ORIGINAL ARTICLE

The importance of proper and prompt treatment of ocular syphilis: a lesson from permanent vision loss in 52 eyes

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Abstract

Background Ocular involvement can occur at any stage of syphilis. Prompt diagnosis and proper treatment of ocular syphilis are vital to avoid long-term consequences.

Objectives To describe the risk factors for ocular syphilis and clinical features of blindness caused by syphilis.

Methods We report risk factors for ocular syphilis amongst patients seen at the Shanghai Skin Disease Hospital between October 2009 and October 2017. We identify patients with ocular syphilis resulting in blindness and report the clinical characteristics, laboratory findings and treatment outcomes of these patients.

Results A total of 8310 new cases of syphilis were seen, of which 213 patients had ocular disease and 50 patients had blindness due to syphilis. Increasing age and higher RPR titres were associated with ocular involvement but there was no association with HIV status. Blindness in syphilis was restricted predominantly to patients with optic nerve involvement and not patients with isolated uveitis. Fifty patients (and a total of 67 eyes) met the WHO definition of blindness prior to treatment for syphilis. At the end of follow-up, vision had improved in 24 of 67 eyes (35.8%) after treatment. Successful treatment of uveitis was associated with the best improvement in visual acuity, whilst patient with underlying optic atrophy prior to treatment had the worst visual outcome.

Conclusions Ocular involvement is an important manifestation of syphilis which may result in blindness. Our data demonstrate outcomes for ocular syphilis are poor if detected late; early recognition and diagnosis is therefore vital to avoid permanent visual loss.

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Conflict of interests

The authors have no conflict of interests to declare.

Introduction

Syphilis, caused by *Treponema pallidum* (TP), remains a major global health problem. China has experienced a marked increase in the incidence of syphilis from 0.2 cases per 100 000 in 1993 to 31.97 cases per 100 000 in 2016.[1,2] Outside of China, the incidence of syphilis has also increased substantially throughout the world in recent years, including many developed countries, predominantly among 'men who have sex with men' (MSM), many of whom are co-infected with the human immunodeficiency virus (HIV).[3–5]

Syphilis is a multisystem disease with involvement of nearly every organ system reported.[6] Ocular involvement is a particularly well-described phenomenon and has been observed in up to one third of all HIV co-infected patients with neurosyphilis.[7] Comparatively, less is known about ocular syphilis in HIV-negative patients. Syphilis is believed to be an uncommon cause of ocular inflammation in HIV-negative patients in the postpenicillin age, and as a consequence,

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delayed diagnosis of ocular syphilis is not uncommon in this group.[8–11]

Ocular involvement can occur at any stage of syphilis in both HIV-positive and HIV-negative individuals. Eye involvement may be asymptomatic or present as an anterior, intermediate or posterior uveitis, a retinal vasculitis, retinitis, optic neuritis or scleritis.[11] Uveitis has been the most reported presentation and can occur as early as 6 weeks after initial infection.[12,13] Ocular involvement may be the only manifestation of syphilis and, because the wide range of clinical presentations, may mimic many eye diseases, can be associated with delayed diagnosis and treatment. Delayed recognition and treatment may result in irreversible visual loss.[14] The most common complaint in patients with ocular involvement is blurred or decreased vision but true blindness caused by syphilis is rarely reported, especially in immunocompetent patients.[15,16]

The aim of this study was to describe risk factors for ocular syphilis and clinical features of blindness due to syphilis amongst patients seen at the sexually transmitted diseases (STD) clinic in Shanghai Skin Disease Hospital.

Methods

This was a retrospective cohort study which included all patients diagnosed with syphilis seen at Shanghai Skin Disease Hospital between October 2009 and October 2017. Enrolled patients included those seen because of a skin rash or genital symptoms, patients undergoing routine examination due to high-risk sexual behaviours and patients referred by ophthalmologists. All patients were managed with input from the hospital syphilis multidisciplinary team which includes a neurologist, ophthalmologist, dermatologist and physician. For each individual, we extracted basic demographic, clinical and laboratory data including age, gender, HIV status, rapid plasma reagin (RPR) titre, the clinical stage of syphilis, whether the patient had ocular involvement and whether the patient met the World Health Organization (WHO) definition of blindness (best-corrected visual acuity of less than 0.05).[17] The study was approved by the Shanghai Skin Disease Hospital Ethics Committee (NO.2016-011).

