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Neurosyphilis

Current Drug Treatment Recommendations

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Summary

Neurosyphilis is a symptom of the tertiary stages of syphilis (a chronic systemic infection of *Treponema pallidum* subspecies *pallidum*). Classical neurosyphilis has become a rare condition in Western countries because of the use of penicillin for the treatment of early or latent syphilis. Although textbook neurosyphilis is now uncommon, modified neurosyphilis as a consequence of intercurrent antibiotic use for other conditions may be more common. This latter condition is harder to diagnose than classical neurosyphilis because of atypical clinical and cerebrospinal fluid (CSF) findings. The coexistence of HIV infection and syphilis has further complicated the picture.

There have been no well controlled trials of treatments for neurosyphilis. Nevertheless, the treatment of choice for established neurosyphilis has been shown to be benzylpenicillin (penicillin G). The drug is administered as an intensive therapy of frequent intravenous high doses or high doses of an intramuscular repository formulation with probenecid. Other agents that can be used include

high dose amoxicillin (amoxycillin) with probenecid (but compliance cannot be monitored), tetracyclines, macrolides or ceftriaxone. If the individual is HIV-positive or of unknown serostatus, benzylpenicillin should be used to prevent or treat neurosyphilis. In patients who are allergic to penicillin, rush desensitisation can be used to allow administration of benzylpenicillin. Alternatively, non-penicillin antibiotics can be used.

Much work has been performed to establish the bactericidal concentrations of penicillin and other antibiotics in serum and CSF. However, the significance of these values is uncertain because the causative pathology of neurosyphilis may lie in the perivascular space.

Follow-up and counselling of patients with neurosyphilis, and repeat lumbar puncture for analysis of CSF where initially abnormal, are recommended.

1. Definition, Clinical Features and Diagnosis

1.1 Definition

Syphilis is a chronic systemic infection caused by the spirochaete *Treponema pallidum* subspecies *pallidum*. The bacterium is usually transmitted via sexual contact with infectious lesions. *In utero* infection can also occur (congenital syphilis).[1]

1.2 Clinical Features

Syphilis is characterised by 4 stages:

- An incubation period of approximately 3 weeks, followed by a primary phase associated with lesions (chancres) and regional lymphadenopathy.
- A secondary bacteraemic stage commonly associated with generalised mucocutaneous lesions and generalised lymphadenopathy.
- A latent period of subclinical infection lasting many years [divided into early (the first year of infection) and late (beginning 1 year after infection) latent stages] or with a high reagin titre.
- A tertiary (or late) stage characterised by progressive destructive mucocutaneous musculoskeletal or parenchymal lesions, aortitis or CNS disease (i.e. neurosyphilis).[1]

Late syphilis can present as either asymptomatic or symptomatic. Neurosyphilis is one manifestation of late symptomatic syphilis, and can include meningovascular and parenchymatous forms. The latter category includes general *paresis* (disorders of *p*ersonality, *a*ffect, *r*eflexes, *e*ye, *s*ensorium, *in*tellect and *s*peech) and tabes dorsalis. Classical neurosyphilis develops in up to 10% of patients with untreated syphilis. The clinical picture of classical neurosyphilis has been well described elsewhere.[2]

In the pre-antibiotic era, symptomatic neurosyphilis predominately presented as general paresis and/or tabes dorsalis. In more recent years, some authors describe the incidence of these modes of presentation as unchanged,[3] but others describe a greater preponderance of meningovascular and vascular syphilis, which may represent partially treated syphilis, with symptoms such as hyporeflexia, absent ankle jerks and pupillary abnormalities.[4,5]

1.3 Diagnosis

With the intercurrent use of treponemacidal antibiotics for other conditions and, more recently, the coexistence of HIV infection and syphilis, neurosyphilis may not present with a classical clinical picture.[6-8] Diagnosis and treatment may, therefore, be difficult and complex.

