Ocular Syphilis
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Introduction

Syphilis, a sexually transmitted disease, is a systemic infection caused by a
gramnegative bacterium, Treponema pallidum subsp. pallidum, a member of the
order Spirochaetales, family Spirochaetaceae, and genus Treponema. T. pallidum
enters the body through small abrasions on the skin or mucous membranes. After
local multiplication the treponemes will spread to the regional lymph nodes and from
there to the whole body via hematogenous dissemination. Vertical transmission via
transplacental infection from the infected mother to the unborn child occurs after the
first three months of pregnancy and may result in intrauterine death or cause
congenital syphilis.(1)

The natural history of untreated acquired syphilis has been divided in four
stages: primary syphilis, secondary syphilis, the latent stage, and tertiary
syphilis.(2,3)

Primary syphilis is characterized by the presence of a single, painless,
nonsuppurative ulcer with a hard base, the syphilitic chancre. This highly infectious
lesion appears 2 to 6 weeks after exposure and heals within 3 to 6 weeks.
Proliferation and spread to regional lymph nodes causes painless lymphadenopathy.
Most chancres are located in the genital area, but extragenital chancres on sites such
as the conjunctiva and the eyelids have been reported.

If no appropriate antibiotic treatment is given, the treponemes disseminate in
the blood and signs of secondary syphilis appear about 6 weeks after the
appearance of the primary chancre. Secondary syphilis is characterized by a flu-like
illness with sore throat, arthralgias, myalgias, headache, fever, and very often a
painless, maculopapular skin rash. The rash disappears spontaneously after some
weeks. Invasion of the central nervous system occurs in about 40% of patients with
secondary syphilis. Acute meningitis is observed in only 1% to 2% of patients. Neuro-
ophthalmological manifestations of secondary syphilis include optic neuritis, optic perineuritis, or cranial nerve palsy. Anterior uveitis is the most common eye finding in this stage and was reported to occur in about 5% of syphilitic patients before the introduction of penicillin.

The latent stage is divided in the early latent stage, the first year following infection, and the late latent stage, the subsequent period. During the early latent stage relapses of secondary syphilis are still possible. In the late latent stage clinical disease is no longer detectable and the patient is no longer contagious, although dormant treponemes may be present in liver and spleen. Re-awakening and multiplication of dormant treponemes in one third of the patients sets the stage for the development of tertiary syphilis. This may happen from several years to several decades after the secondary stage. Tertiary syphilis is divided in three groups: benign tertiary syphilis, cardiovascular syphilis, and neurosyphilis. Benign tertiary syphilis is characterized by gumma formation. Gumma are granulomatous lesions mainly found in skin and mucous membranes but also described in the uveal tract. Cardiovascular syphilis is the result of an obliteratorative endarteritis of the vasa vasorum of the aorta and causes aortitis, aortic aneurysms, and aortic valvular insufficiency. Neurosyphilis includes meningovascular syphilis and parenchymatous neurosyphilis. Meningovascular syphilis is the result of small-vessel endarteritis and vascular occlusion leading to stroke syndromes or seizures. Visual field defects due to vascular occlusions affecting the visual pathways are commonly seen at this stage. Parenchymatous neurosyphilis is the endresult of postinflammatory neuronal degeneration: general paresis, tabes dorsalis, optic atrophy, and pupillary disturbances (Argyll Robertson pupil) are all manifestations of parenchymatous neurosyphilis.

Congenital syphilis causes intrauterine death in one half of infected fetuses. In those children who survive congenital abnormalities, mainly mucocutaneous lesions and osteochondritis, may be obvious at birth (early congenital syphilis). In others congenital infection may not be apparent until about two years of age when facial and tooth deformities develop (late congenital syphilis). Interstitial keratitis is a common inflammatory sign of untreated late congenital syphilis and is, together with peg-shaped upper central incisors and sensory deafness part of the classic triad of Hutchinson.