In individuals who met the WHO definition of blindness, we extracted detailed ocular examination data. We also extracted data on care-seeking including the duration and date of initial onset of ocular symptoms, first date of seeking medical care, time to seeking medical care, number of health care facilities seen before final diagnosis, the duration between onset of symptoms and the final diagnosis of ocular syphilis, and any treatment received. All patients underwent a complete physical examination and HIV screening regarding previous HIV status alongside serological testing for syphilis. Patients with ocular syphilis underwent lumbar puncture (LP) for cerebrospinal fluid (CSF) analyses. The diagnosis of ocular syphilis was based on positive results of both non-treponemal and treponemal serological tests alongside ocular examinations.

The diagnosis of confirmed neurosyphilis was made on the basis of a reactive CSF-Venereal Disease Research Laboratory (VDRL) and CSF-*Treponema pallidum* particle agglutination (TPPA) tests in the absence of substantial contamination of CSF with blood. Presumptive neurosyphilis was defined as patients with a non-reactive CSF-VDRL test but reactive CSF-TPPA with either or both of the following: (i) CSF protein concentration >45 mg/dL or CSF white blood cell (WBC) counts ≥8/μL in the absence of other known causes for the abnormalities and (ii) clinical neurological or psychiatric manifestations consistent with neurosyphilis without other known causes for such abnormalities as previously reported.[18,19] For the purposes of analyses, we categorized RPR as ≤1 : 8 or >1 : 8. For patients meeting the definition of primary or secondary syphilis, with or without ocular disease, we report the stage as early. For patients without ocular disease, we classify the patients as having latent stage, a category that would capture both patients with early-latent and late-latent syphilis according to the 2018 CDC definitions. For patients meeting the definition of tertiary syphilis, with or without ocular disease, we report the stage as late in line with the 2018 CDC definitions. By definition and unlike patients without ocular disease, no patient with ocular syphilis can be classified as having latent infection. As some patients presented with ocular disease but without meeting the case definition for primary, secondary or tertiary syphilis, we classified these patients as having active syphilis of unknown duration. Primary syphilis was defined as presence of a chancre accompanied by visualization of spirochaetes by dark-field microscopic examination or positive RPR and TPPA. Secondary syphilis was classified as patients with skin or mucocutaneous lesions and a positive RPR and TPPA. Latent syphilis was defined as an asymptomatic individual with a positive RPR and TPPA. Tertiary syphilis was defined as an individual with manifestations of late neurosyphilis, cardiovascular syphilis, or gummatous syphilis and a positive RPR and TPPA. As the duration of disease was not available for all patients with ocular disease, we report only proportions of patients in each category but did not include stage of syphilis in our regression model.

The treatment of ocular syphilis was one of the following: (i) aqueous crystalline pencillin G, 4MU intravenously every 4h for 14 days;[20] (ii) ceftriaxone intravenously, 2g daily for 14 days, because of allergy to penicillin;[20] and (iii) oral doxycycline (200 mg daily) for 30 days due to allergy to both penicillin and cephalosporin.[20,21]

The best-corrected visual acuity was evaluated using a standard logarithmic visual acuity chart. A change of one line indicated visual improvement or worsening.

Univariable logistic regression was used to identify demographic, clinical and laboratory features associated with ocular syphilis and blindness. Variables that appeared to have significant association ($P < 0.1$) in the univariable analysis were included in a multivariable logistic regression model. We

Table 1 Demographics of study participants

		Non-Ocular Syphilis	Ocular Syphilis	Overall	P
Age (Mean and SD)		40.3 (14.2)	55 (11.2)	40.6 (14.3)	<0.001
Gender	Male	4942 (61%)	140 (65.7%)	5082 (61.2%)	0.188
	Female	3155 (39%)	73 (34.3%)	3228 (38.8%)	
RPR	<=1 : 8	4203 (51.9%)	30 (14.1%)	4233 (50.9%)	<0.001
	>1 : 8	3894 (48.1%)	183 (85.9%)	4077 (49.1%)	
HIV	Positive	192 (2.3%)	7 (3.29%)	199 (2.39%)	0.748
	Negative	4645 (57.4%)	206 (96.7%)	4851 (58.4%)	
	Unknown	3260 (40.3%)	0	3260 (39.2%)	
Stage	Early	3862 (47.7%)	11 (5.2%)	3873 (46.6%)	<0.001
	Latent	4235 (52.3%)	N/A	4235 (51%)	
	Active Syphilis of Unknown Duration	N/A	136 (63.8%)	136 (1.6%))	
	Late	0 (0%)	66 (31%)	66 (0.8%)	

N/A, not applicable

considered age and gender as forced confounders for the purpose of logistic regression. Finally, factors with a level at $P < 0.05$ were considered statistically significant in the multivariable logistic regression. All statistical analysis was performed in the R Foundation for Statistical Computing (R 3.4.3).

