84%) complained of decreased visual acuity of variable duration: 15 (33.33%) for days, 16 (35.56%) for weeks and 14 (31.11%) for months. Ocular pain, hyperemia and photophobia were reported in 10

**Table 1.** Demographic characteristics, symptomatology reported and clinical features in OS patients (n=49).

Demographic characteristics	
Age (mean ± SD)	54.29 ± 14.84 years
Gender	
Male (n,%)	36 (73.47%)
MSM (n,%)	16 (44.44%)
Female (n,%)	13 (26.53%)
HIV co-infection (n,%)	12 (24.49%)
Other co-infection	
A hepatitis (n,%)	2 (4.08%)
B hepatitis (n,%)	1 (2.04%)
C hepatitis (n,%)	1 (2.04%)
Latent tuberculosis (n,%)	2 (4.08%)
<i>Neisseria gonorrhoeae</i> / <i>Chlamydia trachomatis</i> (n,%)	1 (2.04%)
Lumbar puncture (n,%)	27 (55.10%)
Positive lumbar puncture (n,%)	13 (48.15%)
Median RPR titer	1:64
Symptomatology reported	
Decreased visual acuity (n,%)	45 (91.84%)
Decreased visual acuity for days (n,%)	15 (33.33%)
Decreased visual acuity for weeks (n,%)	16 (35.56%)
Decreased visual acuity for months (n,%)	14 (31.11%)
Ocular pain, hyperemia or photophobia (n,%)	10 (20.41%)
Floaters or photopsias (n,%)	9 (18.37%)
Central scotoma (n,%)	1 (2.04%)
Systemic manifestations	19 (38.78%)
Clinical features	
Intraocular inflammation (n,%)	41 (83.67%)
Bilateral presentation (n,%)	33 (67.35%)
Anterior segment involvement (n,%)	
Synechiae	10 (41.67%)*
Granulomatous precipitates	7 (29.17%)*
Fibrinous reaction	1 (4.17%)*
Posterior segment involvement (n,%)	
Posterior placoid chorioretinitis	21 (50.0%)*
Multifocal outer retinitis	8 (19.05%)*
Retinal vasculitis	5 (11.90%)*
Posterior hyaloid precipitates	5 (11.90%)*
Inner or ground-glass retinitis	2 (4.76%)*
Panuveitis	
Optic nerve involvement	19 (38.78%)
Optic disc edema	12 (63.16%)*
Optic neuropathy	7 (36.84%)*

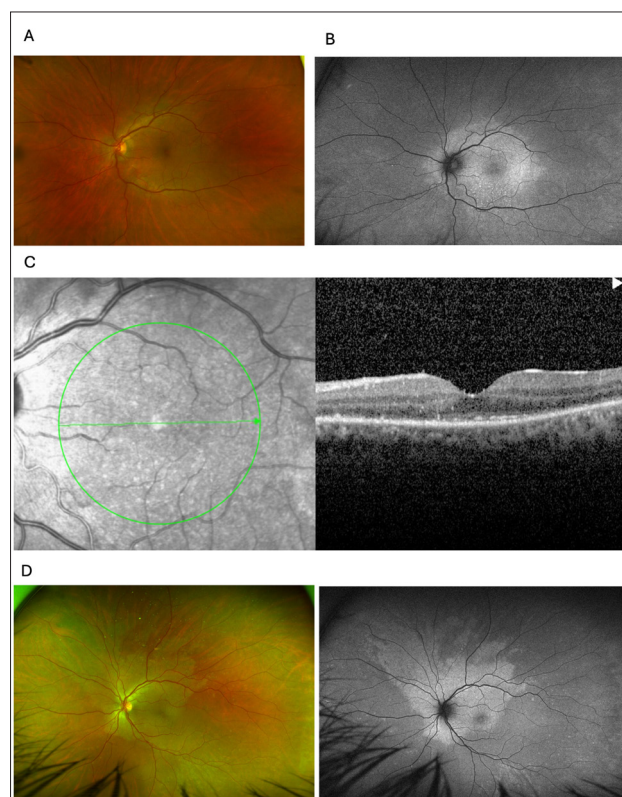
This percentage refers to each subgroup.\*

patients (20.41%), photopsias and/or floaters in 9 (18.37%) and a central scotoma in 1 (2.04%). Nineteen patients (38.78%) had systemic findings, mostly skin rash - 14 (73.68%), but also adenopathies - 2 (10.53%), fatigue and fever - 2 (10.53%), hyperemia of the pharynx - 2 (10.53%), urethral discharge and penile lesions - 1 (5.26%), syphilitic hepatitis - 1 (5.26%) and syphilitic arteritis - 1 (5.26%) (Table 1).