**Ocular manifestations of syphilis**

Ocular involvement in primary syphilis is rare and mainly limited to chancres of the eyelids and the conjunctiva due to direct inoculation from contaminated fingers or secretions.(2) The protean manifestations of ocular syphilis affecting all structures of the eye occur mainly in secondary and in tertiary syphilis. Despite the widespread but erroneous belief that ophthalmic lesions are signs of tertiary syphilis, corneoscleral, uveal, retinal, and optic nerve inflammation may be observed as well in secondary as in tertiary syphilis. There are however differences: chronic gummatous or granulomatous inflammation of the ocular structures is typical of late stage disease, whereas more aggressive inflammation (iritidocyclitis with vascularized nodules or roseolae and necrotizing retinitis) is associated with early disease. It is important to stress that many patients who present with ocular signs of syphilis do not have systemic signs of the disease. In fact the ocular manifestations in secondary syphilis often occur up to 6 months after the initial infection when most systemic
manifestations such as the skin rash have already resolved. Only half of the patients with ocular manifestations in the tertiary stage have concomitant non-ocular signs of disease. (2)

Anterior uveitis

Anterior uveitis in secondary syphilis starts as an acute unilateral iridocyclitis. The severity may range from mild nongranulomatous to severe, granulomatous disease. The second eye becomes involved in about one half of the patients. (2,3) Typical of secondary syphilis but rarely observed are the iris roseolae which are vascular tufts in the middle third of the iris surface, corresponding to the infectious mucocutaneous lesions. (4) In tertiary syphilis the anterior uveitis may be chronic and granulomatous (Koeppe and Busacca nodules). Gummas of the uveal tract can mimic iris tumours and even erode through the sclera. Poor response to topical steroid treatment and a history of a skin rash in the recent past should alert the clinician to the possibility of syphilitic anterior uveitis.

Posterior segment involvement

Unlike other infectious agents that have a predilection either for the retina (cytomegalovirus) or for the choroid (M. tuberculosis), treponemes seem to be able to thrive in all the layers of the eye, resulting in a wide variety of clinical manifestations: focal/multifocal chorioretinitis, acute posterior placoid chorioretinitis, necrotizing retinitis, retinal vasculitis, intermediate uveitis, and panuveitis. (2,3,5) Deep chorioretinitis used to be considered the most common form of posterior segment involvement. Focal syphilitic chorioretinitis presents as a deep, yellow gray lesion often with a shallow serous retinal detachment and inflammatory cells in the vitreous. Multifocal lesions from one half to one disk diameter can coalesce to become confluent. Fluorescein angiography shows a pattern of early hypofluorescence of the lesion followed by late staining. Since the original description by Gass of a specific entity referred to as acute syphilitic posterior placoid chorioretinitis (ASPPC) in 6 patients with secondary syphilis, 16 similar cases are reported in the literature. (6,7) These patients present with vitritis associated with large, solitary, placoid, pale-yellowish subretinal lesions usually in both eyes. The lesions show evidence of central fading and a pattern of coarsely stippled hyperpigmentation of the pigment epithelium. The placoid lesions in ASPPC are larger in size and often solitary which differentiates them from the lesions observed in acute posterior multifocal placoid pigment epitheliopathy (AMPPE). The pattern of small leopard-spot alterations of the pigment epithelium seen on fluorescein angiography in the cicatricial phase of ASPPC is not seen in AMPPE and is sufficiently characteristic to suggest a diagnosis of syphilis according to Gass. Necrotizing retinitis mimicking herpetic retinal necrosis has been reported in the recent literature with increasing frequency. (8,9,10) This form of syphilitic retinitis presents as one or more yellow-white patches of necrosis, often associated with vasculitis, vitreous inflammation and discrete anterior segment inflammation, mimicking the acute retinal necrosis syndrome (ARN) of herpetic origin. In the absence of adequate antibiotic therapy, the lesions will progress and cause serious visual disability in a matter of weeks. The tendency for bilateral disease and the more aggressive course observed in immunodeficient patients dictate the need for prompt diagnosis and effective treatment in this patient group. Although the differential diagnosis with ARN may be difficult, careful observation of the lesions may yield a clue to the diagnosis of syphilitic retinal necrosis. In ARN the necrotic lesions start in
the periphery whereas in syphilitic retinitis they often are located in the posterior pole. In syphilitic retinal necrosis one has the impression that the surface of the lesion is somewhat indistinct, as if a layer of exudate obscures the underlying retina from view, whereas in ARN one can clearly identify the surface of the lesions as the surface of the thickened, necrotic retina. The retinal necrotic tissue tends to be homogeneous in ARN whereas the areas of necrosis in syphilitic retinitis have a mottled aspect that becomes even more obvious in the healing phase. The response to intravenous penicillin in syphilitic necrosis is excellent and halts further progression. The necrotic areas heal with scarring of the retinal pigment epithelium resulting in the picture of pseudo-pigmentary retinopathy. Syphilitic eye disease may mimic intermediate uveitis especially if mild inflammation of the anterior segment is associated with a more pronounced vitreal reaction. (fig 8) Other signs often present in intermediate uveitis such as retinal vasculitis, cystoid macular oedema and a hot disk may also be present, further confusing the observer. A frank pars plana exudate is not present in syphilitic vitreitis. (11) The reported prevalence of simultaneous involvement of the anterior and the posterior segment or panuveitis is highly variable and ranges from 27% to 66%. (9,11,12)

