Trends in management of ocular syphilis in tertiary uveitis centre in Prague, Czech Republic

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Aims. To analyse the hallmarks of ocular manifestations of and therapeutic modalities for syphilis in the last two decades. The clinical features of syphilitic uveitis, and association with the human immunodeficiency virus (HIV) coinfection are described.
Methods. Retrospective study of 16 patients diagnosed with ocular syphilis confirmed by serological tests in the General University Hospital in Prague between the years 2004 and 2021. General characteristics of ocular and systemic manifestations and visual functions were analysed.
Results. An increasing incidence of syphilitic uveitis correlates with a general rise in syphilis cases. In our study, the ocular manifestation of syphilis was panuveitis (44%), posterior uveitis (31%) and anterior uveitis (25%). Posterior uveitis was found in 3 patients (19%) associated with preretinal infiltrates, that are often present in syphilitic uveitis. The worst visual outcomes were among patients with human immunodeficiency virus (HIV) coinfection and/or neurosyphilis, however the data were not significant. Optic disc edema was present in 56%, macular involvement in 37% of patients. Overall, 31% of patients in our cohort had persistent visual field defects due to impairment of their optic nerve or macula despite the final median Snellen visual acuity of 1.0. Two out of sixteen patients were treated with corticosteroids in addition to antibiotics.
Conclusion. Posterior uveitis with preretinal infiltrates and optic disc edema should arouse suspicion of ocular syphilis. Recent data show the advantages of adjacent systemic corticosteroid treatment for severe forms of syphilitic uveitis and/or neuritis. Our observation supports this finding.

Key words: syphilis, uveitis, corticosteroids, optic neuritis, optic disc edema

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INTRODUCTION

Syphilis remains a public health problem worldwide despite available serological tests and penicillin treatment. A global syphilis outbreak has been seen throughout the world over the past two decades, observed most frequently in the community of men having sex with men, corresponding with the decline in HIV mortality[1].

The characteristic feature of chronic bacterial infection by *Treponema pallidum* (*T. pallidum*) is invasiveness and activation of a prolonged immune response. Clinical manifestation is caused by local immune reaction to replicating spirochetes. The health impact of syphilis results from years-long progression leading to irreversible neurological or cardiovascular complications. Patients with syphilis have an increased risk of other sexually transmitted diseases, e.g. human immunodeficiency virus (HIV). *T. pallidum* is an obligatory human pathogen and can invade any tissue[2]. The outer membrane does not contain any lipopolysaccharides and thus is not protected from the innate immunological mechanisms that are capable of stopping the invasion and replication of spirochetes. Due to the low antigenicity of *T. pallidum*, the response to produce antibodies by the adaptive immune system is avoided[2].

The interpretation of serological tests to evaluate the therapeutic response is sometimes difficult, the development of titres can take many months and some patients do not serologically react to treatment[3]. Parenteral penicillin G is the preferred drug, the treatment regimen for ocular syphilis is stated in guidelines of Centres for Disease Control and Prevention (CDC) from year 2021 as for neurosyphilis: 18–24 million units of penicillin per day for 10–14 days. An alternative is procaine penicillin G 2.4 million units intramuscularly once daily plus probenecid 500 mg orally 4 times/day, both for 10–14 days[4].

For practical reasons, syphilis is divided into early and late stages. Primary, secondary and early latent stage are the stages of early syphilis. Late syphilis is a non-infectious condition, emerging as an overreaction of the immune system to treponemal antigens.

Ocular syphilis can occur in any stage, but it is found to most frequently arise in the secondary and latent stages of infection. Any ocular structure can be involved, but the most common ocular manifestation of syphilis is uveitis, with bilateral involvement in more than 50% of cases. The

Table 1A. The ocular features of the cohort of 16 patients diagnosed with ocular syphilis in our Uveitis Centre.

	Number of patients
Laterality	
Bilateral	10 (63%)
Unilateral	6 (37%)
Panuveitis	7 (44%)
Posterior uveitis	5 (31%)
Anterior uveitis	4 (25%)
Preretinal infiltrates	3 (19%)
Optic disc edema	9 (56%)
Macular involvement	6 (37%)
Persistent visual field defects	5 (31%)

Table 1B. The visual acuity of 22 eyes of 14 patients, recorded as Snellen decimal.

