Diagnostic and therapeutic challenges in inflammatory eye diseases

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3 CLINICAL MANIFESTATIONS AND OUTCOME OF SYPHILITIC UVEITIS

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ABSTRACT

Purpose: To analyze visual outcome, effectiveness of various modes of antibiotic treatment and prognostic factors in patients with serologically proven syphilitic uveitis.

Methods: The clinical records of 85 patients (139 eyes) diagnosed with syphilitic uveitis between 1984 and 2013 at tertiary centers in the Netherlands were retrospectively analyzed.

Results: Mean age was 47 years (range 27 – 73), 82.4% were male. HIV positivity was found in 28 (35.9 %) patients, 13 were newly diagnosed. Most patients had pan (45.9%) or posterior (31.8%) uveitis. On average, LogMAR VA improved significantly from 0.55 at the start of syphilis treatment to 0.34 at 1 month and to 0.27 at 6 months follow up. Most patients (86.7%) reached disease remission. No differences in efficacy between the various treatment regimens were found. A high LogMAR VA at the start of syphilis treatment and a treatment delay of more than 12 weeks were prognostic for a high LogMAR VA at six months follow up. Chronicity was not related to any form of treatment, HIV status or VDRL test outcome.

Conclusion: In this large cohort of 85 patients with syphilitic uveitis, visual outcomes were favorable in the majority of cases. Visual outcome was dependent on VA at the start of syphilis treatment and treatment delay.

INTRODUCTION

Syphilis is caused by an infection with the bacterium Treponema pallidum (T. pallidum) and classified as acquired or congenital. As with other spirochete infections, the clinical course of acquired untreated syphilis can be divided into four different stages depending on the clinical manifestations[1]. Syphilitic uveitis can occur in all stages except in the primary stage.

Different tests are available for the diagnosis and staging of syphilis. These include the so-called nonspecific tests like the VDRL (Venereal Disease Research Laboratory) and RPR (Rapid Plasma Reagin), which quantify the amount of serum anticardiolipin antibodies by flocculation and T. pallidum specific tests like the FTA-ABS (Fluorescent treponemal antibody absorption test), TPPA (Treponema pallidum particle agglutination) and TPHA (Treponema pallidum haemagglutination assay), which measure the amount of serum antibodies specifically directed against treponemal antigens[1]. As was shown by Grange et al[2], newer PCR-based techniques have very low sensitivity to detect syphilis in blood, and thus cannot replace the above-mentioned serological tests.

The clinical presentation of ocular syphilis has been described in many publications. It has been dubbed "The Great Imitator" as it can mimic a wide range of ocular disorders. The most common presentation of ocular syphilis is uveitis. Before 1940, syphilis was the second cause of uveitis after tuberculosis. With the introduction of penicillin and improved diagnostics, syphilitic uveitis is a rare disease nowadays, accounting for 1 to 2% of all uveitis patients[3]. However, the outcomes of the different serologic tests for syphilis can be confusing, the optimal treatment of syphilitic uveitis is debatable and it is unknown which factors will determine visual prognosis.

To contribute to clarification of these aspects, we retrospectively evaluated visual outcomes in 85 patients with syphilitic uveitis. Specifically, factors that correlated with a worse visual prognosis or a chronic disease course were investigated.

PATIENTS AND METHODS

Patients with a confirmed diagnosis of syphilitic uveitis between 1984 and 2013 at the University Medical Centers of Leiden (n=12), Groningen (n=19), Utrecht (n=33), the VU University Medical Center Amsterdam (n=3) and the Rotterdam Eye Hospital (n=18) were included. The diagnosis of syphilitic uveitis was made in uveitis patients with positive results for specific anti T. pallidum serologic tests (i.e. a positive TPPA or TPHA and/or a positive FTA-ABS test) and agreement on the diagnosis syphilitic uveitis between ophthalmologist, dermatologist,

infectious disease specialist and neurologist. In the above centers, serologic testing for syphilis is part of the work-up in uveitis of unknown cause[4]. This work-up depends on the clinical presentation of the uveitis and may include blood tests (e.g. ESR, CRP, Hb, Ht, erythrocyte, thrombocyte and leukocyte counts, leukocyte differential, kreatinin, sodium, potassium, calcium, albumin, liver transaminases, angiotensin converting enzyme, auto-antibodies, tests for tuberculosis and chest X-rays. Additional tests may be ordered in special situations (e.g. anterior chamber fluid tests for infectious uveitis). (Uveitis Guidelines Dutch Opthalmic Society, 2007)[4]. However, since all these centers are tertiary referral centers, patients are often referred by ophthalmologists working in general practices. A systematic work-up for uveitis has not always been performed prior to referral. Medical records were retrospectively analyzed. The study was conducted in accordance with the Declaration of Helsinki and the study design was evaluated by the Medical Ethical Committee of the University Medical Center of Groningen who ruled that approval was not required for this study.

