REVIEW

Neurosyphilis with optic neuritis: an update

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There is currently a resurgence of infectious syphilis in the UK (<http://www.hpa.co.uk>) and the rate remains high in the USA (<http://www.cdc.gov/std>) and in the Russian Federation states.¹ In the past the protean manifestations of syphilis earned it the title of “the great imitator”. The high prevalence of syphilis before, and during, the second world war meant that it always featured highly in the differential diagnosis of any ophthalmic problem. Antibiotic treatment has reduced the prevalence to the extent that it is seldom considered first nowadays.²

The interaction of syphilis and HIV has stimulated renewed interest in this ancient disease and has challenged some of the long held ideas about the investigation and treatment of syphilis.

A case of secondary syphilis is presented in which a sudden loss of vision occurred despite initial treatment with benzathine penicillin and doxycycline with corticosteroid cover. The natural history, investigation, treatment and follow up for neurosyphilis are discussed.

A TYPICALLY ATYPICAL CASE

A 44 year old homosexual man presented with a macular rash on his palms and soles, but not elsewhere. He was diagnosed as having secondary syphilis. Serological examination disclosed positive syphilis ELISA IgG/IgM, positive rapid plasma reagin (RPR) (1:32), moderately positive *Treponema pallidum* particle agglutination assay (TPPA) consistent with recent active treponemal infection. He was also found to have concomittant non-gonococcal, non-chlamydial urethritis. There was no regional lymphadenopathy and examination of the rectum and penis was normal. Neither he, nor his partner, gave a history of injecting drug misuse or previous sexually transmitted infection (STI). In particular he was HIV negative and remained so throughout follow up. Treatment, based on local guidelines, was started with weekly benzathine penicillin 2.4 million units intramuscularly for three weeks and doxycycline 100 mg orally twice daily for one week for the urethritis. He was also given prednisolone 30 mg orally once a day for five days, started one day before the penicillin. He was asymptomatic after the first injection but at the time of his second injection of benzathine penicillin he complained that his vision was “like looking through tissue paper” with his left eye. The Snellen visual acuity (VA) was 6/5 in the right eye and hand movements in the left eye. Examination of the right eye was normal. Slit lamp examination of the left anterior segment showed no sign of iritis, while mottled retinal pigment epithelium (RPE) and scattered haemorrhages were noted at the macula on fundoscopy. The optic nerve head appeared normal at this stage. When reviewed after his third and final injection of benzathine penicillin the VA in the left eye had improved to counting fingers. The anterior segment remained quiet, but there were now scattered cells in the vitreous and a swollen optic nerve head with adjacent neuroretinitis, (fig 1A). A left relative afferent pupillary defect (RAPD) was elicited. The macula was oedematous, with dot and flame haemorrhages, (fig 1B). Fundus fluorescein angiography

showed patchy leakage through the RPE into the retina (fig 1C) and leakage of dye from the optic nerve head (fig 1D) compatible with the diagnosis of optic neuritis. He was admitted for a two week course of aqueous crystalline penicillin G 4×10^6 U intravenously four hourly. A cerebrospinal fluid (CSF) tap showed that CSF protein and glucose were within the normal range. The CSF white cell count was 6 mm^{-3} (monocytes). The CSF TPPA was mildly positive. There was no microbiological growth from the CSF. T1 flair magnetic resonance images (MRI) showed normal optic nerves and no evidence of parenchymal neurosyphilis or meningitis. Ten days into re-treatment the VA in the left eye improved to 6/18+4 and the optic nerve head appeared less swollen.

One year after the completion of treatment the VA in the left eye had improved to 6/6 and the optic nerve head appeared normal. The colour vision in the left eye remained abnormal. The right eye remained normal throughout.

NATURAL HISTORY

In a patient with syphilis the presence of ocular involvement is strongly suggestive of involvement of the CNS and should be considered synonymous with neurosyphilis. The spirochaete *Treponema pallidum* enters via an abrasion during sexual contact. During this primary infection there is rapid lymphatic and haematological spread. After an incubation of three weeks (range: 9–90 days) an infectious painless ulcer (primary chancre) develops at the site of sexual contact. The genitalia, anus, and mouth should all be examined. The primary lesion heals in two to six weeks even without treatment.

Secondary syphilis occurs four to eight weeks after the chancre. In secondary syphilis early dissemination of the organism frequently includes the CNS.³

NEURO-OPHTHALMIC MANIFESTATIONS

In the pre-antibiotic era ocular complications occurred in 3% of patients with secondary syphilis. The CNS can be involved at any stage of syphilis.

Among patients with secondary syphilis about 18% may have neurological (including ophthalmological) signs or symptoms.³ Ocular involvement may be silent or present as anterior uveitis, choroiditis, interstitial keratitis, retinal vasculitis, retinitis, optic neuritis, dacryoadenitis, or scleritis.^{2,4} In this case the presenting symptoms of neurosyphilis were non-specific, as were the mottled appearance of the RPE and scattered haemorrhages at the macula.