Results

Demographics

Between October 2009 and October 2017, a total of 8,310 new cases of syphilis were diagnosed in our STD outpatient department. During this period, a total of 2.6% of patients ($n = 213$) had ocular involvement as a manifestation of their syphilis and a total of 0.6% of patients ($n = 50$) had involvement of at least one of their eyes sufficient to meet the definition of blindness. The mean age of patients with syphilis was 40.0 ± 14.3 years, and the majority were male (61.2%, $n = 5082$). Overall, the HIV status was known for 60.8% ($n = 5050$) of patients of whom 3.9% ($n = 199$) were HIV-positive. Patients with ocular syphilis were older (mean 55.0 ± 11.2 vs. 40.3 ± 14.2 years) than patients without ocular syphilis and were more likely to have an RPR titre >1 : 8 (85.9% vs. 48.1%; Table 1). Of 213 patients with ocular syphilis, 14 (6.6%) patients were MSM and 7 (3.3%) patients were HIV-positive. The most common ocular diagnoses were uveitis (42.3%, $n = 90$) and optic neuritis (14.7%, $n = 31$).

Risk factors for ocular syphilis

In univariable logistic regression, a high RPR titre and increasing age were both associated with a significantly increased risk of ocular syphilis, but there was no association with gender (OR 1.0, 95% CI 0.7–1.3, $P = 0.821$) or HIV status (OR 0.6, 95% CI 0.3–1.2, $P = 0.142$). In multivariable regression both a high-titre RPR (aOR 3.2, 95% CI 2.2–4.9) and increasing age remained associated with a significantly increased risk of ocular disease (Table 2). In univariable analysis, comparing patients with

non-blinding ocular syphilis to patients with blinding ocular syphilis, there was no association between risk of blinding ocular disease and baseline RPR titre ($P=0.984$), age ($P=0.985$), gender ($P=0.161$) or HIV status ($P=0.234$). Compared to patients with uveitis, individuals with optic neuritis had an increased risk of blindness although this did not achieve statistical significance (OR 2.2, 95% CI:0.8–5.7, $P = 0.1$), whilst individuals with optic atrophy had a statistically significantly increased risk of blindness (OR 28.7, 95% CI :10.0–97.8, $P < 0.001$).

Ocular manifestations of the 67 eyes with blindness

In the fifty patients who met the WHO definition of blindness, a total of 99 eyes were affected, and 67 eyes were classified as blind (Table 3). Seventeen patients (34.0%) had bilateral blindness, whilst 33 patients (66.0%) had unilateral blindness. Of 33 eyes, which did not meet the WHO definition of blindness, visual

Table 2 Risk factors for ocular syphilis

	OR	95% CI	P*	aOR	95% CI	P*
RPR						<0.001
≤1 : 8						
>1 : 8	3.4	2.3–5.1	<0.001	3.2	2.2–4.9	
HIV						
Negative						
Positive	0.6	0.3–1.2	0.142			
Gender						0.099
Male						
Female	1.0	0.7–1.3	0.821	1.3	1.0–1.8	
Age*						
≤30						
31–40	3.3	1.5–8.0	<0.001	3.7	1.6–9.0	<0.001
41–50	7.2	3.5–16.7		8.1	3.9–18.9	
51–60	20.5	10.5–42.3		21.6	11.0–49.0	
61–70	45.3	22.7–103.7		48.1	23.9–110.8	
>70	25.6	10.3–67.0		30.8	12.2–81.6	