All participating centers collect data on uveitis patients in a database. However, the inclusion of patients started at different time points at the different centers. Therefore, the inclusion period varied per center (years are given between brackets): Leiden University Medical Center (1985 to 2008), University Medical Center Groningen (2001 to 2013), University Medical Center Utrecht (1991 to 2011), VU University Medical Center Amsterdam (2009 to 2012) and the Rotterdam Eye Hospital (1996 to 2010).

The following data were recorded on an anonymized standard entry form: sex, age at the start of syphilis treatment, race, affected eye(s), interval between the date of onset of uveitis symptoms and the date of final diagnosis of syphilitic uveitis and initiation of anti-syphilis treatment, laboratory data including HIV status and the results of various serologic tests for syphilis, the results of cerebrospinal fluid analyses, classification of the uveitis based upon standardization of uveitis nomenclature (SUN) criteria[5], various clinical features, treatment modalities, visual acuity in logarithm of the minimal angle of resolution units (LogMAR) at the start of syphilis treatment, and at one and six months follow-up. The Snellen VA was converted to LogMAR VA for calculations. Visual acuity at one and six months was analyzed in relation to type of uveitis, treatment before syphilis treatment, interval between uveitis and syphilis treatment, administration route of syphilis treatment, HIV-status and immunosuppressive treatment during syphilis treatment.

Uveitis was classified as anterior, intermediate, posterior or panuveitis. The presence of cystoid macular edema (CME) was confirmed by fluorescein angiography (FA) or optical coherence tomography (OCT). Retinitis, retinal ischemia and papillitis were diagnosed by FA. Serous retinal detachments were

diagnosed by fundoscopy or ultrasound (US). Fundoscopically observed retinal hemorrhages and retinal vasculitis were recorded. Chronic uveitis was defined as persistent uveitis with relapse within 3 months after discontinuing treatment [5] or as an active uveitis at 6 months follow up.

The following treatment regimens were included: 1. Benzyl penicillin 0.15 million units/kg/day intravenously for 14 days, 2. Procaine penicillin 1.2–2.4 million units intra-muscularly during 10–17 days, and 3. Oral doxycycline 200 mg twice per day for 28 days or ceftriaxone intravenously 2 g/day for 14 days. Patients were divided into three groups based on the time interval between presentation of uveitis and the start of syphilis treatment. The first group received treatment within 4 weeks after presentation of the uveitis, the second was treated within four to twelve weeks after presentation and the third started treatment after a twelve week interval.

Adjunctive treatment with corticosteroids (eye drops, peri-ocular injections and systemic) and other immunosuppressives (systemic) was recorded. For statistical analyses, three groups were made. 1. Patients without adjunctive treatment with steroids. 2. Patients who received adjunctive treatment with steroid eye drops. 3. A combined group of patients (n=36) who received adjunctive treatment with subconjunctival (n=4) or systemic corticosteroids (n=32).

Statistical analysis was performed by SPSS® software version 20 (SPSS, Inc., Chicago, IL). A $P < 0.05$ was considered statistically significant. Analysis of VA improvement was done by comparing VA at the start of syphilis treatment to that at one and six months by Friedman ANOVA with post hoc Wilcoxon signed-rank test and Bonferroni correction. The Mann-Whitney test was used to test for statistical differences in VA at one and six months between the groups that were treated with local or systemic corticosteroids and between HIV negative and positive patients. The chi-squared test was used to test for relationships between HIV status and anatomical location of the uveitis or cerebrospinal fluid abnormalities, respectively. A multiple linear regression model was used to assess the weight and value of the prognostic factors for visual outcome at six months.

RESULTS

Of the 89 patients classified as having syphilitic uveitis, a cohort of 85 patients could be evaluated in detail, while 4 patients were excluded because of lack of documentation. Patients' characteristics are summarized in Table 1. As shown, only patients with a positive TPHA or TPPA test were included. In addition, VDRL testing was done in all patients, 69 (81.2%) of whom were positive. Of the 16 VDRL negative patients one patient was HIV positive. Two patients had a documented

re-infection, they were both VDRL positive. FTA-Abs tests were positive in all 43 tested patients. The majority of patients (82.4%) were male and most (63.5%) had bilateral disease. Lumbar punctures had been performed in 62 (72.9%) patients (Table 1). Cerebrospinal fluid (CSF) tested positive for TPHA or TPPA in 33/57 (57.9%) patients, VDRL in 12/31 (38.7%) and FTA-Abs in 4 out of 6 tested patients. In 28 (35.9%) patients, a HIV co-infection was present. Of these, 15 (53.6%) had previously been diagnosed with HIV, and 13 (46.4%) were newly identified. No statistically significant relationship was found between anatomical location of the uveitis, HIV status and cerebrospinal fluid abnormalities.

