

Letters

Ocular Syphilis or Neurosyphilis?

The November *EyeNet* Clinical Update “Be on the Lookout for Ocular Syphilis”¹ and the recent CDC “Clinical Advisory: Ocular Syphilis in the United States”² mentioned in the article raise questions regarding the optimal management of syphilitic eye disease. Both documents equate all types of ocular syphilis with neurosyphilis. Accordingly, the Clinical Advisory states, “A lumbar puncture with cerebrospinal fluid (CSF) examination should be performed in patients with syphilis and ocular complaints. Ocular syphilis should be managed according to treatment regimens for neurosyphilis.”²

The Clinical Advisory defines an “ocular syphilis case” as “a person with clinical symptoms or signs consistent with ocular disease (i.e., uveitis, panuveitis, diminished visual acuity, blindness, optic neuropathy, interstitial keratitis, anterior uveitis, and retinal vasculitis) with syphilis of any stage.”² Presumably, additional causes of decreased visual acuity would be considered before peremptorily attributing low vision or blindness to syphilis. Most ophthalmologists would reasonably agree that uveitis, vitritis, retinitis, retinal vasculitis, and optic neuritis in a person with reactive serologic confirmation of syphilis signal neurosyphilis and should be managed with a penicillin treatment regimen recommended for neurosyphilis. Some would also advise CSF evaluation to uncover asymptomatic neurosyphilis in a seropositive patient with scleritis.

What is the justification that interstitial keratitis and other forms of stromal keratitis are necessarily neurosyphilis? Similarly, what about other ophthalmic manifestations of syphilis outlined in the comprehensive table of acquired and congenital syphilis in the online version³ of the *EyeNet* article, such as granulomatous conjunctivitis, dacryoadenitis, and orbital periostitis?

We propose that neurosyphilis is no more likely in patients with syphilitic stromal keratitis than among people

with untreated latent syphilis.⁴ Indications for lumbar puncture in a patient with syphilitic keratitis would include optic atrophy, neuroretinitis, posterior uveitis,

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sclerouveitis, pupillary abnormality, cranial nerve palsy, HIV infection, or a high nontreponemal test titer.⁴ Contrary to the proposal to treat all patients with any form of ocular syphilis with a neurosyphilis treatment regimen, an alterna-

tive approach is to use the treatment regimen for late latent syphilis for a previously untreated patient who has syphilitic keratitis but who does not have scleral or posterior segment inflammation or neurological abnormality.⁴

We and other corneal and external disease specialists consider adult-onset syphilitic stromal keratitis, with or without mild iritis, to be either a late manifestation of congenital syphilis or late syphilis of unknown duration, not neurosyphilis. For this entity, we would care for a previously untreated patient using the recommended regimen for late latent syphilis, namely, intramuscular benzathine penicillin G, 3 doses of 2.4 million units each given at 1-week intervals,⁵ and would not routinely advise a lumbar puncture in the absence of other clinical signs.

The recommendation that patients with any form of ocular syphilis incur the potential risks of a lumbar puncture and the costs of a regimen involving intravenous aqueous crystalline penicillin G or intramuscular procaine penicillin with probenecid for 10 to 14 days requires further supportive evidence and risk-benefit analysis.

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1 *EyeNet Magazine*. 2015;19(11):39-40.

2 Centers for Disease Control and Prevention. www.cdc.gov/std/syphilis/clinicaladvisoryos2015.htm. Accessed Nov. 10, 2015.

3 www.aao.org/eyenet/article/be-on-lookout-ocular-syphilis.

4 Wilhelmus KR. Syphilitic keratitis. In: Mannis MJ, Holland EJ (eds): *Cornea*, 4th edition (in press).

5 Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep*. Recommendations and Reports. June 5, 2015;64(3):39.

A Response From the CDC

The letter by Drs. Jones and Wilhelmus entitled “Ocular Syphilis or Neurosyphilis?” highlights the nuances related to the diagnosis of syphilis, including ocular syphilis, which are important given the current syphilis epidemic in the United States. Syphilis cases increased between 2012 and 2013, and in 2014 there was a 15% increase compared with 2013.¹ After clusters of ocular syphilis cases were reported² and a Clinical Advisory issued,³ CDC began collecting reports of cases. To date, over 150 cases of ocular syphilis have been reported to CDC from 2014 and 2015. Most cases (over 90%) are in men, especially in men who have sex with men (MSM). Several of the cases have resulted in significant sequelae, including blindness. In some cases, there was a delay in final

diagnosis and treatment due to the lack of awareness of ocular syphilis.