In syphilis, optic nerve involvement may be unilateral or bilateral and manifest as perineuritis, anterior or retrobulbar optic neuritis or papilloedema, (fig 2). In syphilis, optic perineuritis is usually asymptomatic, in optic neuritis however, there is usually rapid visual failure.

Abbreviations: RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination assay; VA, visual acuity; RAPD, relative afferent pupillary defect; CSF, cerebrospinal fluid; CNS, central nervous system; STI, sexually transmitted infection

In syphilis, optic neuritis is rare and there is nothing characteristic about its appearance to distinguish it from non-syphilitic involvement of similar distribution.⁵ In anterior optic neuritis the optic nerve head appears inflamed and there is often cellular activity in the posterior vitreous,⁵ there may be patchy diffuse neuroretinitis with areas of haemorrhage. In retrobulbar neuritis, the optic nerve head may appear normal, but a RAPD and poor colour vision indicate poor optic nerve function. The history may not suggest a diagnosis of syphilis so patients with optic neuritis should be tested for syphilis.

INVESTIGATIONS

The specific antitreponemal tests such as TPPA, microhaemagglutination (MHA), and FTA-Abs (fluorescent treponemal antibody) are said to be sensitive, and specific in all stages of syphilis.⁴ However, treponemal test reversion ($\leq 16\%$) after treatment⁶ and false positive (2%) syphilis serology may occur during pregnancy or because of infection with non-venereal spirochaetes, for example, *Borrelia burgdorferi*.

Lipid antigen tests such as VDRL (venereal disease research laboratory) or RPR are a better reflection of disease activity and are important for assessing the patient's response to treatment. The VDRL turns positive one to two weeks after chancre formation. However, false positives because of cross reaction with cardiolipin may occur in pregnancy, after vaccination, after myocardial infarction, or any febrile illness. False negatives ($\leq 32\%$) can occur in early primary, latent, or late syphilis and with concomitant HIV infection.^{2,4} A specific antitreponemal test and a lipid antigen test should be performed together and all patients with syphilis should be evaluated for HIV and vice versa.^{2,4} In some cases more elaborate tests and variables may be useful.^{7,8}

Radiological investigations such as computed tomography or MRI may show signs of intracranial involvement. Apparently normal scans cannot be used to rule out a diagnosis of neurosyphilis.

Lumbar puncture for CSF analysis and culture may be useful in certain circumstances (see box). The CSF VDRL alone is unreliable because, although highly specific, it is not sensitive and can be negative in up to 50% of samples from patients with active neurosyphilis.^{2,4,9} However, the presence of two or more abnormal laboratory variables (among them CSF leucocyte count, CSF protein concentration, and CSF VDRL) is significantly associated with isolation of *T pallidum* from the CSF.³ The HIV status of the patient is important because patients with concurrent HIV have a higher incidence of neurosyphilis, including ocular complications, which are more likely to be bilateral.^{4,10} Neurosyphilis in patients with HIV infection may follow a more aggressive course because of the reduced immunological response found in these patients.⁴ Occasionally the serological response may be reduced, delayed, or absent making diagnosis difficult.⁶⁻⁸

TREATMENT

The European,⁷ Russian Federated states, and American Centers for Disease Control (CDC)⁸ guidelines for the treatment of the various subtypes of syphilis are all slightly different. This may result in confusion and the adoption of local protocols, as in this case. Patients with inadequately treated syphilis are at risk of relapse, especially if there is concurrent HIV infection.³

Table 1 shows a treatment summary. Procaine penicillin may also be used.^{7,8} More detail on the CDC and European guidelines can be found on line.^{7,8} Benzathine penicillin intramuscularly is used because it is simple, cheap, can be given on an outpatient basis, and is less susceptible to patient non-compliance than oral treatment. However, there are concerns that useful levels may not be achieved in the CSF or eye.⁹⁻¹² The addition of probenecid to penicillin G increases the ocular concentration of penicillin in proportion to the rise in serum level of penicillin and increases the intraocular half life of penicillin.¹¹

The CSF and aqueous levels of penicillin may not be vital. There are few treatment failures with benzathine penicillin

Figure 1 (A) The optic nerve head is swollen with blurring of the disc margin and adjacent pallor of the retina (arrows). (B) There is mottling of the macular retinal pigment epithelium (white arrow) and foveal haemorrhages (black arrow). (C) The retinal pigment epithelium is mottled and leaking suggestive of epitheliitis (fundus fluorescein angiogram at 20 seconds). (D) Leakage of fluorescein from the optic nerve head (fundus fluorescein angiogram at four minutes).