*Likelihood ratio test

Table 3 Characteristics of patients with blinding syphilis

Case number	Age/ Gender	Best-corrected visual acuity (L/R) before treatment	Ocular diagnosis*	Other syphilis symptoms	Serology	CSF (W/P)	CSF-VDRL/ CSF-TPPA	Treatment	Follow-up (month)	Best-corrected visual acuity (L/R) after treatment
1	61/M	0.02/NLP	Optic atrophy	Dysesthesias and weakness of the limbs	RPR1:8 TPPA (+)	2.2/56	1 : 1/+	Doxycycline0.2 g P.O/day * 30 days	24	0.02/NLP
2	64/F	0.6/NLP	Retinitis	–	RPR1:128 TPPA (+)	36/48	1 : 32/+	PCN 24 MUI iv/day *14 days	72	0.6/LP
3	71/M	NLP/NLP	Optic neuritis	–	RPR1:128 TPPA (+)	5.5/40	1 : 8/+	PCN 24 MUI iv/day *14 days	80	LP/LP
4	54/F	LP/0.1	Optic neuritis	–	RPR1:128 TPPA (+)	53.9/40	1 : 8/+	PCN 24 MUI iv/day *14 days	60	LP/0.1
5	61/M	LP/NLP	Optic atrophy	Dysesthesias in the lower limbs	RPR1:32 TPPA (+)	30.8/52	1 : 8/+	PCN 24 MUI iv/day *14 days	12	LP/NLP
6	39/M	LP/0.04	Optic atrophy	–	RPR1:16 TPPA (+)	0/63	–/+	PCN 24 MUI iv/day *14 days	36	LP/0.04
7	78/M	LP/LP	Optic atrophy	Mental disorder	RPR1:512 TPPA (+)	105.6/60	1 : 4/+	PCN 24 MUI iv/day *14 days	36	0.5/LP
8	70/M	NLP/NLP	Optic atrophy	Mental disorder	RPR1:64 TPPA (+)	47.3/73	1 : 4/+	Ceftriaxone 2 g iv/day *15 days	33	NLP/NLP
9	61/F	NLP/0.8	Optic neuritis	–	RPR1:32 TPPA (+)	34.1/48	1 : 1/+	PCN 24 MUI iv/day *14 days + prednisone 30 mg/day orally	24	NLP/0.8
10	43/M	LP/0.01	Optic atrophy	–	RPR1:4 TPPA (+)	0/95	1 : 8/+	PCN 24 MUI iv/day *14 days	24	LP/0.01
11	62/F	0.6/LP	Uveitis	–	RPR1:256 TPPA (+)	32/29	1 : 2/+	PCN 24 MUI iv/day *14 days + methylprednisolone pulse therapy	15	1.2/0.8
12	56/M	LP/NLP	Optic atrophy	Dysesthesias in the left lower limb	RPR1:32 TPPA (+)	10/99	1 : 8/+	PCN 24 MUI iv/day *14 days	24	LP/NLP
13	57/F	0.02/LP	Optic atrophy	–	RPR1:64 TPPA (+)	12/42	1 : 4/+	PCN 24 MUI iv/day *14d+ methylprednisolone pulse therapy	24	0.02/LP
14	54/F	0.3/NLP	Optic neuritis	Dysesthesias in the lower limbs	RPR1:32 TPPA (+)	134/39	1 : 2/+	PCN 24 MUI iv/day *14 days + prednisone 30mg/day orally	12	0.5/LP
15	52/M	LP/0.5	Optic atrophy	–	RPR1:32 TPPA (+)	154/66	1 : 8/+	PCN 24 MUI iv/day *14 days	40	LP/0.5
16	63/M	LP/LP	Optic atrophy	–	RPR1:128 TPPA (+)	4/88	1 : 1/+	PCN 24 MUI iv/day *14 days	12	LP/LP
17	53/M	FC/LP	Optic atrophy	–	RPR1:128 TPPA (+)	48/66	1 : 2/+	PCN 24 MUI iv/day *14 days + prednisone 30mg/day orally	12	0.12/LP
18	57/F	NLP/HM	Uveitis	–	RPR1:128 TPPA (+)	140/44	1 : 4/+	PCN 24 MUI iv/day *14 days	9	LP/0.3
19	63/M	0.15/LP	Uveitis	–	RPR1:512 TPPA (+)	24/50	1 : 2/+	PCN 24 MUI iv/day *14 days	11	0.6/0.02
20	59/M	LP/0.12	Optic atrophy	–	RPR1:64 TPPA (+)	0/61	1 : 4/+	PCN 24 MUI iv/day *14 days	5	LP/0.12