Best corrected visual acuity (22 eyes)	
Baseline median 0.6	Final median 1.0
0.001 in 4 eyes (18%)	amaurosis 1 eye (5%)
0.05 to 0.4 in 5 eyes (23%)	≤ 0.5 in 1 eye (5%)
0.5 to 0.7 in 6 eyes (27%)	0.6 to 0.9 in 6 eyes (27%)
1.0 in 7 eyes (32%)	1.0 in 14 eyes (63%)

inflammation could be granulomatous or non-granulomatous. The most common presentation is posterior uveitis (vasculitis, necrotizing retinitis, chorioretinitis, papillitis and neuroretinitis) and panuveitis, followed by anterior uveitis.

The data regarding the incidence of ocular manifestation in systemic syphilis varies in different parts of the world. The frequency of ocular manifestation is mostly reported as being found in 2 to 10% of systemic infections[5,6], Israeli authors document 25% (ref.[7]), whereas authors from Great Britain state a rate of 0.6% (ref.[8]).

SUBJECTS AND METHODS

A retrospective study of 16 Caucasian patients (15 men, 1 woman) observed with ocular syphilis between January 2004 to December 2021 was performed in the Centre for Diagnosis and Treatment of Uveitis at the General University Hospital in Prague, Czech Republic. The mean age was 42 years (26 to 71 years). HIV coinfection was present in 5 patients (31%), who were all diagnosed for HIV simultaneously with syphilis primoinfection. 9 patients (56%) were men having sex with men. Reinfection of syphilis was detected in 3 patients (19%), in two patients after 3 years and in one patient after 2 years; all were men having sex with men, and one was HIV positive. According to Czech law, no institutional review board approval was required for the study.

RESULTS

The syphilis was diagnosed by serological tests on the basis of ocular findings in all patients. Bilateral eye involvement prevailed. The most frequent presentation was panuveitis, followed by posterior uveitis and anterior uveitis. Optic disc edema was present in 9 patients, in 5 patients with panuveitis and in 4 patients with posterior uveitis. The characteristic ocular features are presented in Table 1A.

An increasing trend in number of patients has been documented since 2004 in our Uveitis Centre (Fig. 1).

In patients with panuveitis, vitritis was mild to severe and vitreous haze was cellular, presenting as dispersed infiltration or formed in preretinal infiltrates (Fig. 2A). Panuveitis was complicated by retinal detachment in one patient, therefore, pars plana vitrectomy was performed. After that, the best corrected visual acuity improved from baseline 0.001 to a final 0.6 Snellen decimal. Two patients with panuveitis had severe inflammation in the anterior chamber which complicated the examination of the posterior segment.

Posterior syphilitic uveitis has variable clinical features, presenting as confluent retinochoroiditis (Fig. 2B), neuroretinitis with macular edema (Fig. 2 C,D) or acute syphilitic posterior placoid chorioretinitis (ASPPC) (Fig. 3A,B).

Anterior uveitis was diagnosed in 4 patients (25%), with bilateral involvement in all cases. Anterior uveitis was

