Neurosyphilis : Current Understandings

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Abstract

Neurosyphilis is neurological complication of syphilis, a sexually transmitted disease caused by infection of Treponema pallidum. In pre-antibiotic era, it was considered almost incurable condition. After the introduction of penicillin for treatment, survival dramatically improved. Recently, upsurge is seen in neurosyphilis especially in Human Immunodeficiency Virus (HIV) infected patients and homosexual population. In current scenario, concurrent HIV and syphilis infections poses a major challenge as both conditions have similar modes of transmission and risk factors. Development of neurosyphilis is more common in HIV infected syphilis patients than non-HIV infected patients and presence of syphilis poses a negative impact on viral load (increases viral load) in HIV infected patients which further enhances the transmission of HIV.

Introduction

Neurosyphilis is neurological complication of syphilis, a sexually transmitted disease caused by infection of Treponema pallidum. Most of the neurological complications are thought to occur late after primary syphilitic infection. But, neurosyphilis can occur early as well as late in the syphilis. There are evidences which suggest that involvement of nervous system by disease process occurs early in the syphilis (within days to weeks).

In pre-antibiotic era, neurosyphilis was considered almost incurable condition. People used to think that it was sent from the God as a punishment to the mankind [1]. Before the advent

of penicillin, a number of therapies (some of them were very bizarre) were used for the management of this condition including mercury, arsenicals with bismuth, fever therapy (fever induced by malaria) and suspension therapy (suspending patients by their necks in an apparatus) [2,3]. After the introduction of penicillin, treatment and survival dramatically improved. Recently resurgence in incidence of neurosyphilis is seen particularly in HIV patients which compels us to review this condition in changing scenario.

Pathophysiology of neurosyphilis

After primary infection of Treponema pallidum, partial immunity develops which is insufficient to eradicate the bacteria from the human body. This results in persistent latent infection in some patients. There are evidences which suggest that invasion of nervous system occurs very early. In around 25% of untreated patients, the bacteria can be seen in cerebrospinal fluid (CSF) in the early syphilis [4].

After the initial invasion, course may vary in individual patients depending upon the host factors and the virulence of strain. In some patients, spontaneous resolution occurs without any inflammatory reaction. In others, transient meningitis may develop which may resolve spontaneously. In some others, persistent meningitis may develop if organism was not cleared from the CSF. These patients may have asymptomatic meningitis. It has been demonstrated that higher the abnormality seen in the CSF in asymptomatic meningitis, higher the chances of developing symptomatic neurosyphilis later.

Changing epidemiology

In pre-antibiotic era, neurological complications of syphilis were very common and used to be seen in about one third of patients. At that time, one third used to have asymptomatic neurosyphilis and another one third used to have tabes dorsalis [5]. Around 10% used to have general paresis and in about the same proportion, meningovascular syphilis was seen. Other forms of neurosyphilis were less common and was seen in remaining proportions.

In current era, due to wide use of antibiotics, late complications of syphilis including neurosyphilis are uncommon. Tabes dorsalis, once the most common form of neurosyphilis, is now rarely seen. Now-a-days, neurosyphilis is seen mostly in homosexual men, most of them are also having concurrent human immunodeficiency virus (HIV) infection [6]. It has also been shown that HIV patients with lower CD4 lymphocyte counts are more likely to develop symptomatic neurosyphilis.

Clinical presentations of neurosyphilis

Neurosyphilis can affect the meninges, parenchyma of brain and spinal cord and vessels. On the basis of duration between neurological presentation following the primary infection, neurosyphilis can be categorized as early and late neurosyphilis. Early complications include asymptomatic meningitis, symptomatic meningitis and meningovascular syphilis. Late neurosyphilis includes general paresis of insane and tabes dorsalis. Ocular syphilis (posterior uveitis and panuvieitis) and otitic syphilis (hearing loss with or without tinnitus) can occur early as well as late.