Diagnostic confirmation of neurosyphilis is based on abnormal cerebrospinal fluid (CSF) findings in patients with positive serological tests for *T. pallidum* and suggestive or obvious clinical findings (see table I). CSF abnormalities include pleocytosis, raised protein levels and a positive reagin antibody test.

Serological tests used include reagin tests such as the Venereal Disease Reference Laboratory (VDRL) test, and treponemal tests of the CSF such

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Table I. Criteria for the diagnosis of neurosyphilis

CSF changes	Classical neurological signs	Atypical neurological signs
VDRL positive, ↑WBC, ↑protein	N	N
VDRL positive only	N	N
↑WBC and/or ↑protein only	N	N[a]
FTA-ABS	N	N[a]
TPHA index and/or CSF TPHA IgG/total IgG: serum TPHA IgG/total IgG	N	N[a]

a In the absence of other causes of neurological disease.

Abbreviations and symbol: CSF = cerebrospinal fluid; FTA-ABS = fluorescent treponemal antibody-absorption test; IgG = immunoglobulin G; N = diagnosis of neurosyphilis; TPHA = *Treponema pallidum* haemagglutination assay; VDRL = Venereal Disease Research Laboratory test; WBC = white blood cell; ↑ = increase.

as the fluorescent treponemal antibody-absorption test (FTA-ABS) and the *T. pallidum* haemagglutination assay (TPHA). The VDRL has a sensitivity of 30 to 70% in diagnosing neurosyphilis. Interpretation can be difficult because blood-stained specimens cause false-positive results, and a non-reactive VDRL test does not exclude neurosyphilis. Treponemal tests can give a positive result because of active neurosyphilis, asymptomatic neurosyphilisor-treated neurosyphilis, and false-positive reactions where serum leaks into the CSF. These tests are, therefore, oversensitive and tend to overdiagnose neurosyphilis.

The TPHA index[9] and CSF TPHA immunoglobulin G (IgG)/total IgG : serum TPHA IgG/total IgG[10] ratio are 2 methods of estimating true intrathecal treponemal antibody production. Rabbit inoculation and polymerase chain reaction (PCR) of the CSF can be used to detect the presence of *T. pallidum*, but are not used for routine clinical diagnosis at present.[6]

2. Epidemiology

Syphilis is much more common in certain areas of the world than others. It is more common in Africa and the US than in the UK. Worldwide figures are difficult to obtain, but there has been a downward trend in the incidence of the disease in Western countries since 1960. This trend has recently been reversed in the US with an increase in the incidence of primary and secondary syphilis and the re-emergence of congenital syphilis. In 1992, there were 112 581 cases of all types of syphilis, 3850 cases of congenital syphilis and 33 973 cases of primary and secondary syphilis. This compares with a total of 50 000 cases in 1990. The incidence of the disease in the UK has not shown such an increase: 1307 cases of syphilis were reported in 1992, of which 343 were infectious.

3. Neuropathology

Although predominantly a symptom of late syphilis, meningovascular syphilis may complicate secondary syphilis; however, there are no neuropathological studies in patients with early syphilis (i.e. the primary and secondary phases of the disease). Classical work demonstrates changes in the CSF, such as pleocytosis and an increase in the protein level, in up to 70% of patients with this early stage of syphilis.[1] However, positive reagin antibody tests (e.g. VDRL) from samples of CSF are more common as the duration of the infection increases.

