HHS Public Access

Author manuscript

Sex Transm Infect. Author manuscript; available in PMC 2017 August 14.

Published in final edited form as:

Sex Transm Infect. 2016 December ; 92(8): 563–565. doi:10.1136/sextrans-2016-052570.

Ocular syphilis: opportunities to address important unanswered questions

Susan Tuddenham and **Khalil G Ghanem**

Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

The US Centers for Disease Control and Prevention (CDC) issued a clinical advisory late last year on ocular syphilis. Between December 2014 and March 2015, 12 cases of ocular syphilis were reported from two US cities, San Francisco and Seattle.[1] Subsequent case finding identified more than 200 cases reported over the last 2 years from 20 states. Whether this is the result of one or more oculotropic strains (neuroinvasive strains have been described)[2] or enhanced case detection due to, for example, the increasing use of the reverse sequence algorithm for syphilis screening, is unclear. In Maryland, to date, following the release of the advisory, 13 cases have been identified through careful record reviews with 9 (70%) of the 13 presenting as late ocular syphilis (personal communication Elisabeth Liebow and Alexandra Goode, Maryland Department of Health and Mental Hygiene). If this increasing case detection is the result of a circulating strain, the strain has been circulating for a while. Irrespective of the cause of this observed increase in the number of cases of ocular syphilis, there are several important yet unanswered clinical questions: what is the relationship between ocular and neurosyphilis? How does HIV impact ocular syphilis and this relationship? Is a lumbar puncture (LP) necessary for the evaluation of patients suspected of having ocular syphilis? What is the best treatment of ocular syphilis? Other issues to clarify include the relationship of ocular syphilis presentation to stage of syphilis infection, the risk of ocular syphilis in serofast patients, and whether ocular syphilis in patients with a previous record of treatment represents recrudescence or reinfection. Several studies have tried to address one or more of these questions. All of these studies suffered from a small sample size that limited their power to draw meaningful conclusions.

In this issue, Tsuboi *et al* have published a case series drawn from a retrospective chart review of patients attending an HIV clinical centre. They examine the clinical course and prognosis of ocular syphilis in 20 HIV-infected Japanese men. The patients were followed for an average of 21 months after their diagnosis. The paper highlights the need for prompt

Correspondence to Dr Susan Tuddenham, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Johns Hopkins Bayview Medical Center, Mason F. Lord Building, Center Tower, Suite 381, 5200 Eastern Avenue, Baltimore MD 21224, USA, studden1@jhmi.edu.

Contributors Both authors contributed equally to the manuscript. KGG conceived of the editorial. ST and KGG wrote and edited the manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Additional references are published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/sextrans-2016-052570).

recognition and treatment of the syndrome, as having ocular symptoms for >28 days before treatment was associated with poor prognosis. Of the 17 patients who had an LP performed, 53% were diagnosed with neurosyphilis based on a positive serum serology and one or more abnormalities on cerebrospinal fluid (CSF) examination. This is a timely paper, given the recent CDC clinical advisory, however, it is still a retrospective review with a relatively small sample size, and includes only HIV-positive patients. As such, important questions still remain (Tsuboi *et al*, in this issue).

Ocular syphilis may occur during any stage of infection and may involve almost any portion of the eye. Save for preretinal opacities and acute posterior placoid chorioretinitis,[3] two ocular manifestations that have been reported to be specific for syphilis, most clinical manifestations of ocular syphilis are non-specific. Thus, most diagnoses of ocular syphilis tend to be presumptive based on ocular signs and symptoms and positive syphilis serologies. Involvement of most of the eye structures can occur at different stages of syphilis, though Spoor *et al* make a distinction between acute ocular inflammation (presenting as anterior and posterior uveitis, optic neuritis or perineuritis) being more commonly associated with early syphilis, and optic atrophy and pupillary abnormalities as well as chorioretinitis being associated with late syphilis.[45] However, a systematic characterisation of associations between ocular syphilis presentations and syphilis stage in a large cohort of patients is still lacking.

What is the relationship between ocular syphilis and neurosyphilis? What is the impact of HIV on ocular syphilis and this relationship? Questions regarding the need for an LP and the best treatment for ocular syphilis hinge on the distinction (or lack thereof) between ocular and neurosyphilis. Although CDC guidelines recommend the same treatment for ocular as for neurosyphilis (aqueous crystalline penicillin G 18–24 million units per day for 10–14 days), the syndromes may not always overlap.[6] Certain parts of the eye are developmentally separate from the central nervous system. In the embryo, the surface ectoderm forms the lens, corneal epithelium, conjunctiva and eyelid; the extracellular mesenchyme (mesoderm and neural crest cells) forms the sclera, cornea, blood vessels, muscles and vitreous and the neuroectoderm forms the retina, posterior layers of the iris and optic nerves.[7] Some suggest that since structures derived from the neuroepithelium should be regarded as part of the brain, retinitis and optic neuritis should be classified as neurosyphilis.[89] There is ongoing debate as to whether anterior uveitis, which involves some structures of the eye that are technically not derived from the neuroepithelium, should be classified as neurosyphilis.[4] Others suggest that involvement of any eye structure, irrespective of its ontogeny, should be managed identically to neurosyphilis.[89]