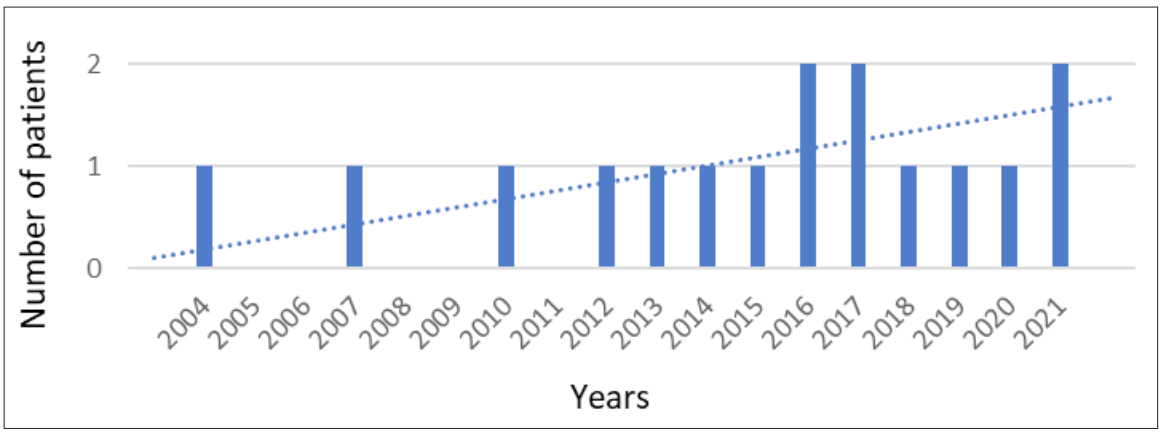

Fig. 1. Patients diagnosed with syphilitic uveitis in our Uveitis Centre in Prague between years 2004 and 2021. The blue dashed line shows the increasing trend of incidence.

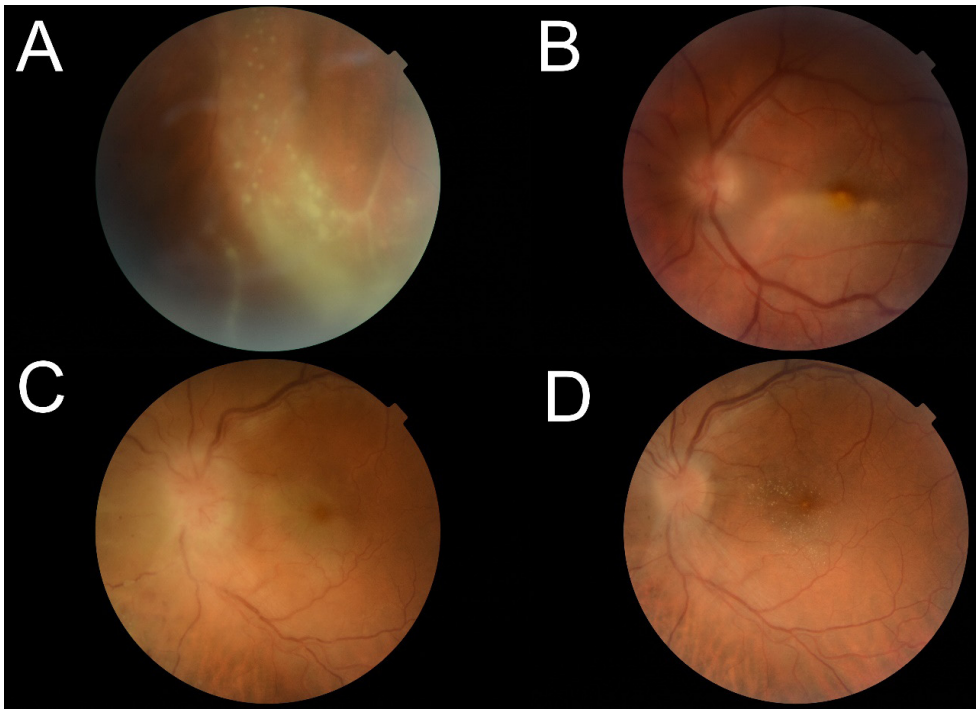

Fig. 2. A. Vitritis with preretinal infiltrates. **B.** Confluent retinochoroidal lesions in active stage regressed after 14 days on penicillin treatment. **C.** The posterior uveitis was complicated by central retinal vein occlusion with optic disc and macular edema, **D.** the regression 15 days after initiation of antibiotic treatment in the same eye.