Table 3 Continued

Case number	Age/Gender	Best-corrected visual acuity (L/R) before treatment	Ocular diagnosis*	Other syphilis symptoms	Serology	CSF (W/P)	CSF-VDRL/CSF-TPPA	Treatment	Follow-up (month)	Best-corrected visual acuity (L/R) after treatment
21	48/M	LP/0. 25	Optic neuritis	–	RPR1:32 TPPA (+)	70/60	1 : 8/+	PCN 24 MUI iv/day *14 days + prednisone 30mg/day orally	12	LP/0.25
22	64/M	FC/LP	Optic atrophy	–	RPR1:8 TPPA (+)	0/30	1 : 1/+	PCN 24 MUI iv/day *14 days	9	0.02/HM
23	39/M	0.4/FC	Optic neuritis	–	RPR1:128 TPPA (+)	2/208	1 : 2/+	PCN 24 MUI iv/day *14 days	22	0.8/0.6
24	31/M	0.6/0.02	Optic neuritis	–	RPR1:128 TPPA (+)	48/34	–/+	Ceftriaxone 2g iv/day *15 days	10	0.8/0.3
25	40/M	0.3/FC	Optic atrophy	–	RPR1:8 TPPA (+)	237/55	1 : 4/+	PCN 24 MUI iv/day *14 days	36	0.3/FC
26	73/M	0.3/HM	Optic atrophy	–	RPR1:64 TPPA (+)	45/34	1 : 2/+	Ceftriaxone 2g iv/day *15 days	36	0.3/HM
27	51/M	0.5/0.04	Retinitis	–	RPR1:2 TPPA (+)	28/45	–/+	PCN 24 MUI iv/day *14 days	24	0.5/0.04
28	68/F	0.12/FC	Optic neuritis	Secondary syphilis rash	RPR1:128 TPPA (+)	22/34	–/+	PCN 24 MUI iv/day *14 days + prednisone 30mg/day orally	35	0.12/FC
29	62/M	0.02/0.4	Optic atrophy	–	RPR1:16 TPPA (+)	13/40	1 : 2/+	PCN 24 MUI iv/day *14 days	24	0.02/0.4
30	61/F	0.01/0.4	Uveitis	–	RPR1:64 TPPA (+)	416/67	1 : 8/+	PCN 24 MUI iv/day *14 days	12	0.12/1.2
31	51/F	0.6/0.04	Uveitis	–	RPR1:8 TPPA (+)	294/27	–/+	PCN 24 MUI iv/day *14 days	12	0.8/0.8
32	55/M	FC/0.2	Uveitis	Dysesthesias in the lower limbs	RPR1:64 TPPA (+)	174/130	1 : 32/+	PCN 24 MUI iv/day *14 days + prednisone 30mg/day orally	16	1.0/1.0
33	48/M	1.2/FC	Optic neuritis	–	RPR1:32 TPPA (+)	0/59	–/+	PCN 24 MUI iv/day *14 days	12	1.2/FC
34	69/M	FC/FC	Optic atrophy	–	RPR1:64 TPPA (+)	0/34	1 : 1/+	Ceftriaxone 2g iv/day *15 days	12	FC/FC
35	60/M	HM/0.2	Optic atrophy	–	RPR1:32 TPPA (+)	210/147	1 : 8/+	PCN 24 MUI iv/day *14 days	15	NLP/0.1
36	32/M	0.5/FC	Uveitis	–	RPR1:512 TPPA (+)	20/57	1 : 4/+	PCN 24 MUI iv/day *14 days	12	0.8/0.25
37	74/M	LP/0.25	Uveitis	–	RPR1:16 TPPA (+)	32/57.4	1 : 4/+	PCN 24 MUI iv/day *14 days	12	LP/0.25
38	55/M	NLP/LP	Optic atrophy	Dysesthesias and weakness of the lower limbs	RPR1:16 TPPA (+)	4/196	1 : 2/+	PCN 24 MUI iv/day *14 days	12	NLP/LP
39	55/F	LP/0.02	Optic neuritis	–	RPR1:32 TPPA (+)	0/27	–/–	PCN 24 MUI iv/day *14 days + prednisone 30mg/day orally	10	0.1/0.12
40	51/M	HM/0.2	Uveitis	–	RPR1:64 TPPA (+)	20/15	1 : 4/+	PCN 24 MUI iv/day *14 days	23	0.3/0.3