Figure 2 Diagnosing optic nerve involvement in syphilis. Other field abnormalities include enlarged blind spot, peripheral constriction, sector defects, central or paracentral scotoma, altitudinal, binasal, or quadrantic hemianopsia. ICP, intracranial pressure.

despite its failure to reach treponemocidal levels in the CSF, possibly because the pathology is at the endarterial level where it is the serum level that is more important. None the less persistence of *T pallidum* in CSF and aqueous after penicillin treatment has been reported,¹² and may have occurred in this case. Although tetracycline and doxycycline are used as alternative treatments for syphilis there is less experience with their use, and patients receiving these regimens should be closely monitored.^{2 7 8 13 14} The oral administration of tetracycline or doxycycline, which are less lipophilic than minocycline, results in a low concentration in the spinal fluid. There is little information on the ocular penetration of doxycycline. Oral minocycline penetrates well into the eye achieving vitreous levels of about 50% of the plasma levels.¹⁵ This patient still manifested neurosyphilis despite benzathine penicillin and doxycycline. Doxycycline interferes with the bacterial protein synthesis by binding to the bacterial S30 ribosomal unit. It is treponemostatic and its effects are reversible when the drug is stopped. Although penicillin is treponemocidal it is only effective against multiplying organisms. It may be that simultaneous administration of doxycycline and penicillin was in part responsible for the treatment failure. Prolonged treatment with intravenous penicillin was required. Similarly azithromycin and penicillin probably should not be used together in patients with non-gonococcal urthritis.¹⁶ However, quinolones, which are inactive against spirochaetes, may be the best treatment choice for patients with syphilis and non-gonococcal urthritis.

Indications for lumbar puncture in adults with syphilis

- Positive TPPA and neurological or neuro-ophthalmic signs (optic neuritis, active chorioretinitis or anterior or posterior uveitis), even if previously treated
- HIV positive and TPPA positive
- Treatment failures
- Patients to be treated with a non-penicillin regimen
- Untreated syphilis for more than one year

Serious reactions to penicillin occur in 3%–5% of patients, usually within 15–20 minutes of penicillin injection. By contrast the Jarish Herxheimer reaction occurs 4–12 hours after the first injection and is attributable to endotoxin release from killed spirochaetes. Its severity is related to the total number of spirochaetes in the body, not the dose of penicillin given. Treatment with corticosteroids does not prevent the reaction but may ameliorate it.

Properly treated the visual prognosis for patients with syphilis and optic neuritis is good.³ Oral and intravenous corticosteroids are an appropriate adjunct for posterior uveitis, scleritis, and optic neuritis.⁴ Secondary optic atrophy is uninfluenced by antisyphilitic treatment.

FOLLOW UP

Acquired immunity develops three to six months after infection. This immunity is incomplete and re-exposure to syphilis can bring about asymptomatic re-infection. Therefore after treatment the VDRL should be repeated at one, three, six, and 12 months. A persistent fall in VDRL titre after treatment provides essential evidence of an adequate response to therapy. HIV positive patients may relapse even after treatment with high dose intravenous penicillin. Lumbar puncture should be repeated every six months for two years in patients who have had neurosyphilis. The CSF VDRL titre should decrease fourfold, typically within the first 6 to 12 months. An increased CSF protein falls more slowly. If these parameters do not fall as predicted then re-treatment may be indicated.

SUMMARY

- The incidence of syphilis is rising
- Patients with neurosyphilis may present with ophthalmic symptoms and signs.
- Neurosyphilis should be considered in patients with otherwise unexplained visual loss, and syphilis should be considered as a cause of optic neuritis
- All suspected cases should be investigated with both a specific antitreponemal test and a lipid antigen test
- All patients with syphilis should be evaluated for HIV and vice versa

Table 1 Treatment of acquired adult syphilis

	Early syphilis (primary, secondary, early latent (syphilis acquired less than one year previously) and early reinfection)	Latent syphilis (syphilis acquired more than one year previously or of unknown duration)	Neurosyphilis
Recommended treatment	Benzathine penicillin 2.4×10 ⁶ U IM once	Benzathine penicillin 2.4×10 ⁶ U IM Weekly for three weeks	Aqueous crystalline penicillin G 3–4×10 ⁶ U IV 6× daily 14 days
Penicillin allergy	Skin test, if necessary desensitise then treat with penicillin OR Doxycycline 100 mg twice daily orally 14 days OR Ceftriaxone* 1g IV 10 days	Skin test, if necessary desensitise then treat with penicillin OR Doxycycline 100 mg twice daily orally 28 days	Skin test, if necessary desensitise then treat with penicillin OR Doxycycline 100 mg twice daily orally 28 days OR Ceftriaxone* 2 g IV 10 days
Pregnant and penicillin allergic	Skin test, if necessary desensitise then treat with penicillin OR Azithromycin 500 mg once daily orally 10 days	Skin test, if necessary desensitise then treat with penicillin OR Erythromycin 500 mg qds po 28d	Skin test, if necessary desensitise then treat with penicillin OR Ceftriaxone* 2g IV 10 days
HIV positive	Benzathine penicillin 2.4×10 ⁶ U IM weekly 1 to 3 weeks	Benzathine penicillin 2.4×10 ⁶ U IM Weekly for three weeks	Aqueous crystalline penicillin G 3–4×10 ⁶ U IV 6× daily 14 days