Ocular features are shown in Table 2. In case of posterior and panuveitis, optic nerve and retinal involvement and vitritis probably explain the low VA at presentation. Visual field defects at any moment during follow up were found in 44 out of 52 (84.6%) tested eyes. These were predominantly eyes with posterior (n=14, 31.8%) or panuveitis (n=22, 50%).

In Table 3 and 4, the LogMAR VA per eye at the start of syphilis treatment and at 1 and 6 months is shown. On average, a statistically significant improvement in VA was observed at 1 and 6 months as compared to VA at start of syphilis treatment.

Most patients were treated with intravenous (IV) benzyl penicillin G (n=55, 64.7%) or ceftriaxone (n=2, 2.4%) for 2 weeks (Table 4). Intra muscular (IM) treatment with procaine penicillin was given in 15 (17.6%) patients, 5 (5.9%) patients were treated with oral antibiotics (doxycycline in all cases) and 8 (9.4%) patients were treated with a combination of IV, IM and oral treatment.

Table 1. Patient Characteristics (N=patients)

Syphilitic uveitis	**N (%)**
Mean age (range)	46.96 (27 – 73)
Male	70/85 (82.4%)
Bilateral	54/85 (63.5%)
Etnicity	
Caucasian	67/85 (78.8%)
Other*	18/85 (21.2%)
Serological tests for Syphilis	
TPHA/TPPA positive	85/85 (100%)
VDRL positive	69/85 (81.2%)
FTA-Abs positive	43/43 (100%)
Lumbar puncture findings	
Performed lumbar punctures	62/85 (72.9%)
Positive TPHA/TPPA	33/57 (57.9%)
Positive VDRL	12/31 (38.7%)
Positive FTA-Abs	4/6 (66.7%)
HIV status	
HIV positive	28/78 (35.9%)
Already known	15/28 (53.6%)
Newly diagnosed	13/28 (46.4%)
Interval uveitis and syphilis	
< 4 weeks	36/85(42.4%)
4 – 12 weeks	16/85 (18.8%)
>12 weeks	33/85 (38.8%)
Administration route antibiotics for syphilis treatment	85/85 (100%)
Intra-venous	57/85 (67.1%)
Intra-muscular	15/85 (17.6%)
Oral	5/85 (5.9%)
Combination of the above	8/85 (9.4%)

The fraction (x/y) displays the number of patients with a specific characteristic (x) in relation to the total number of patients evaluated (y). * Surinam Blacks n=7, African Americans n=2, Asians n=7, Surinam Indians=2

Table 2. Ocular features

	Anterior uveitis	Intermediate uveitis	Posterior uveitis	Panuveitis	Sclero-uveitis	Total (n)
Number of patients	14	2	27	39	3	85
Visual acuity at presentation						
> 20/50	10	2	8	15	0	35
20/200 – 20/50	2	0	7	13	3	25
>NLP[1] – 20/200	2	0	12	11	0	25
NLP	0	0	0	0	0	0
Number of affected eyes	22	4	42	66	5	139
Vitritis	3	4	18	55	5	85
Cystoid macular edema	2	0	9	20	1	32
Retinitis	0	0	31	50	5	86
Retinal ischemia	0	0	10	20	1	31
Retinal hemorrhages	0	0	14	22	4	40
Retinal vasculitis	0	0	17	30	3	50
Papillitis	0	2	31	39	2	74

[1] NLP: no light perception

Table 3. VA, uveitis type and HIV-status (Log MAR acuity per eye, n=eyes)

	VA at start of syphilis	VA at 1 month	VA at 6 months	P 0 – 1 month*	P 0 – 6 months §	P 1 – 6 months λ
Total group (N=patients)	(139/139) **0.55** (SD 0.66)	(134/139) **0.34** (SD 0.6)	(117/139) **0.27** (SD 0.51)	**< 0.001**	**< 0.001**	**< 0.001**
Type of uveitis						
Anterior uveitis (N=14)	(22/139) **0.32** (SD 0.5)	(22/134) **0.3** (SD 0.63)	(16/117) **0.33** (SD 0.73)	NS	NS¶ (0.021)	**0.003**
Intermediate uveitis (N=2)	(4/139) **0.06** (SD 0.16)	(4/134) **0.009** (SD 0.1)	(2/117) **0.097**	NS	NS	NS
Posterior uveitis (N=27)	(42/139) **0.61** (SD 0.60)	(40/134) **0.33** (SD 0.52)	(39/117) **0.31** (SD 0.56)	**0.01**	**0.016**	NS
Pan uveitis (N=39)	(66/139) **0.56** (SD 0.67)	(64/134) **0.39** (SD 0.67)	(56/117) **0.26** (SD 0.49)	**< 0.001**	**< 0.001**	**0.003**
Sclero-uveitis (N=3)	(5/139) **1.4** (SD 1.1)	(4/134) **0.18** (SD 0.3)	(4/117) **0.1** (SD 0.21)	NS	NS	NS
HIV						
Positive N=28#	(48/139) **0.56** (SD 0.67)	(48/134) **0.28** (SD 0.57)	(37/117) **0.26** (SD 0.52)	**< 0.001**	**0.001**	NS¶ (0.029)
Negative N=50#	(91/139) **0.55** (SD 0.65)	(86/134) **0.37** (SD 0.61)	(80/117) **0.27** (SD 0.5)	**< 0.001**	**< 0.001**	**< 0.001**