In both classical and recent studies, *T. pallidum* has been found in the CSF in up to 40% of patients with uncomplicated early syphilis.[8] The more abnormal the CSF in early or latent syphilis, the more likely it is that classical neurosyphilis will ensue if the infection is not treated. The high frequency of CNS involvement in early syphilis is an interesting finding. The conventionally accepted treatment for early and latent syphilis does not consistently produce treponemacidal concentrations of penicillin in the CSF (see section 4.3) and yet the subsequent occurrence of neurosyphilis is almost nonexistent, except in HIV seropositive patients.[1,6]

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The basic neuropathology of neurosyphilis is an endarteritis with perivascular inflammation of plasma cells and lymphocytes. It is this effect that results in the pathology of tabes dorsalis, meningovascular syphilis, gummata and paretic dementia, rather than a direct action of *T. pallidum* on the brain parenchyma. In this situation, it would be the serum or perivascular antibiotic concentration that would have to be treponemacidal, not the CSF or brain concentrations. In spite of this, it is known that a high, but not a low, level of *T. pallidum* infection disrupts sensory (dorsal root) nerve function. In the past when paretic dementia was common, *T. pallidum* was found in brain parenchyma in up to 40% of patients. These conflicting data are hard to reconcile.

4. Treatment of Symptomatic Neurosyphilis

Fortunately, *T. pallidum* is still exquisitely sensitive to penicillin. This is despite the recent discovery of a plasmid that suggests that penicillin resistance may occur.[11] The treatment of neurosyphilis involves different regimens than those used in non-neurological disease.

4.1 Minimum Bactericidal Concentrations

In rabbit inoculation studies, the division time for *T. pallidum* has been found to be approximately 33 hours.[2,6] Such studies simulate primary syphilitic lesions. In spite of successful treatment of early syphilis, treponeme-like forms persist, suggesting that for some organisms the division time must be much longer and treatment should be prolonged. Even high dose penicillin does not appear to affect *T. pallidum* where the organism is not dividing or is 'indifferent'.[6]

Penicillin has an affinity for enzymes such as transpeptidases that are vital for the construction of the bacterial cell wall. Minimal bactericidal concentrations in rabbits and cell culture are 0.005 to 0.01 mg/L and 0.0025 mg/L, respectively.[2,6-8] The World Health Organization (WHO) recommend that 0.018 mg/L be accepted as a minimal treponemacidal concentration.[2,6-8] Treponemacidal concentrations have also been estimated for a number of other antibiotics.[6]

4.2 Relevance of Cerebrospinal Fluid Antibiotic Concentrations

In order to effectively treat neurosyphilis, antibiotics must penetrate the diseased sites. Much has been written about CSF antibiotic concentrations, the implication being that treponemacidal concentrations of agents in the CSF are necessary to ensure clinical cure.[2] However, we believe that the main pathology in neurosyphilis is at or near the meningeal blood vessels (i.e. the perivascular space), with some treponemes being present within brain tissue itself. Infection of the perivascular space results in ischaemia and infarction of neuronal tissue, although *T. pallidum* can directly produce pathological change when in contact with such tissue. It may not, therefore, be necessary to attain treponemacidal concentrations in the CSF or brain for treatment to be successful. The perivascular concentration may be of greater importance.

Nevertheless, at present, convention dictates that treponemacidal CSF concentrations are a necessary aim of treatment. It should be noted that meningeal inflammation markedly increases antibiotic penetration into the CSF.[6]

4.3 Choice of Antibiotics

There have been no controlled trials of treatments for neurosyphilis. Therefore, treatment recommendations are based on case series of particular regimens. Table II provides a summary of the dosage, route of administration and duration of treatment with antibiotics that can be used in patients with neurosyphilis (regardless of HIV status).

4.3.1 Penicillins

Benzylpenicillin (Penicillin G)

Benzylpenicillin (penicillin G) is the drug of choice for neurosyphilis. It has a short serum elimination half-life. This means that treponemacidal concentrations in the brain and CSF either have to be obtained by high frequency intravenous administration or by lower doses given by the intramus-

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Table II. Treatment recommendations for patients with neurosyphilis regardless of HIV status