Treatment notes: treatment during pregnancy should consist of the penicillin regimen appropriate for the stage of syphilis. Treatment of HIV positive, penicillin allergic patients should be as for HIV negative penicillin allergic patients. Infants of mothers treated with non-penicillin regimens should be treated with penicillin post-partum. Treat previous contacts within the past three months if primary syphilis, and the past year if secondary syphilis. No sexual intercourse during treatment and for two weeks afterwards. Benzathine penicillin G 900 mg = 1.2 megaunits. Aqueous crystalline penicillin G = 0.5 megaunits. All treponemal infections are unaffected by sulphonamides, quinolones, and rifampicin. *Risk of allergic cross reactivity between penicillin and ceftriaxone.

- Negative neuro-imaging and previous treatment with benzathine penicillin cannot be used to exclude a diagnosis of neurosyphilis
- Prolonged treatment with high dose intravenous penicillin remains the treatment of choice for neurosyphilis
- Concomitant use of bacteriostatic drugs, such as doxycycline, may reduce the effectiveness of penicillin
- If adequately treated there is a good visual prognosis for patients with syphilitic optic neuritis

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REFERENCES

- 1 Tichonova L, Borisenko K, Ward H, *et al.* Epidemics of syphilis in the Russian Federation: trends, origins, and priorities for control. *Lancet* 1997;**350**:210–13.
- 2 Tamesis RR, Foster CS. Ocular syphilis. *Ophthalmology* 1990;**97**:1281–7.
- 3 Lukehart SA, Hook EW, Baker-Zander SA, *et al.* Invasion of the central nervous system by *Treponema pallidum*: implications for diagnosis and treatment. *Ann Intern Med* 1988;**109**:855–62.
- 4 Margo CE, Hamed LM. Ocular syphilis. *Surv Ophthalmol* 1992;**37**:203–20.
- 5 Walsh FB, Hoyt WF. Infections and parasitic invasions of the nervous system. In: *Clinical neuro-ophthalmology*. 3rd ed. Vol 2. Baltimore: Williams and Wilkins, 1969:1581–91.
- 6 Gourevitch MN, Selwyn PA, Davenny K, *et al.* Effects of HIV infection on the serologic manifestations and responses to treatment of syphilis in intravenous drug users. *Ann Intern Med* 1993;**118**:350–5.
- 7 Goh BT, van Voost Vader PC. European guidelines for the management of syphilis. *Int J STD AIDS*. 2001;**12**: 14–26. (<http://www.iusti.org/guidelines.pdf>), (suppl 3).
- 8 Centers for Disease Control and Prevention. Sexually transmitted disease guidelines 2002. *MMWR*. 2002;**51**: 18–30. (<http://www.cdc.gov/STD/treatment/rr5106.pdf>).
- 9 Mohr JA, Griffiths W, Jackson R, *et al.* Neurosyphilis and penicillin levels in the cerebrospinal fluid. *JAMA* 1976;**236**:2208–9.
- 10 Johns DR, Tierney M, Felsenstein D. Alteration in the natural history of neurosyphilis by concurrent infection with human immunodeficiency virus. *N Engl J Med* 1987;**316**:1569–72.
- 11 Barza M, Baum J. Penetration of ocular compartments by penicillins. *Surv Ophthalmol* 1973;**18**:71–82.
- 12 Greene BM, Miller NR, Bynum TE. Failure of penicillin G benzathine in the treatment of neurosyphilis. *Arch Intern Med* 1980;**140**:1117–18.
- 13 Abramson JJ, Smibert RM. Inhibition of growth of treponemes by antimicrobial agents. *Br J Vener Dis* 1971;**47**:407–12.
- 14 Yim CW, Flynn NM, Fitzgerald FT. Penetration of oral doxycycline into the cerebrospinal fluid of patients with latent or neurosyphilis. *Antimicrobial Agents Chemother* 1985;**28**:347–8.
- 15 Poirer RH, Ellison AC. Ocular penetration of orally administered minocycline. *Ann Ophthalmol* 1951;**46**:1859–61.
- 16 Odenholt I, Löwdin E, Cars O. Studies of the killing kinetics of benzylpenicillin, cefuroxime, azithromycin, and sparfloxacin on bacteria in the postantibiotic phase. *Antimicrobial Agents Chemother* 1997;**41**:2522–6.