Up to 60% of patients with ocular syphilis will have abnormalities noted on LP. A number of studies, but not all, have suggested that HIV-positive patients with ocular syphilis may be more likely to have CSF abnormalities.[810] Since there is a high baseline prevalence of CSF abnormalities reported in HIV-infected persons, this is perhaps not surprising, but as a result, interpretation of CSF abnormalities in these patients may be challenging.[11] Several small case series (including Tsuboi *et al*, from this issue) and literature reviews have suggested that 57%–90% of HIV-positive patients with ocular syphilis had one or more CSF abnormalities with approximately 60% demonstrating a reactive CSF Venereal Disease

Research Laboratory (VDRL) test. However, the numbers are small and several of the reviews may have included the same patients.[1012–14] In sum, the relationship between ocular syphilis and the presence of CSF abnormalities is not completely clear. There is no definite evidence, for example, that anterior uveitis is associated with a decreased risk of having abnormal CSF compared with posterior uveitis.[8] While there are certainly patients with ocular syphilis who will have a negative CSF examination, a significant (and perhaps larger) proportion, will have one or more abnormalities detected on CSF examination.

While previous studies have not shown an increased incidence of ocular syphilis in HIV infected as compared with non-HIV infected patients,[10] nor a statistically significant relationship between CD4 count, antiretroviral therapy, or HIV viral load and ocular syphilis[14–18] or prognosis of ocular syphilis (Tsuboi *et al*, in this issue), patients with HIV are more likely to present with early neurosyphilis than non-HIV infected patients. As detailed above, the influence of HIV on the risk of neurosyphilis in patients diagnosed with ocular syphilis is not entirely clear either.

Is LP necessary for the evaluation of patients suspected of having ocular syphilis? The current CDC guidelines recommend a CSF examination in all patients with ocular syphilis.[6] How often this happens in clinical practice is unclear. Although the presence of CSF abnormalities is not necessary to make a diagnosis of ocular syphilis, there are several reasons why, in the absence of more data, this recommendation may be reasonable. As discussed above, a majority of patients with ocular syphilis will have CSF abnormalities that suggest neurosyphilis. However, despite similar treatment regimens for both ocular and neurosyphilis, the CDC guidelines currently recommend serial CSF examinations every 6 months in persons with abnormal CSF until the CSF normalises. If normalisation is not achieved within 2 years, additional therapy may be warranted. Consequently, although CSF abnormalities are not necessary to diagnose ocular syphilis, the presence of CSF abnormalities will change management. Second, ocular syphilis is a presumptive diagnosis based upon non-specific clinical signs and symptoms in persons with positive syphilis serologies. In most patients, syphilis will not be the only entity on the differential diagnosis for the ocular manifestations. Consequently, the CSF examination may help confirm the presumptive diagnosis of ocular syphilis. Finally, although no objective data exist to support this, we have observed in clinical practice that some patients with ocular syphilis have a stuttering course after treatment with occasional transient worsening of symptoms. This can create confusion as to whether the patient is failing therapy and needs retreatment. The CSF examination, if abnormal, may provide more objective information that can be followed to help determine whether patients need additional therapy.

What is the best treatment of ocular syphilis and is there a role for steroids? Prior to the early 1980s, three doses of 2.4 million units benzathine penicillin G (BPG) was a recommended alternate regimen for the treatment of neurosyphilis, and was used with good clinical results.[19] There have been multiple case reports of successful treatment of ocular syphilis with BPG.[41620] Additionally, the ubiquitous finding of subclinical uveitis in secondary syphilis[21] suggests that we may be missing a significant number of cases of anterior uveitis which are successfully treated with a single dose of BPG. The use of BPG to treat neurosyphilis, and by extension ocular syphilis, was abandoned in the early 1980's