All uveitic eyes were included in this analysis. At each time point, the fraction (x/y) displays the number of eyes with a specific characteristic (x) in relation to the total number of eyes evaluated (y).To correct for the bias of systemic treatment in bilateral versus unilateral disease, Table 5 was added. *Friedman ANOVA with post hoc Wilcoxon signed-rank test between presentation and 1 month. § Friedman ANOVA with post hoc Wilcoxon signed-rank between presentation and 6 months. λ Friedman ANOVA with post hoc Wilcoxon signed-rank between VA at 1 month and 6 months. # No significant difference in VA outcome between the two groups (Mann-Whitney test). ¶ After Bonferroni correction a P ≤ 0.0167 (0.05/3) is required.

Only in patients treated by IV antibiotics, a statistically significant VA improvement at 6 months (as compared to VA at start of treatment) was seen (Table 4). Patients treated with antibiotics by different routes of administration, also had VA improvement at 6 months, but this was not statistically significant (Table 4). Sixty-seven patients (78.8 %) received systemic, subconjunctival or

Table 4. VA and treatment (Log MAR acuity per eye, n=eyes)

	VA at start of syphilis treatment	VA at 1 month	VA at 6 months	P 0 – 1 month*	P 0 – 6 months §	P 1 – 6 months ^λ
Total group (N=patients)	(139/139) **0.55** (SD 0.66)	(134/139) **0.34** (SD 0.6)	(117/139) **0.27** (SD 0.51)	**< 0.001**	**< 0.001**	**< 0.001**
Treatment before syphilitic treatment						
Missing data	11/139	11/134	9/117			
No treatment (N=41)	(69/128) **0.51** (SD 0.6)	(67/123) **0. 29** (SD 0.52)	(62/108) 0.**29** (SD 0.61)	**< 0.001**	**0.002**	**0.010**
Corticosteroids and other immunosuppressives N=14	(24/128) **0.51** (SD 0.64)	(22/123) **0.42** (SD 0.78)	(20/108) **0.28** (SD 0.47)	NS¶ (0.036)	**0.011**§	NS¶ (0.043)
Other treatment (not adequate) N=23	(35/128) **0.69** (SD 0.76)	(34/123) **0.42** (SD 0.68)	(26/108) **0.20** (SD 0.38)	**0.006**)	**<0.001**	**0.002**
Interval uveitis and syphilis treatment						
< 4 weeks N=36	(56/139) **0.59** (SD 0.73)	(55/134) **0.34** (SD 0.68)	(43/117) **0.20** (SD 0.42)	**< 0.001**	**< 0.001**	**< 0.001**
4 – 12 weeks N=16	(29/139) **0.45** (SD 0.58)	(25/134) **0.22** (SD 0.39)	(22/117) **0.09** (SD 0.22)	**0.012**	**< 0.001**	**< 0.001**
>12 weeks N=33	(54/139) **0.57** (SD 0.63)	(54/134) **0.39** (SD 0.6)	(52/117) **0.40** (SD 0.62)	**0.008**	NS¶ (0.022)	NS
Administration route syphilis treatment						
Intra-venous N=57	(99/139) **0.53** (SD 0.61)	(96/134) **0.30** (SD 0.59)	(86/117) **0.25** (SD 0.52)	**< 0.001**	**< 0.001**	**0.002**
Intra-muscular N=15	(20/139) **0.51** (SD 0.81)	(18/134) **0.4** (SD 0.63)	(16/117) **0.38** (SD 0.64)	NS	NS	NS¶
Oral N=5	(7/139) **0.52** (SD 0.74)	(7/134) **0.51** (SD 0.74)	(7/117) **0.18** (SD 0.28)	NS	NS¶ (0.043)	NS¶ (0.028)
Combination of the above N=8	(13/139) **0.78** (SD 0.75)	(13/134)**0.49** (SD 0.55)	(8/117) **0.43** (SD 0.68)	NS	NS¶ (0.018)	NS¶ (0.046)
Immunosuppressive treatment during syphilis treatment						
Missing data	3/139	1/134	1/117			
Oral or subconjunctival corticosteroids# N=36	(63/136) **0.65** (SD0.65)	(60/133) **0.33** (SD 0.58)	(58/116) **0.28** (SD 0.56)	**< 0.001**	**< 0.001**	**0.003**
Corticosteroid eye drops# N=31	(46/136) **0.44** (SD 0.58)	(46/133) **0.41** (SD 0.72)	(37/116) **0.28** (SD 0.55)	NS	**0.001**	**0.008**
No corticosteroids N=16	(27/136) **0.48** (SD0.7)	(27/133) **0.24** (SD 0.38)	(21/116) **0.25** (SD 0.45)	NS¶ (0.037)	NS¶ (0.035)	NS¶ (0.062)