Table 3 Continued

Case number	Age/Gender	Best-corrected visual acuity (L/R) before treatment	Ocular diagnosis*	Other syphilis symptoms	Serology RPR/TPPA	CSF (W/P)	CSF-VDRL/CSF-TPPA	Treatment	Follow-up (month)	Best-corrected visual acuity (L/R) after treatment
41	54/M	LP/0.6	Optic atrophy	–	RPR1:64 TPPA (+)	35.2/32	1 : 4/+	Ceftriaxone 2g iv/day *15 days	44	LP/0.6
42	56/M	NLP/0.4	Optic atrophy	–	RPR1:8 TPPA (+)	10/62	1 : 2/+	PCN 24 MUI iv/day *14 days	6	NLP/1.0
43	56/M	0.02/0.3	Retinitis	–	RPR1:64 TPPA (+)	46/50	1 : 2/+	PCN 24 MUI iv/day *14 days	6	0.4/0.4
44	42/F	0.02/0.1	Optic atrophy	–	RPR1:32 TPPA (+)	48/28	–/+	PCN 24 MUI iv/day *14 days	12	0.04/0.1
45	54/F	NLP/0.2	Optic atrophy	–	RPR1:64 TPPA (+)	18/61	1 : 2/+	PCN 24 MUI iv/day *14 days	6	NLP/0.2
46	46/F	FC/0.1	Optic atrophy	–	RPR1:16 TPPA (+)	10/51	1 : 8/+	PCN 24 MUI iv/day *14 days	6	FC/0.1
47	62/M	0.02/0.4	Uveitis	–	RPR1:128 TPPA (+)	10/503	1 : 8/+	PCN 24 MUI iv/day *14 days + prednisone 30mg/day orally	18	0.5/0.5
48	64/M	LP/0.04	Optic atrophy	–	RPR1:64 TPPA (+)	28/98	1 : 8/+	PCN 24 MUI iv/day *14 days	6	LP/0.04
49	51/M	LP/0.1	Optic atrophy	–	RPR1:16 TPPA (+)	0/145	1 : 2/+	Ceftriaxone 2g iv/day *15 days	6	LP/0.1
50	64/M	LP/0.5	Optic neuritis	Weakness of the lower limbs	RPR1:64 TPPA (+)	600/157	1 : 32/+	PCN 24 MUI iv/day *14 days	6	LP/0.5

CSF, cerebrospinal fluid; FC (Counting fingers), ability to count fingers at 1 m distance; HM (Hand motion), ability to distinguish if a hand is moving or not in front of the patient's face; L, left eye; LP (Light perception), ability to perceive any light; NLP (No light perception), inability to see any light or total blindness; P, CSF protein mg/dL (≤45); PCN, aqueous penicillin G; R, right eye; RPR, rapid plasma regain; TPPA, Treponema pallidum particle agglutination; VDRL, Venereal Disease Research Laboratory test; W, CSF WBC count cell μL (0–8).

Optic neuritis is an inflammation that damages the optic nerve, inside or behind the eyeball.

Uveitis is inflammation of the uvea.

Retinitis is inflammation of the retina in the eye, may be caused by several infectious agents.

*Optic atrophy is degeneration of, or damage to the optic nerve.

acuity was also frequently impaired. Amongst patients with blindness, the most common ocular diagnosis was optic atrophy (*n* = 26) followed by optic neuritis (*n* = 11), uveitis (*n* = 10) and retinitis (*n* = 3). In patients with blinding disease, the median time from onset of ocular symptoms to diagnosis was 12 months (interquartile range 4–36 months), and the median time from initially seeking care to diagnosis was 9 months (interquartile range 1–18 months; Table S1). Prior to diagnosis, all patients had visited an ophthalmologist, and 42 patients were treated by ophthalmologists, including receiving oral neurotropic drugs (e.g. mecobalamin tablets), glucocorticoids either orally or by injection, topical eye drops and in some cases referral to surgery (e.g. patients with syphilitic chorioretinopathy misdiagnosed as cataract referred to surgery). As expected, no patients had improvement in vision with these therapies. Forty (80%) patients had ocular involvement as the primary clinical manifestation, whilst seven patients also reported dysesthesias or limb weakness. Two patients had findings consistent with syphilitic dementia, and one had a rash of secondary syphilis.

A positive CSF-VDRL test was shown in 84.0% patients (*n* = 42), and the range of CSF-VDRL titres was 1 : 1–1 : 32. Seven patients had negative CSF-VDRL test but a positive CSF-TPPA test and increased total protein (>45 mg/dL) or WBC counts (≥8/μL). Only one case had both a negative CSF-VDRL and CSF-TPPA accompanied by a normal CSF total protein and WBC counts (Table 3). CSF cultures for bacteria and fungi were negative in all 50 patients. Overall, 42 cases met the diagnostic criteria of neurosyphilis, seven met the criteria for presumptive neurosyphilis and one did not meet the criteria for neurosyphilis.