when it was found that BPG failed to achieve adequate treponemicidal concentrations in the CSF.[22] Similar human studies have not been done on ocular fluid, but rabbit studies showed poor penetration into the aqueous humour by BPG, and the presumption has been that BPG likely fails to achieve treponemicidal concentrations in many eye compartments.[23] Whether BPG is adequate therapy for anterior eye involvement, including symptomatic anterior uveitis that occurs in secondary syphilis, is unclear. On the other hand, there have been reports in the past of patients with ocular syphilis who received neurosyphilis regimens of intravenous penicillin developing new ocular symptoms and requiring retreatment.[24] In the current paper by Tsuboi *et al*, three patients experienced recurrence of ocular problems after treatment. Interestingly, while one received 14 days of intravenous penicillin and one received 14 days of Unasyn, the third patient actually received 28 days of intravenous penicillin, but still recurred. Consequently, close follow-up for all treated patients is necessary. Further complicating the therapeutic picture is the need for concomitant corticosteroids. Two reports mention consideration of early steroids to prevent Jarisch–Herxheimer reaction and resultant worsening of ocular symptoms.[2526] However, no clinical trials have compared the benefits of steroid treatment and timing of steroid therapy. In one case series of 13 HIV-infected patients with ocular syphilis, there was no difference in clinical outcomes between those who received steroids (N=6) and those who did not.[27] In one report, three patients with episcleritis or scleritis experienced persistent inflammation despite steroids.[16] Other reports suggest benefit.[26] Most studies, as described above, have been small limiting our ability to extrapolate meaningful data. As such, the benefits of concomitant corticosteroid use are unknown.

Finally, questions remain regarding the risk of progression to ocular syphilis in patients who are serofast, and whether ocular syphilis in patients with a previous record of treatment represents recrudescence or reinfection. Some previous studies have reported that a large number of patients diagnosed with ocular syphilis have had previous treatment, but whether these patients were reinfected or had relapse is not clear.[10] There have been reports of serofast patients progressing to neurosyphilis despite a fourfold decline in rapid plasma reagin (RPR) titres,[28] however, the same concerns regarding relapse versus reinfection apply, and how these data may or may not apply to patients with ocular syphilis is not clear.

As a result of the CDC clinical advisory, and as of 15 April 2016, 20 states had reported over 200 cases of ocular syphilis and these numbers are likely to increase substantially. The enhanced case detection with centralised reporting to the CDC may afford a unique opportunity to address some of these questions in a more robust way. This will require an attempt to standardise the collection of essential data points (syphilis stage, ocular diagnoses, HIV status, CSF examination results, type of therapy—including the type, dose and duration of adjunctive corticosteroids) and may require the active participation of local health departments to obtain follow-up information on these patients post therapy. The association between ocular diagnosis and prevalence of CSF abnormalities (and the interaction of HIV) may become clearer with a larger sample size. Moreover, although the advisory recommends intravenous penicillin for the treatment of ocular syphilis, it is possible that variations in the use of corticosteroids may allow for an (imperfect) assessment of corticosteroid benefits. Finally, the advisory encourages clinicians to collect and store preantibiotic clinical samples such as whole blood, swabs from primary and moist secondary

lesions, CSF and/or ocular fluid for future strain typing. It is imperative that we take full advantage of this situation and ensure adequate support for local health departments to encourage the collection and transmission of baseline and follow-up data that may help address some of these important clinical questions.

Acknowledgments

Funding ST is supported by NIH T32 grant NIH T32 grant (5 T32 AI007291-24).