Asymptomatic meningitis: Patient does not have any symptom or sign suggestive of neurological involvement but CSF examination is abnormal. It occurs within weeks to months after the primary

infection. It is rare after two years of initial infection. Sometimes patient may have symptoms and signs suggestive of simultaneous primary or secondary syphilis. The diagnosis is primarily based on abnormal CSF findings which include CSF lymphocytes> 5 cells/microlitre, CSF protein >45 mg/dl and reactive CSF-VDRL (Veneral Disease Research Laboratory) in different combinations. Most of these patients have milder abnormalities i.e. CSF-cells<100 cells/microlitre, protein <100 mg/dl. In HIV negative patients if asymptomatic meningitis is clinically suspected, abnormal CSF findings are considered consistent with the diagnosis even if CSF-VDRL is non-reactive. In HIV positive patients, if CSF-VDRL is non reactive, the diagnosis of asymptomatic meningitis is difficult to substantiate because mild CSF abnormality can also occur due to HIV infection itself.

Symptomatic meningitis: It usually occurs within a year of initial infection but can also occur later. Patient usually presents with headache, nausea, vomiting, confusion and neck stiffness. Fever is uncommon. Cranial nerves involvement is quite common. Common cranial nerves affected are 7th, 8th, 6th and 2nd cranial nerves. Focal meningeal inflammation may turn into diffuse meningitis or it may form syphilitic gummas (focal inflammatory mass lesions adjoining lepto-meninges). Sometimes meningitis may resolve spontaneously. Most of the times, these untreated meningitis patients develop more severe forms of neurosyphilis later. Syphilitic meningitis sometimes may also involve spinal cord and lead to meningomyelitis and present with back pain, weakness, sensory loss and incontinence. In symptomatic meningitis, CSF abnormality is more severe in comparison to asymptomatic meningitis. In these patients, CSF-VDRL is almost always reactive. CSF-cells are in range of 200-400 cells/microl and protein is found in range of 100-200 mg/dl. Cranial or spinal Magnetic Resonance Imaging (MRI) usually shows enhancement of meninges. Cerebral gummas are enhancing lesions contiguous to meninges with associated surrounding oedema [7].

Meningovascular syphilis: Syphilitic meningitis can cause infectious arteritis of any vessel surrounding the brain or spinal cord which may lead to thrombosis and infarction. This can present as an ischemic stroke, especially in young people. Stroke may develop at any time from the initial few months to few years after the primary infection. In the pre-antibiotic era, the mean duration between primary infection and stroke was seven years [5]. Middle cerebral artery is most commonly involved. Rarely, anterior spinal artery may also get involved and patient may develop spinal cord infarction. Some patients develop headache, dizziness, change in behaviour (due to concurrent meningitis) prior to the onset of ischemic stroke. CSF abnormality found in meningovascular syphilis is less severe in comparison to acute meningitis. CSF-cells range from 10-100 cells/microlitre and protein ranges from 100-200 mg/dl. CSF-VDRL is usually reactive but not necessarily in all cases. Vascular abnormalities in form of focal segmental narrowing, focal narrowing and dilatation, or complete occlusion can be visualized on CT/MR/digital subtraction angiography. The findings are non-specific and can be seen in any infectious or non-infectious vasculitis.

General paresis of insane: It is a form of tertiary syphilis and usually occurs 10-25 years after the primary infection but can also occur early occasionally. It is also known as paretic neurosyphilis or dementia paralytica. In pre-antibiotic era, it usually led to death within few years with a mean of 2.5 years. Initially, these patients develop forgetfulness and personality change. Gradually as disease progresses, the severity of symptoms increases and they develop severe dementia. Occasionally patients also develop predominant psychiatric symptoms in form of depression, psychosis or mania. Neurological examination reveals dysarthria, tone abnormality and reflex abnormality. Argyll-Robertson pupil may also be seen. Pupillary abnormality is more consistent with tabes dorsalis. CSF is always abnormal in this condition [8].