All uveitic eyes were included in this analysis. At each time point, the fraction (x/y) displays the number of eyes with a specific characteristic (x) in relation to the total number of eyes evaluated (y).To correct for the bias of systemic treatment in bilateral versus unilateral disease, Table 5 was added. *Friedman ANOVA with post hoc Wilcoxon signed-rank test between presentation and 1 month. § Friedman ANOVA with post hoc Wilcoxon signed-rank between presentation and 6 months. ^λ Friedman ANOVA with post hoc Wilcoxon signed-rank between VA at 1 month and 6 months. # No significant difference in VA outcome between the two groups (Mann-Whitney test). ¶ After Bonferroni correction a P ≤ 0.0167 (0.05/3) is required.

local steroids next to antibiotic treatment. No statistically significant difference in VA at six months was found between patients who had versus those who had not received any adjunctive treatment with systemic or local steroids (p=0.691). No cases of Jarisch-Herxheimer reaction were reported.

Table 5 displays the course of the disease after treatment. Ten (13.5 %) patients developed chronic uveitis. Chronicity was not related to the duration of treatment delay, any form of treatment or outcome of VDRL testing.

Table 5. Administration route syphilis treatment (N=patients)

Administration route syphilis treatment	N (%)	Remission at 6 months[#]	Chronic at 6 months
Total	85/85	65/75 (86.7%)	10/75 (13.3%)
Intra-venous	57/85 (67.1%)	44/57(77.2%)	7/57 (12.2 %)
Intra-muscular	15/85 (17.6%)	11/15 (73.3)	2/15 (13.3 %)
Oral	5/85 (5.9%)	5/5	0
Combination of the above	8/85 (9.4%)	5/8 (62.5%)	1/8 (12.5%)

[#] In 10 patients data regarding disease status at 6 months was missing.

With Friedman ANOVA statistical analysis, we evaluated VA outcomes at one and six months when compared to VA at the start of syphilis treatment. Delayed treatment in itself was associated with less VA improvement at six months. Whether patients had received any form of treatment not specifically directed at syphilis as compared to no treatment prior to the start of specific treatment directed at syphilis, did not seem to affect VA outcomes at 1 and 6 months (Table 4). Prior treatment regimens differed and consisted of antivirals (n=10) or antibiotics / anti-toxoplasmosis drugs (n=13).

By using a multivariate linear regression model, we analyzed which factors were associated with the outcome variable LogMAR VA at 6 months. Within this model, we took into account: the type of uveitis, delay between onset of uveitis and treatment, bilateral disease, ethnicity, VDRL test results, route of administration of treatment, HIV-positivity, treatment before syphilis treatment, the use of corticosteroids or other steroid-sparing immunosuppressive drugs and VA at the start of syphilis treatment. Regarding VDRL status, the statistical analysis in this regression model was done in two ways. The first analysis was done with the VDRL negative versus the VDRL positive patients. The second analysis was done with the VDRL positive patients versus the combined VDRL negative patients and patients with a low VDRL-titer (below 1:8). With this model, we found that a lower VA at the start of syphilis treatment (P<0.001) and a delay of more than 12 weeks between presentation and treatment for syphilis (P=0.038), were associated with a statistically significantly worse visual outcome at 6 months. These two variables explain 34.6% (R Square 0.346) of the variance in VA outcomes at 6 months.

Table 6. Best eye analysis1 (Log MAR acuity per eye)

Ocular syphilis	VA at presentation	VA at 1 month	VA at 6 months	VA difference 1 and 6 months ‡
All eyes (n=139)	(139/139) **0.55** (SD 0.66)	(134/139) **0.34** (SD 0.6) P=0.001*	(117/139) **0.27** (SD 0.51) P=<0.001§	P=<0.001
Unilateral eyes (n=31)	(31/31) **0.71** (SD 0.77)	(31/31) **0.4** (SD 0.55) P=0.003*	(26/31) **0.25** (SD 0.4) P=<0.001§	P=0.002
Bilateral best eye and unilateral eyes (n=85)	(85/85) **0.39** (SD 0.58)	(83/85) **0.22** (SD 0.47) P=<0.001*	72/85 **0.15** (SD 0.33) P=<0.001§	P=<0.001