**Optic nerve inflammation**

Acute meningitis occurs in 1% to 2% of patients with secondary syphilis and this can cause increased intracranial pressure and papilledema.(13) In pure papilledema there is an enlargement of the blind spot but no signs of inflammatory cells in the vitreous. Papilledema should be differentiated from inflammatory optic disk edema due to optic neuritis, papillitis, and neuroretinitis.(14) These patients have marked loss of visual acuity and display central and cecocentral, or nerve fiber bundle defects, and often have signs of vitreous inflammation. In papillitis there is a swollen disk with intraretinal exudates and perivasculitis around it. When the inflammatory changes extend into the peripapillary retina resulting in hard exudates, the condition qualifies as neuroretinitis. Optic perineuritis is due to an inflammation of the meningeal sheaths of the optic nerve and causes mild swelling of the optic disk, without affecting its function. This condition should be suspected in patients with normal visual acuity and color vision who seem to have papilledema but in whom lumbar puncture reveals normal cerebrospinal fluid pressure and the presence of inflammatory cells or increased protein. Although inflammatory conditions of the optic nerve are more common in the secondary stage, they may occur in tertiary syphilis as well. Optic atrophy is however the prevailing pathology in this stage. It is present in 5% of patients with symptomatic parenchymatous neurosyphilis.

**Syphilitic uveitis in HIV infected patients**

Coinfection with HIV and syphilis is common due to shared risk factors related to sexual behaviour. Syphilitic chancres like any genital ulceration increase the risk of acquiring and transmitting HIV. (15) HIV infected patients with syphilis have a higher treponemal load and are more prone to develop neurosyphilis.(16) Ophthalmic involvement in these patients is often bilateral and several reports suggests that syphilitic uveitis in HIV infected patients tends to run a more aggressive course and may relapse despite adequate treatment.(10,17) Moreover, the serological diagnosis of syphilis is more challenging in HIV infected patients and depending on the stage of
the disease, more false positive (early stage of HIV) or more false negative results (advanced immune dysfunction) may be encountered. (18,19)

**Diagnosis of ocular syphilis (1-3,20-22)**

Because of the wide variety of syphilitic ocular manifestations and the fact that this disease may mimick other etiologic entities, some practitioners routinely order serologic tests for syphilis in patients with intraocular inflammation which may be useful as the presentation of ocular syphilis is protean.