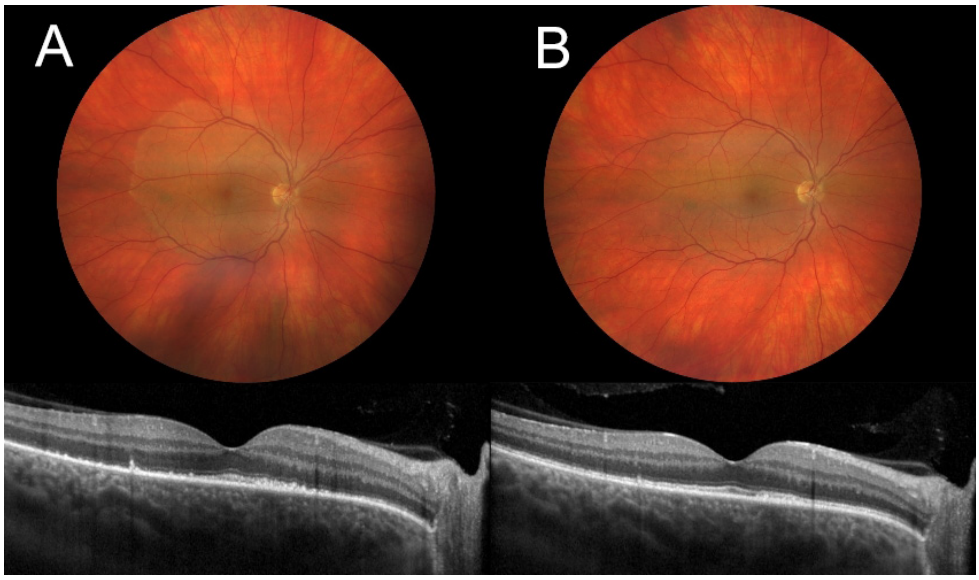

Fig. 3. Acute syphilitic posterior placoid chorioretinitis. **A.** Is represented by round distinct pale macular lesion, on SD-OCT (spectral domain-optical coherence tomography) the loss of ellipsoid zone and the hyperreflective dots in RPE layer (retinal pigment epithelium) is evident. **B.** The lesion disappeared on fundoscopy and the ellipsoid zone has partially recovered 16 days after initiation of antibiotics. The Snellen decimal visual acuity of 1.0 remained stable during the 4 months follow-up.

serofibrinous with small or medium keratic precipitates located on the inferior and central parts of the corneal endothelium. Anterior granulomatous uveitis was present in only one patient. Anterior uveitis had regressed in two weeks in all 4 patients following the use of a combination of the standard topical anti-inflammatory treatment and systemic penicillin.

The best corrected visual acuity of 22 eyes of 14 patients with syphilitic uveitis was evaluated (Table 1B), however 2 patients were not included due to follow-up shorter than 1 month. The average follow-up time was 30 months (1 to 127 months). The median Snellen visual acuity was 0.6 at the first visit. The visual acuity at the first ophthalmologic examination was as poor as 0.001

in 4 eyes of 4 patients, the second eye of one patient in this group was 0.01 on the Snellen chart. All 4 patients had syphilitic panuveitis with macular edema or macular infiltration. Conversely, 7 eyes of 5 patients had a Snellen visual acuity 1.0 on their first visit.

Visual acuity improved, usually rapidly after 2 weeks of therapy, as intravenous penicillin penetrates sufficiently into the soft tissues. The final median Snellen visual acuity was 1.0. The worst outcome of no light perception was in a patient with HIV coinfection. In this patient, cytomegalovirus retinitis developed, which was complicated by retinal detachment, but pars plana vitrectomy was contraindicated due to a critically low thrombocyte count.

The eyes with optic disc edema had a comparable final visual acuity to those with other ocular involvement (median Snellen visual acuity in both groups was 1.0; *P*=0.56; GraphPad Prism 7.04, Mann-Whitney test). From the whole cohort, residual visual field defects were present in 31% of patients (7 eyes of 5 patients) upon the final visit, which were more extensive in 4 eyes of 2 patients, following panuveitis and posterior uveitis with optic disc edema. Sectoral scotomas of various location and extent were present.