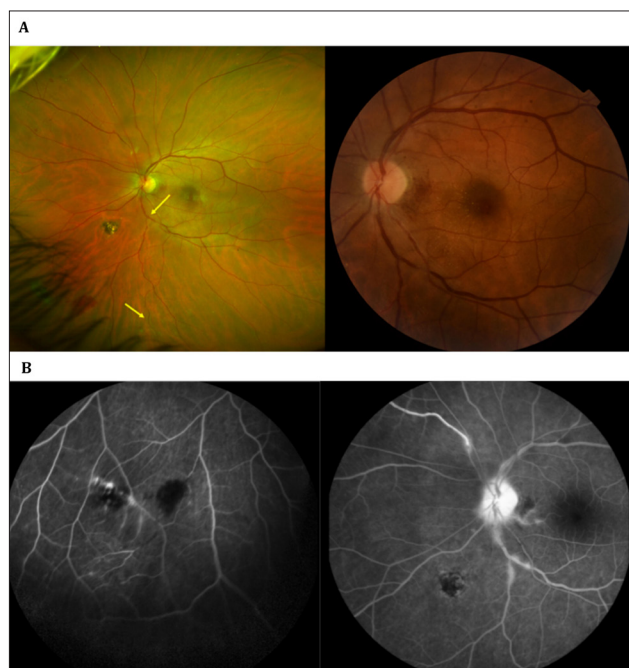
Ocular involvement included intraocular inflammation in 41 cases (83.67%). In 33 cases (67.35%), the presentation was bilateral.

Twenty-four patients (48.98%) presented with anterior segment involvement: 10 (41.67%) with synechiae, 7 (29.17%) with granulomatous precipitates and 1 (4.17%) with fibrinous reaction.

Forty-two patients (85.71%) had posterior segment involvement: 21 (50.0%) with posterior placoid chorioretinitis (Figs. 2A, B, C and D), 8 (19.05%) with multifocal outer retinitis (Figs. 2E), 5 (11.90%) with retinal vasculitis (Fig. 3), 5 (11.90%) with posterior hyaloid precipitates (Fig. 4A) and 2 (4.76%) with inner or ground-



**Figure 2.** Multimodal imaging of patients with posterior placoid chorioretinitis. A: retinography of a patient with active non-elevated, placoid yellowish outer retinal lesion involving the macula, compatible with posterior placoid chorioretinitis. B: On fundus autofluorescence, the affected area of patient A shows hyperautofluorescence. C: IR reflectance and Spectral-domain OCT of patient A, showing irregular thickening of the RPE layer and small nodular elevations, loss of the EZ layer and areas of punctate hyperreflectivity in the choroid. D: A different patient with multifocal outer retinal lesions and posterior placoid retinochoroiditis showed on retinography. Both types of lesions are hyperautofluorescent on fundus autofluorescence.



**Figure 3.** Retinal vasculitis. A: retinography of a patient with retinal vasculitis, showing perivascular hemorrhages and sheathing (yellow arrows), peripheral hemorrhages and an incomplete macular star. B: angiography of the same patient showing peripheral ischemia, vascular leakage and papillary leakage.

glass retinitis (Figs. 4A and 4B). Of note, patients with granulomatous anterior segment inflammation did not have granulomatous posterior segment inflammation and vice versa.

Seventeen patients (34.69%) had panuveitis.

