

## INTRODUCTION

Syphilis (from the greek word syphlos meaning crippled) is a sexually transmitted, chronic, multi-system disease, caused by the bacterium *Treponema pallidum* (TP) belonging to the family Spirochaetaceae<sup>1</sup>.

### Incidence

The incidence of syphilis had declined with the advent of the antibiotic era. It has however re-emerged with the AIDS epidemic, especially in the developing world and certain areas of US<sup>2</sup>. In parts of Africa, the incidence is around 350 cases per 100,000 population<sup>1</sup>. It is twice as common in males as in females<sup>1</sup>. An estimated 4-9% of patients with untreated syphilis develop symptomatic Neurosyphilis (NS)<sup>3</sup>.

## PATHOPHYSIOLOGY

TP is a motile spirocheate, measuring 0.2 µm in diameter and 5-15 µm in length. It gains access to the body by way of minute abrasions in the skin or mucous membrane. Besides venereal spread, it may also be transmitted vertically from mother to child<sup>3</sup>. An obliterative end-arteritis of the terminal arterioles is the primary pathogenesis by which TP causes inflammatory and necrotic changes in the tissues invaded<sup>1</sup>. Invasion of the CNS occurs early in the course of untreated syphilis. Neurosyphilis can manifest with meningeal, meningovascular, and parenchymal syndromes and spans all stages of disseminated disease.

## CLINICAL MANIFESTATION

The chronic, progressive, multi-system infection is characterized by episodes of active disease separated by

periods of latency<sup>3</sup>. Clinically syphilis is classified as primary, secondary, tertiary and quaternary syphilis<sup>1</sup>.

**Primary syphilis** develops 3-90 days post-exposure. It is characterized by skin lesions called chancres at the site of inoculation. Spirochaetes can be demonstrated in the lesions by dark-field illumination microscopy and silver stain<sup>1</sup>. Asymptomatic spread to the CNS occurs in around 30% cases<sup>3</sup>.

**Secondary syphilis** occurs 2 to 12 weeks after contact. Common manifestations include fever, malaise, lymphadenopathy, rash, and ocular changes. Symptomatic neurosyphilis develops in only 1-2% cases<sup>3</sup>. Around 30% cases however, may show CSF evidence of a meningeal infection that is clinically asymptomatic<sup>1</sup>.

**Tertiary syphilis** develops in upto one-third of untreated patients after a latent period of 5 to 30 years<sup>3</sup>. It can take the form of neurosyphilis, cardiovascular syphilis, and late benign gummatous syphilis<sup>1</sup>.

**Quaternary syphilis** is observed primarily, but not exclusively, in patients with coexistent HIV infection. It is characterized by a fulminant organism-laden, anergic, necrotizing encephalitis<sup>1</sup>.

**Neurosyphilis** can be encountered in all stages of syphilis. **Early NS** affects mesodermal structures, i.e., meninges and vessels, and is seen in the first weeks to year after infection<sup>1</sup>. **Late NS** affects brain and spinal cord parenchyma, and occurs years to decades after infection<sup>1</sup>.

The two general categories of NS thus include:

- Meningeal involvement only
- Parenchymal involvement

**CLINICAL NEUROSYPHILITIC SYNDROMES<sup>1</sup>**

- Asymptomatic CNS infection
- Acute syphilitic meningitis
- Meningovascular syphilis
- Tabes Dorsalis
- General paresis of the insane (GPI)
- Optic atrophy

\*Combined forms of NS may occur due to overlap of the above syndromes.

**Asymptomatic NS** may be encountered in upto 30% cases of early, i.e. primary or secondary syphilis<sup>1,3</sup>. There are no signs and symptoms of neurologic disease. CSF is VDRL (Venereal Disease Research Laboratory) positive, and reveals lymphocytic pleocytosis with elevated proteins but normal sugar. CSF analysis is therefore important in all cases with HIV infection or suspected syphilis. Untreated, the cases may progress to symptomatic forms of NS.

**Acute syphilitic meningitis** usually occurs within the first few years after infection (range - 2 months to 26 years)<sup>2</sup>. Signs of meningeal irritation, like stiff neck, headache, nausea and vomiting occur; but fever is unusual. Cranial neuropathy commonly implicates the 7th, 8th, 6th and 2nd cranial nerves in a decreasing order of frequency. CSF is abnormal and reveals positive serology for syphilis. The meningitis may be self-limiting, but untreated infection usually re-expresses itself later as a more severe form of NS<sup>1,2</sup>.

**Meningovascular syphilis** usually develops within months to years after infection (average 7 years)<sup>2</sup>. The basic pathology is an endarteritis and perivascular inflammation of the medium-sized and small intracranial vessels as a consequence of syphilitic meningitis<sup>1,2</sup>. Affected vessels may reveal fibroblastic proliferation of the intima, thinning of the media, and fibrous and inflammatory changes with lymphocytic and plasma cell infiltration in the adventitia. Luminal narrowing predisposes to cerebrovascular thrombosis, ischemia and infarction<sup>1</sup>. Leptomeningeal granulomas called gummas may form and result from a cell-mediated immune response to TP<sup>1</sup>.