Drug	Dosage	Route of administration	Duration (days)
Procaine penicillin[a]	2.4 MU/day	Intramuscular	14-21
Benzylpenicillin (penicillin G)[a]	500 000U 6-hourly	Intramuscular	14-21
Benzylpenicillin	2-4MU 4-hourly	Intravenous	14-21
Amoxicillin (amoxycillin)[a]	2g 8-hourly	Oral	14-21
Doxycycline[b]	100mg 8-hourly	Oral	21
Ceftriaxone[b]	1 g/day	Intramuscular	14-21

a Plus probenecid 1g 6-hourly orally.

b Used in patients with penicillin allergy.

cular route with probenecid (table II). 500 000U of benzylpenicillin intramuscularly 6-hourly plus probenecid orally 1.0g 6-hourly consistently yields treponemacidal CSF concentrations.

When 3.2MU of benzylpenicillin is given intramuscularly just prior to neurosurgery, treponemacidal concentrations are only inconsistently obtained in brain tissue.[12] CSF concentrations of benzylpenicillin are increased when the patient is febrile.

Although benzylpenicillin is the most effective agent, the usefulness of this drug is limited by the fact that it has to be administered 6-hourly and intramuscularly or intravenously. This route of administration is not ideal for outpatients. Therefore, alternative agents that can be administered orally have been used [e.g. amoxicillin (amoxycillin)].

Procaine Penicillin

After 2 doses of 600 000U of procaine penicillin, a regimen generally accepted as successful in clinically curing early syphilis, a treponemacidal concentration of penicillin is not consistently achieved in brain tissue or CSF,[13] even if probenecid is added.[14,15] Procaine penicillin 2.4 MU/day administered intramuscularly plus probenecid 1.0g 6-hourly is generally accepted as achieving treponemacidal concentrations in CSF, but even this finding is inconsistent.[16]

Benzathine Benzylpenicillin

Benzathine benzylpenicillin was launched in 1952. The drug ensures bactericidal penicillin concentrations in the serum for long periods. However, its use is associated with pain at the site of injection. Higher serum concentrations are achieved in older patients than in younger patients. The usual dosage is 2.4MU given weekly. However, treponemacidal concentrations of penicillin are not consistently achieved in either serum or CSF with this regimen and so it should not be used for the treatment of neurosyphilis.[17]

Amoxicillin

Amoxicillin given in high dosages with probenecid consistently produces treponemacidal drug concentrations (>0.42 mg/L) in the CSF.[18] It is thus a very useful oral alternative to benzylpenicillin. However, it should be mentioned that probenecid may hinder the accumulation of amoxicillin in brain tissue.

4.3.2 Tetracyclines

Doxycycline has several advantages over tetracycline. It has a long elimination half-life (20 hours) and, therefore, can be administered once or twice daily. It is well absorbed and its good lipid solubility leads to high CSF concentrations. CSF concentrations have been reported to be 26% of serum concentrations.[19]

With the other tetracyclines, oxytetracycline and chlortetracycline, brain concentrations have been shown to be significantly higher than CSF concentrations.[6,19]

4.3.3 Macrolides

Erythromycin

Erythromycin is treponemastatic and only becomes treponemacidal at high dosages. The minimal bactericidal concentration is 0.005 mg/L. A street strain of *T. pallidum* has been found to be resistant *in vitro* to erythromycin.[11] CSF and brain

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penetration of the drug is poor, and is only improved by meningeal inflammation. Erythromycin is, therefore, not a drug that can be reliably used in the treatment of neurosyphilis.

Azithromycin and Clarithromycin

Azithromycin inhibits *T. pallidum* protein synthesis in vitro as efficiently as erythromycin.[6] However, azithromycin takes longer than benzathine benzylpenicillin to cure rabbit syphilis.[6] Tissue penetration of azithromycin is very high. Clarithromycin seems to have a similar spectrum of activity to azithromycin.