To correct for the bias of systemic therapy in bilateral versus unilateral disease, we performed VA analyses at the various time points for all eyes, unilateral eyes only, and bilateral best eyes plus unilateral eyes. At each time point, the fraction (x/y) displays the number of eyes with a specific characteristic (x) in relation to the total number of evaluated eyes (y).The results of all analyses show a significant improvement of VA between all-time points and in all analyzed groups. *Friedman ANOVA with post hoc Wilcoxon signed-rank test between presentation and 1 month. § Friedman ANOVA with post hoc Wilcoxon signed-rank between presentation and 6 months. ‡ Friedman ANOVA with post hoc Wilcoxon signed-rank between VA at 1 month and 6 months.

Table 7. Characteristics of 6 patients (10 eyes) with visual loss at 6 months.

Patient	No eyes	Type of uveitis	VA at presentation	VA at 1 month	VA at 6 months	HIV	Cause of visual loss	Previous immunosupressives	Treatment within 4 weeks	Administration route
1	2	posterior	0.2	NLP	NLP	-	Ischemic optic neuropathy	Oral corticosteroids	No	IV
			0.2	NLP	NLP					
2	2	posterior	1.2	0.8	0.3	-	Optic neuropathy	No	No	IV
			FC	HM	HM		Sub retinal fibrosis			
3	2	pan	0.8	HM	0.1	+	Retinal detachment	Oral corticosteroids and cyclosporine	No	IV
			HM	HM	0.1		glaucoma		No	
4	1	posterior	*1.2*	*1.2*	*1.2*	-		No	No	IV
			0.1	FC	FC		Sub retinal fibrosis			
5	1	sclero-uveitis	*0.5*	*0.8*	*0.8*	unknown	Optic neuropathy	No	Yes	IV
			HM	NLP	NLP		Sub retinal fibrosis			
6	2	anterior	0.8	0.25	0.25	-		No	No	IM
			0.4	HM	HM		hypopyon			

Ten eyes of 6 patients with bilateral uveitis lost VA during follow-up. (The data of the two eyes that improved are given in italics). VA = Visual acuity (Snellen), IV = Intra venous, IM = Intra muscular, FC = Finger counting, HM = Hand motion, NLP = No light perception.

To correct for the possible bias of systemic treatment in a mixed population of bilateral and unilateral disease we took bilateral disease into account in the regression model and we added Table 6. Bilateral disease did not influence the visual outcome at 6 months (P=0.216).

Table 7 shows the characteristics of the 6 patients (10 eyes) with visual loss at 6 months. Posterior uveitis was the predominant type of uveitis associated with visual loss. Optic neuropathy, subretinal fibrosis, retinal detachment and glaucoma were the main causes of severely reduced VA in these patients. In one patient with hand motion VA, the posterior segment could not be evaluated due to severe persistent anterior segment inflammation (hypopyon) (This patient refused intensive local treatment).

DISCUSSION

Within this cohort of 85 patients with serologically proven syphilitic uveitis , the overall visual prognosis was good if timely and adequate therapy was given. High LogMAR VA (low Snellen VA) outcomes were associated with a treatment delay of more than 12 weeks, and high LogMAR VA at the start of syphilis treatment. A statistically significant improvement of VA at 1 and 6 months as compared to that at the start of syphilis treatment, was observed in patients treated with IV antibiotics, and in those that received adjunct corticosteroids. Absolute values of LogMAR VA at 6 months were not associated with the route of administration of antibiotics, treatment with corticosteroids and HIV status. The majority of patients had one uveitis episode, but chronic uveitis developed in 13.5%. None of the evaluated factors was associated with a chronic course.

Overall, a good visual prognosis in our study is supported by the finding that the 117 eyes included in the per eye analysis showed a statistically significant improvement at one and six months follow up. Also, 16 of the 22 eyes (72.7%) with missing data at 6 months had a Snellen VA above 20/32 (LogMAR 0.2) at 1 month follow up. Therefore, we may assume an even more favorable prognosis than that presented in our tables. An overall good visual prognosis in syphilitic uveitis such as found in this large cohort, confirms previous studies [6-11]. In our study, a higher LogMAR VA at the start of syphilis treatment and a delay of more than 12 weeks between the first presentation of uveitis and treatment for syphilis, were associated with a statistically significantly higher LogMAR VA at 6 months. Possible reasons for diagnostic delay include patients' and doctors' delay. It is hard to reduce the former, whereas the latter can be minimized by following the general advice to test for syphilis in patients with uveitis of unknown origin [1, 12, 13].