The final Snellen visual acuity in the group of HIV positive patients showed slightly worse outcomes (median 0.8 in HIV, 1.0 in non-HIV; *P*=0.12; GraphPad Prism 7.04, Mann-Whitney test). Similarly, patients with neurosyphilis had a slightly worse final Snellen visual acuity compared with patients where neurosyphilis was excluded by lumbar puncture (median 0.8 in neurosyphilis, 1.0 in non-neurosyphilis; *P*=0.12; GraphPad Prism 7.04, Mann-Whitney test). In addition, the combination of HIV and neurosyphilis had worse final visual acuity compared to patients with excluded HIV and neurosyphilis (median 0.85 compared to 1.0; *P*=0.17; GraphPad Prism 7.04, Mann-Whitney test). However, none of these parameters were statistically significant.

Lumbar puncture was performed in 12 patients (75%), cerebrospinal fluid was positive for *T. pallidum* in 5 patients (31%). Lumbar puncture was refused by 3 patients. Neurological examination showed no results in all but one patient, who had a finding of lateralization.

Four patients had enlarged cervical lymph nodes, two patients had ulcerations around the anus. A patient with ulceration around the anal region and in the mouth was concurrently treated by a rheumatologist for Behçet's disease with prednisone and azathioprine. The treatment was discontinued when the diagnosis of syphilis was confirmed. Significant weight loss and tiredness were presented in 4 patients, and one patient had arthralgia and tremor. One patient had alopecia areata, and 4 patients reported skin rashes.

All of our patients with ocular syphilis were referred to an infective diseases specialist or dermatovenerologist to initiate systemic treatment and provide further systemic follow-up.

All of our patients were treated with penicillin, before the year 2015 with intramuscular or intravenous administration, thereafter the treatment was based upon the CDC recommendations for ocular syphilis from 2015 (ref.[9]): solely intravenous aqueous crystalline penicillin G 24 million units per day for 1–3 weeks, followed by intramuscular procaine penicillin 3 million units 4 times in one-week intervals.

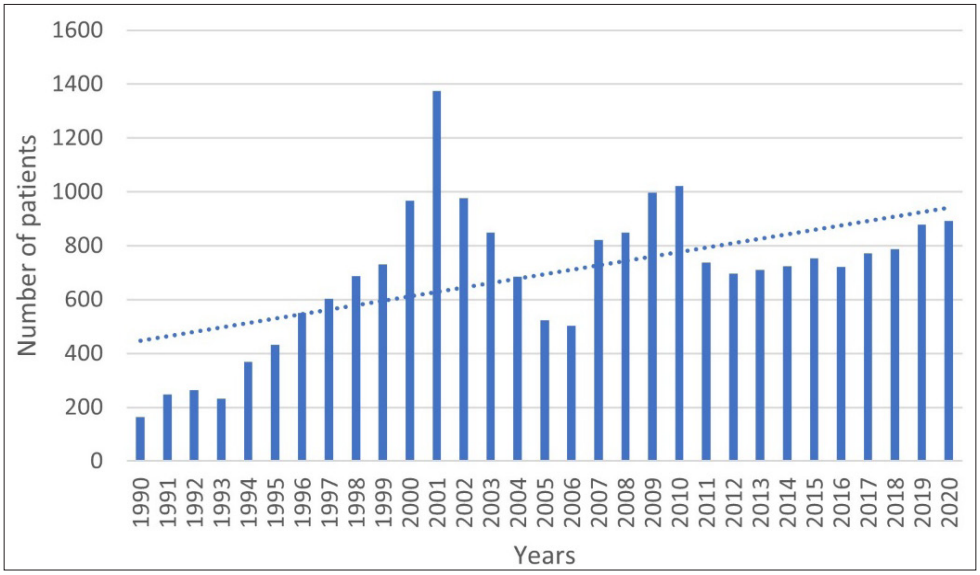

Fig. 4. The incidence of syphilis in the Czech Republic has risen (represented as blue dashed line) in the last two decades compared to the decade prior the turn of third millennium. The annual incidence in 1990 was 1.6/100 000 (164 cases), contrasting with 8.3/100 000 (893 cases) in 2020. The highest incidence was in 2001 (1376 cases), related to increased immigration from North Africa to Europe. The data from 2020 show a highest incidence among people aged 30 to 34 years old, a 4 times higher frequency in men compared to women, 75 cases of pregnant women, and 5 cases of congenital syphilis.