Given the number of cases reported, CDC has worked with both local and national partners to increase awareness of ocular syphilis as a cause of eye inflammation, which can occur in any stage of syphilis. We also encourage syphilis diagnostic testing with treponemal and nontreponemal testing in any patient with visual complaints without another known cause among those at risk, especially MSM and those who are HIV infected.

While ocular syphilis can have a variety of clinical manifestations, the most common presentation of ocular syphilis is uveitis, which is consistent with cases reported to CDC. Interstitial keratitis is a relatively rare presentation of ocular syphilis, accounting for only 1% of cases diagnosed with keratitis in a British national surveillance of ocular syphilis.⁴ Of note, none of the 2014-2015 cases reported to CDC have presented with interstitial keratitis. In addition, a high proportion of these patients with ocular manifestations have a high RPR titer and/or a positive cerebrospinal (CSF) Venereal Disease Research Laboratory (VDRL) test. Of cases reported to the CDC currently, 96% of cases have a rapid plasma reagin titer $\geq 1:16$, and of cases with a lumbar puncture and CSF VDRL, 70% were positive.

The 2015 STD Treatment Guidelines state that “Syphilitic uveitis or other ocular manifestations (e.g., neuroretinitis and optic neuritis) can be associated with neurosyphilis. A CSF examination should be performed in all instances of ocular syphilis, even in the absence of clinical neurologic findings. Ocular syphilis should be managed in collaboration with an ophthalmologist and according to the treatment and other recommendations for neurosyphilis, even if a CSF examination is normal.”⁵ Recommended treatment for neurosyphilis and ocular syphilis is IV aqueous penicillin G for 10-14 days. In addition, while CSF examination is recommended, this should not delay treatment. Coordination with an infectious diseases specialist can be beneficial to get appropriate diagnostic testing, treatment, and long-term follow-up.

Thank you again for your continued effort to increase awareness of ocular syphilis.

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1 Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2014. Atlanta: U.S. Department of Health and Human Services; 2015.

2 Woolston S et al. *MMWR Morb Mortal Wkly Rep.* 2015;64:1150-1151.

3 Centers for Disease Control and Prevention. www.cdc.gov/std/syphilis/clinicaladvisoryos2015.htm. Accessed Dec. 1, 2015.

4 Mathew RG et al. *Invest Ophthalmol Vis Sci.* 2014;55:5394-5400.

5 Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* June 5, 2015 (No. RR-3). www.cdc.gov/mmwr/preview/mmwrhtml/rr6403a1.htm.

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Clinicians' Response

We appreciate the interest that Drs. Jones and Wilhelmus expressed in the recent *EyeNet* article about syphilis. While the article was focused primarily on syphilitic uveitis, they have appropriately emphasized the fact that the ophthalmic manifestations of syphilis include a large variety of disorders, can occur at any stage of the disease, and may require complex treatment decisions. The accompanying letter from representatives of the Centers for Disease Control and Prevention (CDC) provides clarity about CDC recommendations for treatment of syphilis when disease involves the eye.

This conversation provides us the opportunity to restate several points relevant to these management decisions:

- Often we do not know the stage of disease when patients who have syphilis present with inflammatory eye disease, or even when infection occurred.
- Most cases of ocular syphilis reported recently to the CDC have involved intraocular inflammation, and many of the patients were also infected with human immunodeficiency virus. Such cases should be treated with regimens appropriate for neurosyphilis.
- It is important for ophthalmologists to work with an infectious disease specialist, who can assist in making decisions about evaluation, including whether or not to perform lumbar puncture, and specific treatment.

Some of the cases reported to the CDC had gone undiagnosed for extended periods of time before syphilis was diagnosed. An important message that is worth repeating from the original article is that syphilis—“the great imitator”—should be considered by ophthalmologists as a potential cause of disease when they see any patient with unexplained inflammatory eye disease.

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