**Clinical manifestations may include:**

- **Stroke** involving the middle cerebral artery or basilar artery territory in young adults.
- **Subacute encephalitic syndrome** with headache, vertigo, insomnia, seizures, change in personality and intellectual deterioration followed by a gradually progressive vascular syndrome.
- **Cranial neuropathies** due to meningovascular syphilis involving the base of the brain.
- **Spinal cord syndromes** like acute syphilitic transverse myelitis, or an anterior spinal artery syndrome<sup>1,2</sup>.

**Tabes dorsalis** usually develops 15-20 years after the original infection (range-5-50 years)<sup>3</sup>. Primary site of involvement is the posterior nerve roots and posterior column of the spinal cord which show inflammatory change and fibrosis. Usual presentation is with a sensory ataxia due to loss of position and vibration sense. Loss of pain sensation, bladder and sexual function may also occur. Lancinating pains occur in about 90% cases, usually in the lower extremities. Visceral crises can occur in 15% cases and may take the form of excruciating epigastric pain with nausea and vomiting, simulating acute abdomen<sup>1</sup>. Examination may reveal areflexia, loss of proprioceptive sense, and Argyll Robertson pupils. Charcot joints and trophic ulcers may develop.

**General paresis of the insane (GPI)** or dementia paralytica occurs in about 20 to 30 years after the initial exposure (range 3 to 30 years)<sup>1,3</sup>. Pathologically, it is characterized by meningeal fibrosis and cerebral cortical atrophy and gliosis with tissue invasion by spirochaetes. GPI basically represents a chronic progressive fronto-temporal meningoencephalitis. Presentation is with a progressive dementia with severe impairment of memory, judgment and other cognitive functions. Depression, confusion and other psychiatric manifestations are common. Other signs may include seizures, dysarthria, pyramidal deficits and optic atrophy<sup>2</sup>.

**Syphilitic optic atrophy** may accompany acute syphilitic meningitis or present as an isolated complication of secondary syphilis. It evolves over months to years. Progressive contraction of visual fields with preserved acuity is encountered as the optic nerve degeneration usually begins peripherally and extends to the center of the nerve. Other ocular manifestations may include uveitis, chorioretinitis and iritis<sup>3</sup>.

**Differential diagnosis of NS** includes other CNS disorders such as TB, cryptococcal meningitis, brucellosis, lyme disease, CNS sarcoid and cerebral vasculitides<sup>3</sup>.

**Diagnoses***Standard Criterion for the Diagnosis of Syphilis*

- Demonstration of the spirocheates in lesions of primary and secondary syphilis by dark field examination

### Diagnosis of Neurosyphilis is Based on

- Clinical evidence
- Serology (Serum and CSF)
- CSF findings.

### Serologic Tests

Syphilitic infection produces two types of antibodies—the non-specific reaginic antibodies (e.g. anticardiolipin antibodies) and the specific antitreponemal antibodies<sup>1</sup>.

The specific antitreponemal antibodies are measured by treponemal and non-treponemal tests.

### Treponemal Tests

The Treponemal test results become positive 3 to 4 weeks after inoculation, and usually remain positive for life despite adequate therapy and regardless of the disease stage<sup>1,3</sup>.

They include<sup>3</sup>:

- Fluorescent treponemal antibody absorption (FTA-ABS)
- Microhemagglutination assay-T pallidum (MHA-TP)
- Fluorescent Treponemal antibody-absorption double staining
- Hemagglutination treponemal test for syphilis
- Treponema pallidum immobilization

*Note:* The FTA-ABS and the MHA-TP are very sensitive and specific tests in latent, secondary, tertiary and quaternary syphilis and confirm the diagnoses.

### Non-treponemal Tests

The non-treponemal or regain tests detect antibodies to membrane lipids of TP, using antigens such as cardiolipin, lecithin or cholesterol. They include Venereal Disease Research Laboratory Test (VDRL) and Rapid Plasma Reagin Test (RPR). These tests are more sensitive but less specific than treponemal tests. The test results become positive 5 to 6 weeks after exposure and usually become negative in the year following adequate treatment.<sup>1</sup> Both RPR and VDRL are equally sensitive and may be used for initial screening and for serial follow up<sup>1</sup>.

**VDRL** titers usually reach 1:32 or higher in secondary syphilis. A persistent fall in titer following treatment, provides evidence of an adequate response. A rising titer on the contrary signifies a re-infection or inadequate treatment<sup>1</sup>. In tertiary syphilis however the VDRL may

remain positive indefinitely<sup>1</sup>. The cardiolipin antigen used in the nontreponemal test is found in the other tissues resulting in false-positive serologic test results. False Positive VDRL may be encountered in patients with other infections, autoimmune disorders, malignancy, drug usage and after immunization<sup>1,3</sup>.