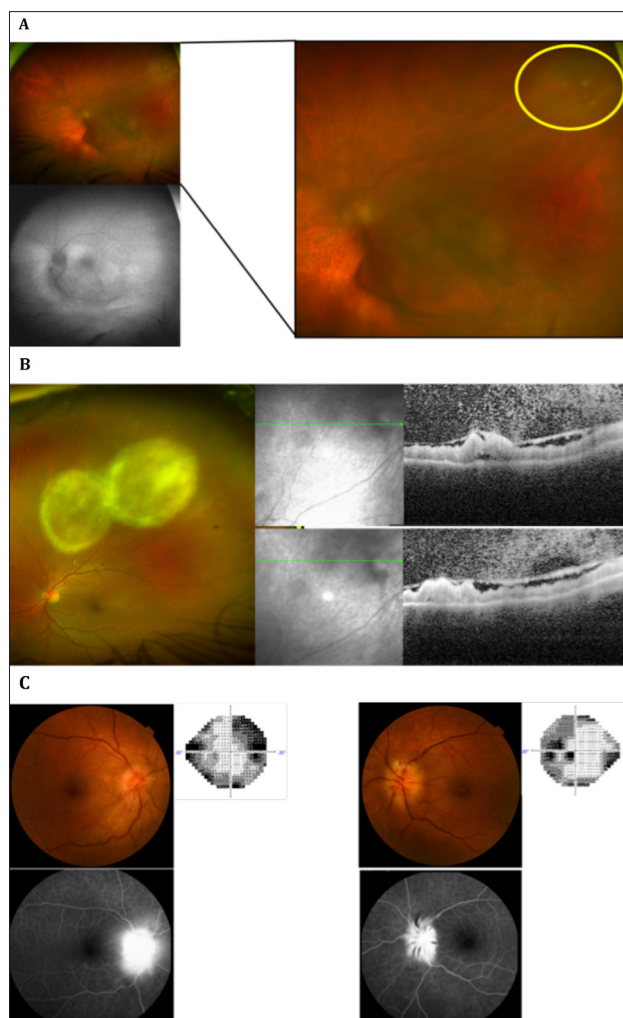
Nineteen patients (38.78%) had optic nerve involvement (mostly atypical neuropathy (Fig. 4C) with or without disc edema). Table 1 summarizes these data.

Eighteen patients (36.73%) had outer retinal layers involvement on OCT (Fig. 2D) and 8 patients (16.33%) had macular edema.

All patients were admitted and underwent a 2-week EV penicillin course (aqueous crystalline penicillin G 18–24 MU/ day, for 10–14 days), except for one patient, who developed a rash and was switched to ceftriaxone. Anterior uveitis was treated with topical corticotherapy, mydriatics and intraocular pressure-lowering agents. All patients received oral corticotherapy with a slow-tapering regimen as an adjuvant therapy, unless contraindicated. Treatment of the co-infections was performed in all patients. Visual acuity improved from logMAR 0.71 to logMAR 0.25 after treatment ( $p < 0.001$ ).

The Annual Epidemiological Report for 2019 from the ECDC and the Surveillance Atlas of Infectious Diseases of the ECDC available online disclose that since 2015, the reported cases of syphilis in Portugal are increasing, from 43 cases in 2015 to 1080 cases in 2021 (Fig. 5A).

The “Transparency Portal” of the Portuguese NHS discloses that since 2014, reported Syphilis cases have been increasing as well, from 112 cases in 2014 to 901 cases in 2018