Laboratory confirmation of syphilis can be obtained via direct detection of *Treponema pallidum* (darkfield microscopy, silver staining, direct fluorescent antibody stains) but this method is of little use in ocular syphilis. Serologic testing that includes non-treponemal tests and treponemal tests is considered the standard detection method. The term non-treponemal is used because the antigens are not treponemal in origin, but are extracts of normal mammalian tissues. Cardiolipin from beef heart allows the detection of anti-lipid IgG and IgM formed in the patient in response to lipoidal material released from cells damaged by the infection, as well as to lipids in the surface of *T. pallidum*. The two tests commonly in use are the VDRL (Venereal Disease Research Lab) and the RPR (rapid plasma reagin). Non-treponemal antibody are not very specific, but the titers decline as a result of treatment and are used as a tool to monitor response to treatment. A fourfold reduction in antibody titer of the same non-treponemal test is considered a significant response to treatment. Lack of expected reduction in titer or an increase in titer suggests treatment failure or reinfection. Non-treponemal tests may give false positive results in conditions other than syphilis (viral infection, pregnancy, post-immunization). Moreover, they may be negative in as many as 30% of patients during the late latent or tertiary stages. Therefore, a specific treponema antibody assay is needed to supplement the non-treponemal tests in all cases of suspected disease. Two commonly used specific tests are the FTA-abs (fluorescent treponemal antibody absorption test) and the TPPA (*T. pallidum* particle agglutination). These tests have a high sensitivity and specificity and are said to stay positive throughout life, although seroreversion may occur in a small number of patients, mainly in those treated for early disease. The CDC recommends lumbar puncture in all patients with ocular syphilis to detect neurosyphilis, (23) but there is debate whether this procedure is justified in patients with isolated anterior segment inflammation. The diagnosis of neurosyphilis is based upon the cerebrospinal fluid leukocytosis, protein changes, and the presence of a positive VDRL. The VDRL test unfortunately has low sensitivity to detect syphilis in the cerebrospinal fluid and therefore a negative VDRL does not rule out neurosyphilis. Specific treponemal tests are not very useful to detect neurosyphilis because antitreponemal IgG antibodies pass the intact blood-brain barrier and hence a positive result is no proof of neurosyphilis.

**Treatment (23)**

Ocular syphilis is treated in exactly the same way as neurosyphilis. Since benzathine penicillin does not penetrate the blood ocular barrier, aqueous penicillin G or procaine penicillin G plus probenecid should be given. For patients with ocular syphilis in the tertiary stage a 3 week course of benzathine penicillin should be added.
### Stage

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<tr>
<th>Stage</th>
<th>Patients not allergic to penicillin</th>
<th>Patients allergic to penicillin</th>
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<tbody>
<tr>
<td>Neurosyphilis (any stage)</td>
<td>Aqueous crystalline penicillin G 3-4 million units IV every 4h or 18-24 million units/day for 10-14 days or Procaine penicillin 2.4 million units IM once daily plus probenecid 500 mg PO 4 times daily for 10-14 days</td>
<td>Ceftriaxone 2g IV or IM daily for 10-14 days</td>
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<tr>
<td>Neurosyphilis (late stage)</td>
<td>Above regimen followed by benzathine penicillin G 2.4 million units IM every week for up to 3 weeks</td>
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Antibiotic therapy is essential in infectious uveitis, but there is certainly a place for adjunctive corticosteroid therapy in the management of syphilitic eye disease. Topical steroids are of benefit as an adjunctive treatment in syphilitis keratitis, scleritis and anterior uveitis. (2) Systemic steroids always in combination with appropriate antibiotic therapy have a role in the treatment of posterior uveitis and optic nerve inflammation.(24,25)

### Conclusion

There seems to be a reemergence of an old plague, syphilis. The ophthalmologist should be aware that the enemy causes a wide variety of ocular inflammatory conditions and that few of them are pathognomonic for the disease. Therefore, a high degree of suspicion for syphilis must be maintained especially in patients with ocular inflammation of unknown etiology, in patients who fail to respond to or worsen on immunosuppressive therapy, or in patients in whom the natural course of the disease does not follow the pattern predicted by the presumed etiology. Prompt diagnosis is particularly important in patients with dual infection, syphilis and HIV, since aggressive, bilateral necrotizing syphilitic retinitis emerges as a potentially blinding disease in this patient group. Finally, since many patients with syphilitic uveitis present in the secondary stage, timely diagnosis and adequate treatment will prevent not only further ocular damage, but will also protect the patient against morbidity and even mortality associated with the tertiary stage of the disease. Once the ophthalmologist suspects the diagnosis of syphilis, the diagnostic workout and the therapeutic strategy should be decided upon in close collaboration with an infectious disease specialist fully familiar with the subject.

### References