4.3.4 Ceftriaxone

50% of *T. pallidum* are immobilised by a concentration of ceftriaxone of 0.01 mg/L. The minimum inhibitory concentration of the drug for *T. pallidum* is 0.006 mg/L. In a rabbit model comparing ceftriaxone and benzylpenicillin, the equivalent of ceftriaxone 1 g/day intramuscularly eradicated inoculated *T. pallidum* in the brains of 6 of 7 rabbits. However, the mean serum VDRL titre and CSF pleocytosis were significantly reduced after treatment in the aqueous benzylpenicillin compared with the ceftriaxone group.[7] The use of ceftriaxone 1 g/day for 14 days resulted in the cure of a single patient with asymptomatic neurosyphilis.[7]

4.4 Patients with Penicillin Allergy

Where there is a suggestive or clearcut history of penicillin allergy in the presence of serious neurosyphilis, one option is to skin test patients to confirm or refute the diagnosis. Patients are then 'rush desensitised' by giving increasing oral dosages of penicillin over a number of hours in order to stabilise mast cells. High dose penicillin is then immediately given. In a series of 44 patients treated in this way, there were no serious allergic phenomena.[20,21] Other nonpenicillin drug options that can be used in patients with penicillin allergy are presented in table II.

5. Treatment of Asymptomatic Neurosyphilis

About 30% of patients with early latent syphilis will have CSF changes indicating neurosyphilis. Approximately 30% of these patients will eventually develop clinical neurosyphilis if left untreated. Thus, of the 40% of patients with *T. pallidum* in the CSF in early syphilis about 30% will eradicate the infection without treatment. This finding shows that of every 100 patients with untreated early syphilis up to 10% may develop neurosyphilis.[2]

Does conventional treatment cure patients who are in the asymptomatic stage? One study in symptomatic patients demonstrated that a single dose of benzathine benzylpenicillin 2.4MU produced almost no detectable penicillin in the CSF, but *T. pallidum* were no longer found in the CSF after 6 to 7 days (during which time low concentrations of penicillin were found in the blood).[8] In 2 combined studies,[22,23] standard low doses of repository penicillins for 1 to 2 weeks resulted in the CSF returning to normal in 994 of 996 treated patients with asymptomatic neurosyphilis. The 2 patients who failed to respond to treatment showed only minor CSF changes after treatment completion.

We believe that when the patient has syphilis as determined by serological tests, but there are no neurological signs, the CSF need not be examined and conventional treatment may be used. Wiesel et al.[24] agree and feel that lumbar punctures only increase morbidity in this situation and confer no clinical benefit.

6. HIV and Neurosyphilis

Syphilis may be difficult to diagnose in HIV seropositive patients because there may be no CSF treponemal or reagin antibody response, particularly if the CD4 count is low. If these tests are positive they may react slowly and only be weakly positive. Conversely, serum reagin titres may be higher than expected in the presence of HIV.[6] Therefore, in the presence of HIV where neurosyphilis is suspected, some reliance may have to be

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placed on histopathology, dark-field microscopy and even the PCR.[25]

The significance of finding a positive VDRL and pleocytosis in the CSF of a patient with HIV and unexplained neurological disease can only be decided by clinical judgement. Both HIV and active syphilis can cause a similar clinical picture because of biological false-positive reagin tests. The TPHA index has been used to diagnose neurosyphilis,[26] and PCR, for *T. pallidum*, is more often positive in patients with neurological signs rather than those without. The significance of this is unclear.[25]

This differentiation is almost academic because high dose antibiotic treatment (see table II) is needed for all patients with syphilis and concurrent HIV infection. However, benzathine benzylpenicillin 2.4MU does not eradicate *T. pallidum* from the CSF in HIV-positive patients with early syphilis[8] and may lead to severe meningovascular disease.[27,28]

7. Treatment Outcome

Rothenberg[29] determined the status of patients who had been treated for neurosyphilis (treatment ranged from a total of 600 000U to 36MU of benzylpenicillin) at a follow-up point of 6 months to 15 years after treatment from 24 studies. About 75% of patients were cured, improved or stabilised. The conditions treated were general paresis or taboparesis (10 studies), tabes dorsalis (6 studies) and meningovascular meningitis (8 studies). There was no correlation between dosage used and outcome.