Syphilis treatment and follow-up

Overall, 43 of the 50 patients with syphilis-associated blindness were treated with aqueous crystalline pencillin G, whilst six received ceftriaxone and a single patient was treated with doxycycline. Ten patients received adjunctive therapy with corticosteroids, most commonly (*n* = 8) prednisone 30 mg/day orally. Two patients were treated with pulsed intravenous methylprednisolone followed by oral steroids. The median follow-up period after treatment was 20.7 (range 6–80) months (Table 3). At the end of follow-up, the visual acuity was improved in 24 of 67 (35.8%) eyes but nine of these eyes still met the WHO diagnostic

Table 4 Treatment effect of blindness caused by syphilis

	Blindness eyes	Patients	Improvement in vision (eyes)
Optic atrophy	40	26	5 (12.5%)
Optic neuritis	13	11	7 (53.8%)
Uveitis	11	10	10 (90.9%)
Retinitis	3	3	2 (66.7%)
Total	**67**	**50**	**24 (35.8%)**

criteria of blindness. Therefore, 52 eyes were finally classified as having permanent vision loss. Improvement in visual acuity following treatment was most common in cases of uveitis (90.9%) and lowest in cases of optic atrophy (12.5%) (Table 4). There was no clear association between adjunctive corticosteroid therapy and improvement in vision. Visual acuity improved in 13 of the 32 eyes with non-blinding diseases (40.6%) (Table 3).

Discussion

In this eight-year retrospective cohort study, we found that the proportion of syphilis patients with ocular involvement was 2.6%. Increasing age and higher RPR titres were associated with ocular involvement. The most common diagnosis was uveitis whilst optic neuritis and optic atrophy were the main causes of blindness and had poor treatment outcomes.

Though syphilis has increased dramatically in China in recent years, national surveillance data on ocular manifestations are not routinely collected by China Centers for Disease Control and Prevention (CDC). As a result, the true rate of ocular syphilis in China is unknown. In other countries where syphilis is resurgent marked increases in ocular syphilis have also been reported.[22] A review of surveillance data during 2012–2013 from King County, Washington, revealed that 4.8% of patients with syphilis reported visual symptoms and 2.7% had objective findings consistent with ocular syphilis.[23] In our study, a total of 213 （2.6%）patients had ocular involvement and 0.6% had at least one eye in which resulted in blindness. The true rate of ocular syphilis may be higher than we have reported, because patients with mild visual symptoms may not have been detected by either the clinician or the patient themselves. Whilst ocular syphilis is a treatable disease if it is diagnosed promptly and treated properly delays can lead to serious sequelae including lifelong blindness[24–26]. In the pre-antibiotic era, about 9% to 12% of patients with ocular syphilis developed blindness.[27] Consistent with our findings, post-treatment visual acuity was dependent on visual acuity at baseline and delayed treatment with no differences in efficacy between treatment regimens.[28] Visual acuity either improved or remained stable in the majority of eyes.[29] We demonstrated a trend towards increased risk of blindness in patients with optic neuritis and a predictable and significantly increased risk associated with optic atrophy which may reflect the long duration between symptom onset and diagnosis in this group of patients.

Syphilis can involve almost any eye structure, but posterior uveitis and pan uveitis are reported to be the most common manifestations. In keeping with this, the most common diagnosis of ocular syphilis was uveitis in our study. Whilst previous research supports evidence of neuropathogenic strains of syphilis, it remains unknown if some TP strains have a greater likelihood of causing ocular infections.[30] In syphilis, optic nerve involvement may be unilateral or bilateral and manifest as perineuritis, anterior or retrobulbar optic neuritis or papilledema,

Table 5 Summary and comparison with previous ocular syphilis studies

	Our Study	Moradi, et al.[29]	Lee, et al.[33]	Shen, et al.[15]	Pratas, et al.[37]	Oliver, et al.[22]	Ghanimi Zamli, et al.[38]
Research period	2009–2017	1984–2014	2008–2014	2009–2014	2012–2015	2014–2015	2013–2017
Research location	Shanghai, China	United States of America	Los Angeles	Zhejiang, China	France	North Carolina	Malaysia
Number of ocular syphilis	213	35	16	13	21	63	10
Blindness patients, % (n)	23% (50)	21% (7)	44% (7)	8% (1)	NR	6% (4)	50% (5)
Mean age, years	55	49	43	50	49	45	70
Male sex, % (n)	66% (140)	74% (26)	100% (16)	54% (7)	100% (21)	94% (59)	30% (3)
Known MSM, % (n)*	10% (14)	35% (9)	44% (7)	0% (0)	76% (16)	71% (42)	0% (0)
Co-infection with HIV, % (n)	3% (7)	54% (19)	63% (10)	8% (1)	29% (6)	56% (35)	0% (0)
Risk factors for ocular syphilis	Increasing age and higher RPR titres	NR	NR	NR	NR	Male, aged ≥40 years, white, infected with HIV, and higher RPR titre	NR
CSF-VDRL reactive†	84%†‡	47%	20%	25%	21%	63%	NR
Most common type of ocular diagnosis	Optic atrophy, optic neuritis‡	Pan uveitis	Pan uveitis, posterior uveitis	Chorioretinitis	Posterior uveitis	Uveitis	Posterior uveitis
Improved vision after treatment	36%†‡	33%	38%	62%	75%	85%	85%

NR, result not reported

*Percentage calculated of males.