### CSF Examination

CSF mononuclear pleocytosis (>5 cells per  $\mu\text{L}$ ) and elevated protein support the diagnosis of NS. CSF abnormalities may be found in upto 70% cases with asymptomatic NS<sup>1</sup>. CSF-VDRL is very specific. It is more sensitive in meningovascular syphilis and GPI than in asymptomatic CNS and Tabes. False-positive CSF-VDRL may occur if blood contaminates CSF, as occurs with traumatic LP<sup>3</sup>.

### Other Diagnostic Markers for NS include

- Oligoclonal bands.
- Intrathecally produced antitreponemal immunoglobulin (1gM and 1gG) antibodies.
- Polymerase chain reaction (PCR) for detection of treponemal nucleic acids in CSF.

### IMAGING STUDIES

**CT/MRI imaging** of brain and spinal cord may reveal ischemic lesions in meningovascular syphilis, fronto-cortical atrophy and disseminated frontal high signal lesions in T2-weighted MRI sequences in GPI, intracerebral gummata or evidence of syphilitic myelitis as per the cases<sup>1</sup>. **Angiography** may reveal multifocal narrowing of the neurovasculature in meningovascular syphilis. **SPECT** (single-photon emission computerized tomography) using I-IMP (Iodine 123-N-isopropyl-P-Idoamphetamine) may demonstrate marked reduction in cerebral blood flow in bilateral frontal and temporal cortices.<sup>1</sup>

### TREATMENT

TP is highly sensitive to penicillin. It acts by interfering with the bacterial cell wall synthesis and is the drug of choice for all stages of syphilis.

### Therapy of Symptomatic NS / Asymptomatic NS in HIV Positive Cases

Alternative therapeutic options include:

- **Crystalline Penicillin G** in a dose of 2 to 4 million units every 4 hours by the IV route for 10 to 14 days. This is the first choice therapy recommended by Center for Disease Control and Prevention (CDC)<sup>1</sup>.

- **Procaine Benzyl Penicillin** in a dose of 2.4 million units daily by IM injection plus Probenecid in a dose of 500 mg four times a day by the oral route for 10-14 days. It is however less effective as compared to crystalline penicillin and more often associated with treatment failure<sup>1,3</sup>.
- **Doxycycline** in a dose of 200 mg twice a day orally for 4 weeks in patients sensitive to penicillin<sup>1</sup>.
- **Tetracycline** in a dose of 500 mg 6 hourly, orally, for 4 weeks<sup>1</sup>. Photosensitivity and or hepatic dysfunction may occur.

### Therapy for Asymptomatic NS in HIV Negative Cases

Alternative therapeutic options include:

- **Benzathine penicillin G** in a dose of 2.4 million units by 1M injection given weekly for 3 weeks.
- **Procaine penicillin** in a dose of 600,000 units by IM injection daily for 15 days.

### Reactions to Therapy

The Jarish-Herxheimer reaction may occur within the first few hours of starting therapy and peak by 6 to 8 hours. Its manifestations may include fever, myalgia, headache, chills, malaise, rigors, hypotension, tachycardia and an elevated neutrophil count<sup>1</sup>. It is probably caused by the release of heat-stable pyrogens from spirochaetes. The fever usually subsides within 12 to 24 hours. Corticosteroids and salicylates may be prescribed for symptomatic relief.

### Response to Therapy and Follow-up

Response to therapy is monitored by:

- **Clinical signs and symptoms**
- **Serum VDRL antibody titers** (usually reach 1:32 or higher in secondary syphilis)
- **CSF examination** repeated every 6 months for 2 years or until CSF becomes normal. A normal cell count and a falling protein content acts as an index of adequate treatment<sup>1</sup>.

### Retreatment should be considered if there is:

- Recurrence of signs and symptoms of NS
- Serum VDRL titers showing a four-fold increase or failure of titers greater than 1:32 to decrease by at least four-fold by 12-24 months post-treatment<sup>1</sup>.
- CSF examination showing an increase in cell count.

### Prognosis and Outcome of Therapy

- **Meningovascular syphilis:** Signs that remain after 6 months usually persist indefinitely<sup>3</sup>.
- **GPI:** Therapy may improve the cognitive or psychiatric disturbance or arrest disease progression in about 50% cases<sup>3</sup>.
- **Tabes Dorsalis:** Residual symptoms of tabes persist even after the CSF has normalized<sup>3</sup>.
- **NS in HIV positive cases:** The course of NS is more rapid and there is no cure<sup>1</sup>. Serologic improvement is less likely after therapy<sup>1</sup>. Fulminant, necrotizing neurosyphilis is regarded as a quarternary form of syphilis and is characterized by the presence of spirochaete laden CNS lesions.

### Prevention

There is no vaccine for syphilis, and preventive treatment of sexual contacts is important.

### REFERENCES

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