Two HIV negative patients with posterior uveitis with optic disc edema were treated by adjacent methylprednisolone 0.4 mg/kg/day in one patient and prednisone 0.5 mg/kg/day in the other patient, which were started immediately after cessation of intravenous penicillin. The edema of the macula and optic disc subsided in both patients after one week of corticosteroid treatment. Residual visual field defects persisted in 2 of 3 eyes of these 2 patients. The first patient resulted in one eye with optic disc atrophy confirmed by retinal nerve fibre layer (RNFL) measurement, and the second eye succeeded to complete recovery of visual field and borderline result on RNFL. In the only affected eye of the second patient, the visual field defects improved, but shallow central scotoma and metamorphopsia persisted due to discrete epiretinal membrane, and the Snellen decimal visual acuity improved from 0.15 baseline to 1.0 final.

The average time from the first examination to initiation of penicillin was 18 days (4 to 45 days), the longest period to treatment initiation was observed in patients with isolated anterior uveitis and in a non-compliant patient.

DISCUSSION

The number of syphilis cases show an increasing trend in the Czech Republic according to the data collected by The National Institute of Public Health (Fig. 4).

This retrospective study describes clinical characteristics of 16 patients diagnosed with syphilitic uveitis over an 18-year period in the Centre for Diagnosis and Treatment of Uveitis in Prague. The ocular manifestations of syphilis are very variable. Finding of preretinal infiltrates combined with posterior uveitis should raise suspicion of ocular syphilis. The preretinal infiltrates are located either superficially or adherent to the retina and it is proposed that precipitates may represent a collection of treponemal bacteria in combination with inflammatory cells on or in the retina[10-12]. They resolve quickly after initiation of treatment.

Acute syphilitic posterior placoid chorioretinitis (ASPPC) is a rare manifestation of ocular syphilis and was introduced by Gass and co-authors in 1990 (ref.[13]). It is characterized by the presence of large, yellowish, circular or oval, placoid, outer retinal lesions, typically in or near the macula. The OCT features of ASPPC are distinctive, showing the primary inflammation of the complex choriocapillaris-retinal pigment epithelium (RPE) as a result of impaired metabolism of the RPE (ref.[10]). This area of retinitis may be accompanied by exudative retinal detachment in some cases[10,11]. In our cohort we examined one patient with ASPPC (Fig. 3).

Our data showed a higher incidence of panuveitis and anterior uveitis compared to those collected by the Ocular syphilis study group in 2017 (ref.[14]). This survey documented posterior uveitis (60.8%) as most frequent, followed by panuveitis (22.5%) and anterior uveitis (3.9%). In our observation, panuveitis was represented most often (44%), followed by posterior uveitis (31%) and anterior uveitis was in 25% of cases. The higher incidence of anterior uveitis in our cohort can be explained by the relatively rapid availability of ophthalmological examination and earlier diagnosis and treatment in our patients.

Complications accompanying syphilitic uveitis in our patients included optic disc edema, macular edema or infiltration and posterior synechiae. Posterior synechiae were present in 50% of our patients and persisted in some form over the cessation of uveitis in all cases. Comparably according to the Ocular syphilis study group[14], posterior synechiae were documented in 50.5% of cases.

In our cohort, 9 patients (56%) had optic disc edema, resulting in optic disc complete or partial atrophy in 3 patients, and 6 patients (37%) had macular edema or infiltration. Our observations are comparable with the literature, Israeli authors documented 78% of optic nerve involvement in a group of 23 syphilitic patients[7,15] and the data from the Ocular syphilis study group found 68.3% with optic neuropathy and 50.5% of cases with macular edema in their observations[14]. Optic disc edema was associated with panuveitis or with other forms of posterior uveitis in our patients. Optic disc edema is also documented in the literature as an isolated ocular manifestation of syphilis, as confirmed by the Israeli study, where 44% of eyes presented with isolated unilateral or bilateral syphilitic optic disc edema[7,15].