After treatment, CSF protein and pleocytosis should revert to normal over a number of months or 1 or 2 years. The VDRL titre should fall significantly, but may remain reactive even when the disease is no longer active. Relapse of CSF abnormalities have not been reported more than 2 years after reversion to normal. Luger and colleagues[9] consistently found that cured or 'burnt out' neurosyphilis yielded a TPHA index of less than 100 (i.e. clinical cure). The fixed clinical deficits that remain after presumed bacteriological cure include impaired reflexes, abnormal pupillary reflexes, lightening pains, sensory ataxia, optic atrophy and hearing loss. The symptoms or signs that may progress are Charcot's joints, lightening pains and optic atrophy.

Unfortunately, studies detailing neurological progression have not controlled for neurological change, i.e. a nonsyphilitic group of matched patients has not been included. Wilner and Brody[30] followed patients with general paresis after treatment for 30 years and found that 30% developed new neurological signs. The significance of these are unclear and the post-mortem studies available suggest that there is no active neurosyphilis in such patients.[30]

In the case of neurosyphilis in the presence of HIV, CSF abnormalities such as raised protein level and pleocytosis may suggest active neurosyphilis or HIV disease. Clinical judgement is needed as to when to retreat such patients. The TPHA index may be useful in this case, being less than 100 in inactive or non-neurological syphilis in the presence of HIV, probably indicating that patients do not need treatment.[26] PCR on the CSF to detect *T. pallidum* DNA may be oversensitive and remain positive in the absence of active infection.

8. Jarisch-Herxheimer and Procaine Reactions

The Jarisch-Herxheimer reaction can occur within 12 hours of commencing treatment for neurosyphilis. This reaction is characterised by swelling of inflammatory tissue associated with neurosyphilis as well as shivering, an increase in body temperature and pulse, and hyperventilation, followed by a hypotensive flush phase with subsquent recovery.

Systemic steroids (prednisolone 40 mg/day starting 36 hours prior to treatment) have been advocated to control exacerbation of signs and symptoms of neurosyphilis associated with the reaction, e.g. psychotic symptoms in general paresis. However, new cranial nerve lesions have appeared after giving systemic steroids before penicillin is started in patients with meningovascular

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disease and, therefore, some authors do not recommend steroid usage.

Meptazinol, a partial opiate agonist, has been used successfully to diminish the Jarisch-Herxheimer reaction in patients with relapsing fever.[31] In patients in whom general paresis is associated with the reaction, symptomatic control with phenothiazines or benzodiazepines may be used.

The procaine reaction is an almost instantaneous short-lived psychotic reaction to the administration of the drug, in which the patient feels 'they are dying'. The patient needs to be restrained and reassured.

9. Other Treatment Issues

9.1 Contact Tracing

Meningovascular neurosyphilis may be a characteristic of untreated secondary syphilis, and so sexual contacts of the patient over the previous 2- to 3-year period should be traced. Tertiary neurosyphilis is noninfectious, and discretion and tact should be used so as not to cause family disruption and the accusation of recent infidelity.

9.2 Psychological Sequelae of the Diagnosis of Neurosyphilis

In spite of syphilis no longer being the fearful scourge it once was, it is not uncommon for patients to be devastated when they learn they have syphilis. Counselling must be part of the treatment of neurosyphilis, to ensure that the patient has come to terms with the diagnosis, treatment and implications of the condition.

10. Conclusions

In the antibiotic and HIV era, syphilis that affects the nervous system can cause a clinical picture that is not typical of those described in the classical texts. Keeping updated on the literature and a divergent mind on therapeutic options are necessary to ensure that patients with neurosyphilis are adequately followed up both physically and psychologically.

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