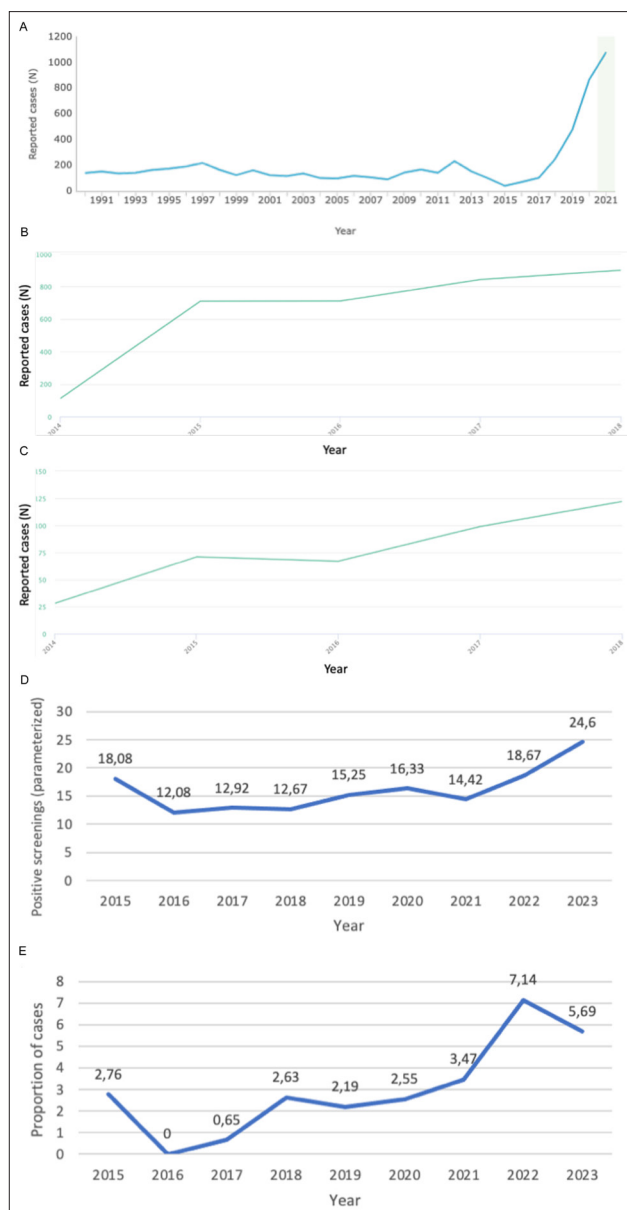


**Figure 4.** Three different patients with 3 distinct presentations. A: Retinography and fundus autofluorescence of vitreous cells and posterior hyaloid precipitates, retinochoroiditis with a “ground-glass appearance” and superficial pre-retinal precipitates (yellow circle). B: Retinography of another patient with ground-glass retinitis. Spectral-domain OCT shows hyperreflective round foci on the vitreous and on the surface of the retina and irregular elevations of RPE with retinal thickening. C: A different patient with bilateral optic neuropathy with arcuate and cecentral defects on perimetry and leakage from the optic disc on fluorescein angiography.

(Fig. 5B). The National Statistics Institute (INE) data from 2015 to 2017 matches these records. Data from the “Transparency Portal” of the NHS also discloses data by region. An increasing incidence was also reported in the center region of Portugal (Fig. 5C).

In our centre, the distribution of confirmed positive syphilis screening tests per year is as follows: 217 in 2015, 145 in 2016, 155 cases in 2017, 152 cases in 2018, 183 cases in 2019, 196 cases in 2020, 173 cases in 2021, 224 cases in 2022 and 123 cases in 2023 (until May). This distribution is shown in Fig. 5D, parameterized by the number of months per year.

The distribution of the proportion of cases of OS per positive syphilis screening tests per year from 2015 to 2023 (May), is shown in Fig. 5E, parameterized by the number of



**Figure 5.** A: Distribution of confirmed syphilis cases in Portugal per year, reported by the ECDC (Adapted from <sup>5</sup>). B: Distribution of confirmed syphilis cases per year in Portugal, reported by the NHS (Adapted from <sup>6</sup>). C: Distribution of confirmed syphilis cases per year in Portugal (central region), reported by the NHS (Adapted from <sup>6</sup>). D: Distribution of confirmed syphilis screening tests per year at CHUC parameterized by the number of months per year. E: Distribution of the proportion of cases of OS per positive syphilis screening tests per year at CHUC, parameterized by the number of months per year.

months per year.

## DISCUSSION

Our retrospective study featuring one of the largest single-center cohorts of studies on serologically confirmed OS stated that OS is a heterogeneous disease and has a wide range of presentations that cause diagnostic challenges.

The age at presentation was widely variable, but aver-

aged in the fifth decade. Male patients represent the majority of the patients, as in most of available series,<sup>7,8,13</sup> with half of them being MSM. One quarter of the patients were co-infected with HIV.