Treatment outcome

Probably, delayed treatment is associated with irreversible structural damage [1, 7, 14, 15]. This is supported by the association between high LogMAR VA at the start of syphilis treatment and at 6 months. Worsening of VA during follow up occurred in ten eyes and was associated with structural damage to the optic disc and retina. In our study, the majority of patients were treated with intravenous penicillin (Table 4). Smaller numbers of patients were treated with intramuscular or oral antibiotics. These different treatment modalities were not prognostic for a higher LogMAR VA at 6 months.

Previous studies on prognostic factors in ocular syphilis [6, 16, 17] showed no difference in visual outcome when comparing the "classic" regimen of intravenous penicillin with other antibiotics. But, these studies [6, 16, 17] were all in small groups, with different kind of antibiotics and therefore results should be interpreted cautiously.

Corticosteroids

Another finding in our study is that patients who received local, subconjunctival or systemic corticosteroids next to antibiotic treatment for syphilis had on average a statistically significant improvement in VA at 1 and 6 months, when compared to VA at the start of syphilis treatment. The absence of a statistically significant difference between patients treated with additional oral steroids or steroid injections versus those not treated in this way, seems to indicate that additional steroids may be ineffective. However, the fact that mean LogMAR VA at the start of syphilis treatment was higher in patients receiving additional oral steroids or steroid injections than in patients not receiving this (Table 4), indicates that adjunct corticosteroid treatment may have been preferably given to the more severe cases. Since LogMAR VA outcomes in these possibly more severe cases are similar to outcomes in the probably less severe groups (Table 4), a beneficial effect of adjunct corticosteroid treatment cannot be excluded. Some authors have reported on their clinical experience with corticosteroids in ocular syphilis [18, 19] but on a smaller scale and not at set time points. Previous studies advised local corticosteroids in case of interstitial keratitis or anterior uveitis [14, 20] and systemic corticosteroids in case of profound visual loss, posterior uveitis [21], scleritis, and optic neuritis [14, 20]. Because of our results and recommendations in the literature, we suggest considering adding corticosteroids to antibiotic treatment in all cases of syphilitic uveitis. The use of oral corticosteroids is also considered beneficial in preventing a Jarisch–Herxheimer reaction [20, 22]. The use of corticosteroids without antibiotic treatment, though not associated with worse VA outcomes at 6 months in our study, may aggravate syphilitic uveitis. Zamani and Garfinkel [23] published a case report on a patient who developed yellow placoid chorioretinal lesions during treatment with oral corticosteroids, which disappeared after their discontinuation.

HIV

In our study, HIV positivity was found in 28 patients, 13 of whom were newly diagnosed. This re-emphasizes the risk of co-infection with other sexually transmitted diseases in this patient group, and the desirability to test for HIV in case of ocular syphilis. Previously, HIV-positivity has been associated with a worse visual outcome in syphilitic uveitis, a finding we and other recent studies [9-11, 24, 25] could not confirm. Also, previous studies described that HIV-positive patients tended to have a higher proportion of posterior and panuveitis and neurosyphilis than HIV-negative patients. In contrast, we did not find statistically significant associations between HIV- positivity, anatomical location of the uveitis and CSF abnormalities. Differences between our outcomes and those in previous studies may be due to an improved immune-status of HIV-positive patients because of highly active antiretroviral therapy (HAART) [26, 27]. In line with this, current IUSTI guidelines [1, 12, 13] state that HIV co-infected syphilitic patients should be treated as immunocompetent patients, except for those who have CD4+ cell counts of less than or equal to 350/µl.

Clinical presentation

Our study confirms previous reports [6, 7, 16, 28, 29] that ocular syphilis occurs predominantly in men. Further, it confirms that syphilitic uveitis is a variable condition with a high diversity of clinical features. It can be uni- or bilateral, all anatomical locations may be affected, and it may run an acute or chronic course. In our study, bilateral uveitis was seen in 63.5%, whereas posterior (n=27, 31.8%)) and panuveitis (n=39, 45.9%) were far more often present than anterior uveitis (n=14, 16.5%). This is in line with recent papers [6, 7, 16, 24], but it differs from some older studies that observed uveitis to be located mainly anteriorly [30, 31].

VDRL test outcome

VDRL test results give some information on the duration and activity of the infection and they can be used to monitor the response to treatment. The interpretation of the VDRL test is sometimes difficult and debatable. A VDRL test becomes positive 4 to 5 weeks after infection, but it can sometimes be negative due to the prozone phenomenon[1]. Next to that, in 20 - 30% of the patients the test becomes negative over time [32]. Therefore, a negative VDRL test result does not rule out the diagnosis of syphilitic uveitis[10]. A previous study reported that HIV positivity may be associated with higher than expected VDRL serologic titers, false-negative serologic results and delayed appearance of sero-reactivity [32]. These findings were not confirmed within our study. Also, we did not observe an effect of VDRL test outcome on VA at 6 months in the multivariate linear regression model. Neither did we find a difference in chronicity at 6 months between VDRL-negative or positive patients.