References

1. Woolston S, Cohen SE, Fanfair RN, et al. A Cluster of Ocular Syphilis Cases - Seattle, Washington, and San Francisco, California, 2014–2015. MMWR Morb Mortal Wkly Rep. 2015; 64:1150–1. [doi]. DOI: 10.15585/mmwr.mm6440a6 [PubMed: 26469141]
2. Tantalo LC, Lukehart SA, Marra CM. Treponema pallidum strain-specific differences in neuroinvasion and clinical phenotype in a rabbit model. J Infect Dis. 2005; 191:75–80. doi:JID32801 [pii]. [PubMed: 15593006]
3. Davis JL. Ocular syphilis. Curr Opin Ophthalmol. 2014; 25:513–8. [doi]. DOI: 10.1097/ICU.0000000000000099 [PubMed: 25237932]
4. Spoor TC, Wynn P, Hartel WC, et al. Ocular syphilis. Acute and chronic. J Clin Neuroophthalmol. 1983; 3:197–203. [PubMed: 6226720]
5. Spoor TC, Ramocki JM, Nesi FA, et al. Ocular syphilis 1986. Prevalence of FTA-ABS reactivity and cerebrospinal fluid findings. J Clin Neuroophthalmol. 1987; 7:191,5–196–7. [PubMed: 2963024]
6. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015; 64:1–137. doi:rr6403a1 [pii].
7. Schoenwolf, GC., Larsen, WJ. Larsen's human embryology. Philadelphia: Churchill Livingstone/Elsevier; 2008. p. 687
8. Amaratunge BC, Camuglia JE, Hall AJ. Syphilitic uveitis: a review of clinical manifestations and treatment outcomes of syphilitic uveitis in human immunodeficiency virus-positive and negative patients. Clin Experiment Ophthalmol. 2010; 38:68–74. [doi]. DOI: 10.1111/j.1442-9071.2010.02203.x [PubMed: 20447104]
9. Margo CE, Hamed LM. Ocular syphilis. Surv Ophthalmol. 1992; 37:203–20. [PubMed: 1475754]
10. Shalaby IA, Dunn JP, Semba RD, et al. Syphilitic uveitis in human immunodeficiency virus-infected patients. Arch Ophthalmol. 1997; 115:469–73. [PubMed: 9109754]
11. Marra CM, Maxwell CL, Collier AC, et al. Interpreting cerebrospinal fluid pleocytosis in HIV in the era of potent antiretroviral therapy. BMC Infect Dis. 2007; 7:37. doi:1471-2334-7-37 [pii]. [PubMed: 17475004]
12. Levy JH, Liss RA, Maguire AM. Neurosyphilis and ocular syphilis in patients with concurrent human immunodeficiency virus infection. Retina. 1989; 9:175–80. [PubMed: 2687992]
13. Balaskas K, Sergentanis TN, Giulieri S, et al. Analysis of significant factors influencing visual acuity in ocular syphilis. Br J Ophthalmol. 2011; 95:1568–72. [doi]. DOI: 10.1136/bjo.2010.194498 [PubMed: 21398411]
14. Tucker JD, Li JZ, Robbins GK, et al. Ocular syphilis among HIV-infected patients: a systematic analysis of the literature. Sex Transm Infect. 2011; 87:4–8. [doi]. DOI: 10.1136/sti.2010.043042 [PubMed: 20798396]
15. Balba GP, Kumar PN, James AN, et al. Ocular syphilis in HIV-positive patients receiving highly active antiretroviral therapy. Am J Med. 2006; 119:448.e21–448.e25. doi: S0002-9343(05)01083-1 [pii].
16. Parc CE, Chahed S, Patel SV, et al. Manifestations and treatment of ocular syphilis during an epidemic in France. Sex Transm Dis. 2007; 34:553–6. [doi]. DOI: 10.1097/01.olq.0000253385.49373.1a [PubMed: 17667532]

17. Mathew RG, Goh BT, Westcott MC. British Ocular Syphilis Study (BOSS): 2-year national surveillance study of intraocular inflammation secondary to ocular syphilis. Invest Ophthalmol Vis Sci. 2014; 55:5394–400. [doi]. DOI: 10.1167/iovs.14-14559 [PubMed: 24925878]
18. Tran TH, Cassoux N, Bodaghi B, et al. Syphilitic uveitis in patients infected with human immunodeficiency virus. Graefes Arch Clin Exp Ophthalmol. 2005; 243:863–9. [doi]. DOI: 10.1007/s00417-005-1137-6 [PubMed: 16158310]
19. Centers for Disease Control and Prevention (CDC). Syphilis: CDC recommended treatment schedules–1976. Obstet Gynecol. 1976; 48:727–9. [PubMed: 995345]
20. Wilhelmus KR, Yokoyama CM. Syphilitic episcleritis and scleritis. Am J Ophthalmol. 1987; 104:595–7. [PubMed: 3688101]
21. Zwink FB, Dunlop EM. Clinically silent anterior uveitis in secondary syphilis. Trans Ophthalmol Soc U K. 1976; 96:148–50. [PubMed: 1070845]
22. Mohr JA, Griffiths W, Jackson R, et al. Neurosyphilis and penicillin levels in cerebrospinal fluid. JAMA. 1976; 236:2208–9. [PubMed: 989815]
23. Goldman EE, McLain JH, Smith JL. Penicillins and aqueous humor. Am J Ophthalmol. 1968; 65:717–21. [PubMed: 5651629]
24. Browning DJ. Posterior segment manifestations of active ocular syphilis, their response to a neurosyphilis regimen of penicillin therapy, and the influence of human immunodeficiency virus status on response. Ophthalmology. 2000; 107:2015–23. doi: S0161-6420(00)00457-7 [pii]. [PubMed: 11054325]
25. Danesh-Meyer H, Kubis KC, Sergott RC. Not so slowly progressive visual loss. Surv Ophthalmol. 1999; 44:247–52. doi: S0039625799000995 [pii]. [PubMed: 10588443]
26. Fathilah J, Choo MM. The Jarisch-Herxheimer reaction in ocular syphilis. Med J Malaysia. 2003; 58:437–9. [PubMed: 14750386]
27. Li JZ, Tucker JD, Lobo AM, et al. Ocular syphilis among HIV-infected individuals. Clin Infect Dis. 2010; 51:468–71. [doi]. DOI: 10.1086/654797 [PubMed: 20604717]
28. Zhou P, Gu X, Lu H, et al. Re-evaluation of serological criteria for early syphilis treatment efficacy: progression to neurosyphilis despite therapy. Sex Transm Infect. 2012; 88:342–5. [doi]. DOI: 10.1136/sextrans-2011-050247 [PubMed: 22363023]