†Percentage calculated of those with CSF analysis performed.

‡Data from 50 cases of blindness.

and may lead to decreased visual acuity including permanent blindness, especially in patients with optic atrophy.[31] Our data suggest the risk of blindness is restricted predominantly to patients with optic nerve involvement and not those with isolated uveitis. Syphilis is a relatively rare cause of optic atrophy and cannot be easily distinguished from non-syphilitic disease. Of patients with blinding disease, the majority (80%, $n = 40$) had no other systemic manifestations. The absence of the characteristic findings of ocular syphilis, in particular uveitis, may lead ophthalmologists not to consider syphilis as a differential diagnosis and thus lead to delayed treatment.

Ocular syphilis is frequently associated with neurosyphilis.[32] In this study, all patients with blindness underwent a LP to allow evaluation of CSF findings. Given the importance of making a diagnosis of ocular syphilis, otosyphilis or neurosyphilis, it is clear that all patients who receive a diagnosis of syphilis should be asked screening questions to identify visual, hearing or neurologic symptoms and receive a careful neurologic examination. An immediate ophthalmologic evaluation and CSF examination is recommended for patients with syphilis and ocular complaints. In our study, the proportion of individuals with a positive CSF-VDRL test (84%) was higher than most previously published reports (Table 5).[22,29,33] One reason for this may be the longer duration of illness and high proportion of optic nerve involvement compared to other studies. Another reason is that the patients in our study were all with blindness. In keeping with national and CDC guidelines, our study supports the need for CSF analyses and management of patients with ocular syphilis according to treatment recommendations for neurosyphilis.[30,34,35]

The diagnosis of ocular syphilis is challenging due to lack of pathognomonic findings. In the context of the current resurgence of syphilis, all patients with uveitis, optic neuritis and optic atrophy should be tested for syphilis even though the history may not clearly suggest it as the diagnosis.[31] Conversely, for patients with syphilis, clinicians should pay increased attention to whether there are eye symptoms, including decreased vision, visual field defects, floaters, redness of the eye or eye pain. In a 35-country study of syphilitic uveitis, optic neuropathy and initial misdiagnosis were both identified risk factors for poor outcomes.[36] Consistent with this, our data highlight the importance of early diagnosis of ocular syphilis to prevent blindness. Many patients were left with lifelong blindness likely related to delays in seeking care and diagnosis. At the most extreme end, one case (No.18 in Table S1) presented to seven different hospitals and visited doctors 25 times before a diagnosis of ocular syphilis was made.

The major limitation of this study is its retrospective nature which may have resulted in incomplete data, such as on HIV status, or misclassification of patients' syphilis stage. Despite this, the current study is, to our knowledge, the largest reported series cases of blindness caused by ocular syphilis reported since the

start of the HIV epidemic. In developed countries, most recent reports of ocular syphilis, including blindness, have been amongst HIV-positive MSM.[30,32] By contrast, severe visual loss, including blindness, has rarely been reported in immunocompetent patients in the postpenicillin era.[9] Unlike most previous series in Western countries, our patients were predominantly heterosexual HIV-negative patients and we did not demonstrate an association between HIV and ocular syphilis or blindness. Consistent with other studies, increasing age and a high baseline RPR titre however were associated with risk of ocular disease (Table 5).

Lifetime blindness is a tragedy. However, if detected early and treated, there is a good visual prognosis for patients with syphilitic optic neuritis and uveitis.[32] Our data highlight the importance of considering syphilis even in patients with isolated ocular symptoms and initiating prompt diagnostic testing and treatment to avoid irreversible blindness.

Authors Contribution

PZ designed the study. PZ, XG, YG, YY and MM interpreted data and wrote the report. XG, YY and MM analysed data. XG, YG, LZ, HL, ZG, MS, LN, RP, WZ, JW, TQ, YQ, WG and SL collected data. XG wrote the first draft of the manuscript. PZ, XG, YG, YY and MM revised the report from preliminary draft to submission. PZ supervised the study.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Delays in care of patients with blinding subjects.