Antibiotic Treatment

According to the European guidelines, the gold standard for the treatment of syphilitic uveitis is intravenous (IV) benzyl penicillin 12–24 million units daily, given in 3–4 million units doses every four hours for 10–21 days [1, 12, 13]. In special situations (pregnancy, allergy or refusal of intravenous treatment), oral or intramuscular treatment can be considered. Improvement in VA at 1 and 6 months was seen in all groups of patients independent of the route of administration of antibiotics. Based upon the multiple linear regression model , the group of patients treated with IV penicillin, showed a tendency towards a somewhat better VA result. The absence of a statistically significant difference in this model may probably be explained by the modest sizes of the non IV treated groups. A similar argument may apply to the absence of an effect of route of administration on the development of chronic uveitis. At present, the results of our study support the current guidelines on treatment for ocular syphilis.

Strengths and limitations of the study

The strengths of this study are its relatively large study population, the systematic way in which data were collected, and its adherence to the SUN classification system and guidelines for publications. The limitations of this study are its retrospective nature, and its long inclusion period. The latter may theoretically have influenced treatment strategies. However, the mainstay of syphilis treatment is penicillin, and this has not changed over the past decades. Some statistically significant relations may have been missed because of small numbers of patients in some subgroups. Also, the study was conducted in tertiary uveitis centers, and therefore, this population may not represent the total spectrum of syphilitic uveitis. Personal experience and preferences of ophthalmologists may have influenced their choice of treatment. Despite this, we feel that the study results can contribute to optimum care for patients with syphilitic uveitis.

CONCLUSION

Overall, VA outcomes in syphilitic uveitis are good. A low VA at the start of syphilis treatment and treatment delay of more than 12 weeks results in a less favorable visual prognosis. To shorten this delay, low threshold testing for syphilis should be done in uveitis of unknown cause. Intravenous benzyl penicillin is an effective treatment for syphilitic uveitis. It is not clear whether adjunct steroid treatment is beneficial. Structural damage to the optic nerve and retina are the main causes of permanent visual loss.

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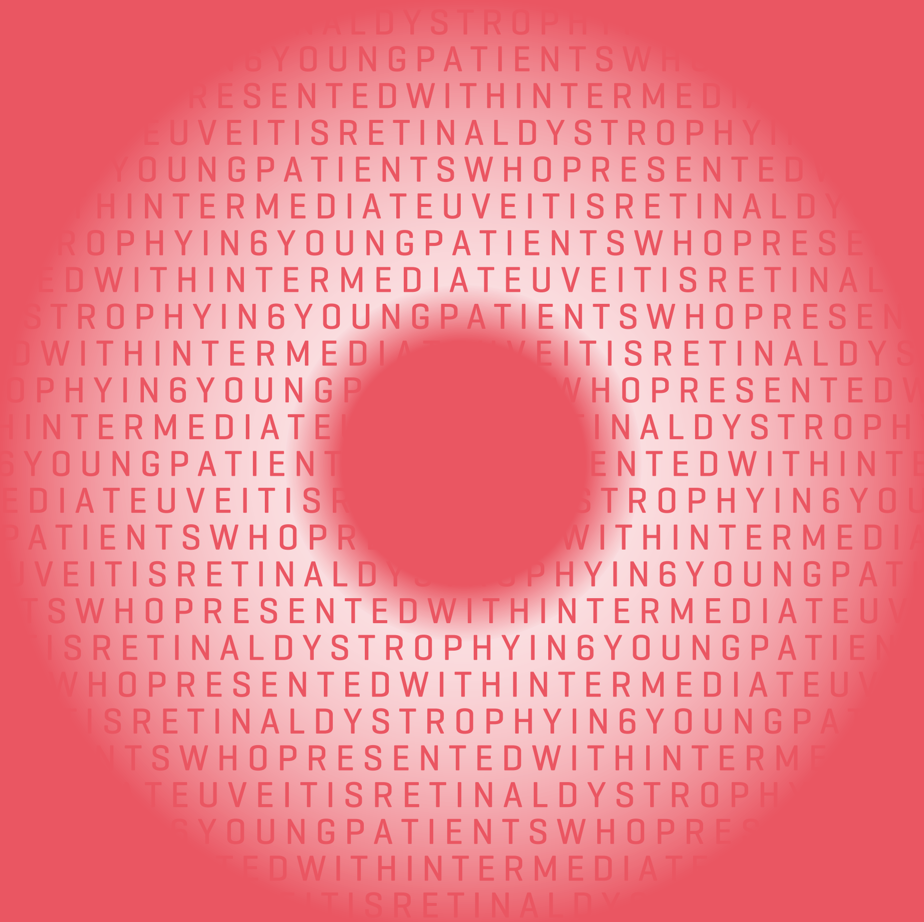
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