The most recognized syphilitic ocular manifestation is uveitis. Posterior uveitis seems to be the most common presentation of ocular syphilis followed by anterior uveitis and panuveitis.<sup>14</sup> The most common posterior segment manifestation is chorioretinitis.<sup>8,9</sup> Our work confirmed this. Almost 86% of our patients had posterior segment manifestations, most commonly posterior placoid chorioretinitis, followed by outer multifocal retinitis, retinal vasculitis, posterior hyaloid precipitates and inner or ground-glass retinitis. Of note, these conditions may occur simultaneously. Regarding the anterior segment involvement, almost half of the patients had anterior segment inflammation, of which half had synechiae and almost one third granulomatous precipitates. Interestingly, patients with granulomatous anterior segment inflammation did not have granulomatous posterior segment inflammation and vice versa. Fibrinous uveitis was rare. Almost one third of the patients had panuveitis and more than one third of the patients had optic nerve involvement. Of note, optic neuropathy may occur with other manifestations or may be isolated. However, other signs of ocular inflammation or posterior uveitis are almost always present, even if very subtle or only appreciated on fundus autofluorescence.<sup>10</sup>

Most of our cases were bilateral. Multimodal imaging seems to be crucial in diagnosis, because of the unique imaging characteristics of syphilis. This was most prominent with the OCT and the FAF, which were widely used in our work, with emphasis on the outer retinal layers changes which were observed on OCT and hyperautofluorescence of the affected areas on FAF. We also found that standard automated perimetry and angiography were useful in selected cases.

Treatment effectively improved visual outcomes. First line treatment<sup>15,16</sup> is IV aqueous penicillin G, following the CDC recommendations for treatment of ocular syphilis.<sup>17,18</sup> Regarding corticotherapy, there are no guidelines but some reports suggested good results in reducing inflammation when given along with antibiotherapy.<sup>19-21,22</sup>

In our cohort, lumbar puncture was performed in almost all of the patients with OS in the first years. However, there was a trend in more recent years to perform it only in patients with suspicion of neurosyphilis. Some authors<sup>23</sup> argue that lumbar puncture should be a routine investigation for all patients diagnosed with ocular syphilis. However, according to the Center for Disease Control and Prevention (CDC), there are specific indications:<sup>9</sup> "1) Patients presenting with neurological, ocular or auditory involvement evidence of active tertiary syphilis disease and 2) Treatment failure defined as a long-lasting quadruple VDRL or RPR increase or elevated RPR titer (> 1:32) that does not decrease 2 titers for 6-12 months in early syphilis or 12-24 months in latent syphilis".

The maximum number of patients diagnosed with OS in one year was 16, in 2022. Considering all the new syphilis diagnoses per year in our center, the proportion of ocular syphilis per year ranged from 0% to 7.14%. A peak of

disease diagnosis in 2022 was noted, after the COVID-19 pandemic, perhaps related to deconfinement.

Even though OS is a relatively rare cause of uveitis, the incidence is on the rise. This treatable cause of ocular inflammation is an important differential diagnosis to consider in every patient with uveitis or optic neuritis, because it may mimic any systemic or ocular inflammatory disease.<sup>24</sup> Syphilis is a public health challenge with increasing incidence in the past few years. Data from ECDC and NHS demonstrated a gradual increase in syphilis incidence in the years considered, with slight discrepancies between national registries and between national and European registries (European registries reporting less cases than national registries), so a standardization of the epidemiologic data is mandatory in order to allow for optimal public health surveillance.

## CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

CC and TM: Responsible for gathering the data, presenting the results, and writing the manuscript.

CF and PF: Concept and design of the study and revision of the manuscript. Supervised this project and contributed with their expertise to its conclusion.

RS: Management of Inpatient patients and collaboration on systemic management.

FR: Management of laboratory data.

All authors: read and approved the final manuscript.

CC e TM: Responsável pela recolha dos dados, apresentação dos resultados e redação do manuscrito.

CF e PF: Conceito e desenho do estudo e revisão do manuscrito. Supervisionaram este projeto e contribuíram com a sua experiência para a sua conclusão.

RS: Gestão dos doentes internados e colaboração na gestão sistémica.

FR: Gestão dos dados laboratoriais.

Todos os autores: leram e aprovaram o manuscrito final.

## RESPONSABILIDADES ÉTICAS

**Conflitos de Interesse:** Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

**Fontes de Financiamento:** Não existiram fontes externas de financiamento para a realização deste artigo.

**Confidencialidade dos Dados:** Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

**Proteção de Pessoas e Animais:** Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

**Proveniência e Revisão por Pares:** Não comissionado; revisão externa por pares.

## ETHICAL DISCLOSURES

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

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**Confidentiality of Data:** The authors declare that they have followed the protocols of their work center on the publication of data from patients.

**Protection of Human and Animal Subjects:** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

**Provenance and Peer Review:** Not commissioned; externally peer reviewed.

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