The synergy of sexually transmitted diseases is well known, as it enhances the susceptibility to other sexual infections. It is presumed that HIV coinfection simplifies the penetration of *T. pallidum* and may change the course of syphilis due to immunosuppression induced by HIV. The situation is probably dependent on CD4 count and other factors which have not yet been identified. If HIV testing is negative, it is recommended to repeat the test 3 months later.

The association between the severity of ocular syphilis and HIV coinfection remains ambiguous. Data from high-income countries from the last decade show a high incidence of HIV among ocular syphilis patients, ranging from 31–39% (ref.[7,8,15]), which is comparable with our finding of 31%. Some reports suggest that HIV coinfection tends to present with posterior uveitis and worse visual outcomes[16], and others do not show any impact on visual acuity[17,18]. Our observations show a severe course of inflammation with more frequent panuveitis in patients with HIV coinfection (29% HIV patients with panuveitis, versus 21% in non-HIV with panuveitis).

There are no controlled studies that report the benefits of adjunctive systemic corticosteroid treatment in ocular syphilis, although there is supportive data in the literature. The administration of additional corticosteroids is generally not recommended by infection disease specialists. As reported by the International Ocular Syphilis Study Group, adjunctive systemic corticosteroid treatment was used in 82% of responders, mostly administered during but after the start of antibiotics[14]. According to Prokosch and Thanos adjunctive corticosteroids play a crucial role in the improvement of optic nerve functional outcomes

in patients with syphilitic optic neuropathy based on their small observational case series[19]. Thai authors recommend corticosteroid therapy in syphilitic optic neuropathy starting at least 7 days after initiation of intravenous antibiotic therapy, either in the form of intravenous methylprednisolone 3 g or oral prednisone 1 mg/kg/day[20]. Our experience in 2 patients with systemic corticosteroids, started at the end of intravenous antibiotic treatment and lasting 1 and 3 months, is limited. Despite the improvement of best corrected visual acuity, the visual field defects are permanent in both patients. The indication of adjunctive corticosteroids in syphilitic uveitis should be tailored, considered especially in cases with optic neuritis/papillitis or severe posterior uveitis.

In our cohort of 22 eyes of 14 patients, the median Snellen visual acuity was 0.6 baseline and 1.0 final, which is comparable to Israeli data which presented a baseline of 0.5 and final of 0.8 (ref.[7]). The overall visual prognosis is good and visual recovery is usually fast, within 2 to 3 weeks of the commencement of antibiotic treatment, which is compatible with our results. The worst visual acuity at the final visit was observed in our patients with HIV coinfection and/or neurosyphilis. However, the difference was small and statistically non-significant.

Residual visual field defects were present in 31% of patients at the final visit, all were patients with posterior uveitis with optic disc edema or macular involvement. The visual field defects occurred despite the final median Snellen visual acuity being 1.0 in those eyes. Hamann and co-authors also stated that patients with papillitis and retinitis are at an increased risk for persistent visual dysfunction[21]. A large retrospective study of Dutch authors documented that the final visual prognosis is also dependent on the visual acuity at the start of syphilis treatment and on the treatment delay[22]. Our data did not show any correlation between treatment delay and final visual acuity, even though 4 patients had a delay of more than 30 days, with the maximum of 45 days.

CONCLUSION

According to observation in our tertiary uveitis centre, there is an increasing incidence of syphilis detection with ocular manifestation, in conjunction with a rising number of syphilis cases. The most severe course of syphilitic panuveitis were detected in patients with HIV coinfection or with neurosyphilis. The recovery of central visual acuity was quick when on high dose penicillin treatment, however, the residual visual field defects persisted in almost a third of our patients due to changes resulting from optic disc edema or macular impairment. Our observations support the use of adjacent systemic corticosteroids in syphilitic neuritis and chorioretinitis or other severe and recalcitrant forms of syphilitic uveitis. Further prospective study should be performed to establish the benefits of concurrent systemic corticosteroid treatment and define the indications of this therapy.

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