Tabes dorsalis: In pre-antibiotic era, this was the most common presentation of neurosyphilis which is now very rare. It usually occurs after 20 years of primary infection but can also occur as early as after three years of primary infection. In this, posterior column of spinal cord and dorsal roots are affected. Clinically patients present with sensory ataxia and lancinating pains. Sensory ataxia causes difficulty in walking especially when eyes are closed. It may lead to frequent falls especially in the dark. The pain occurs in the form of sudden, severe episodes of stabbing pain. It may affect limbs or back and may last for minutes to days. Sometimes patient may develop recurrent attacks of epigastric pain, nausea and vomiting. Bladder dysfunction in the form of urinary retention or overflow incontinence can occur early in the course. Other important clinical features include pupillary irregularities, absent lower limb reflexes, impaired vibratory and joint position sense in feet, optic atrophy. One very important pupillary sign seen in tabes dorsalis, is the Argyll Robertson pupil which is observed in around half of the patients. Argyll Robertson pupil is characterized by small sized pupil which does not respond to light but contracts normally to accommodation and convergence. It also does not dilate in response to painful stimuli and dilates poorly to mydriatics. In tabes dorsalis, CSF examination may be entirely normal or it may show mild lymphocytic pleocytosis (10-50 cells/microl) and mildly raised protein (45-75 mg/dl). In around one fourth of patients, CSFVDRL test may be nonreactive.

Atypical forms of neurosyphilis: Some authors proposed the entity of 'atypical neurosyphilis' for those patients who do not fulfill the clinical criteria for one of the classically described forms neurosyhilis i.e. symptomatic meningitis, meningovascular syphilis, general paresis, and tabes dorsalis. They hypothesized that widespread use of antibiotics for unrelated infection in an undiagnosed syphilis patient may lead to incomplete treatment which further may produce atypical forms or forme fruste of typical syndromes. They reported milder forms and mono-symptomatic clinical presentations e.g. reflex abnormality, sensory abnormality, seizure or pupillary abnormality [9]. There is another school of thought which says that such milder forms were always existed [5] and their proportion has not increased in recent reports.

HIV and neurosyphilis: There are evidences that suggest that HIV infection modulates the clinical presentation of syphilis in form of greater organ involvement, atypical and florid skin rashes.

It may also lead to more rapid progression to neurosyphilis [10]. Status of HIV infection may also affect the results of serologic tests for syphilis. Apart from that, there are also evidences which suggest that simultaneous syphilis infection may lead to increased HIV viral load. The risk factors for developing neurosyphilis in HIV infected patients include CD4 count of <350 cells/microl, RPR (rapid plasma reagin) titer >1:128, and male gender [11].

Diagnosis of Neurosyphilis

Diagnosis of neurosyphilis is established using CSF examination findings and clinical criteria. Cell count (WBCs either polymorphs and/or lymphocytes) of >5/ml, proteins >0.45g/l in CSF or IgG index of >0.6 are indicators of the disease. The findings are nonspecific and have a low sensitivity. These parameters should be carefully interpreted in patients with HIV as the rise in cell count and proteins may be present without the disease.

A single test cannot be used to confirm the diagnosis. Ruling in the diagnosis, relies upon the detection of intrathecal antibodies which can either come via blood brain barrier through circulation or may be produced from plasma cells intrathecally. There are two types of test which can be used for diagnosing neurosyphilis. The non-treponemal tests detect the antiphospholipid antibodies which can be nonspecific while treponemal tests detect the anti-treponemal antibodies. Non-treponemal tests include venereal disease research laboratory (VDRL) and rapid plasma reagin (RPR). Treponemal tests include fluorescent treponemal antibody absorption (FTAABS), treponema pallidum particle agglutination assay (TPPA) and syphilis enzyme immunoassays (EIAs).

Neurosyphilis is confirmed when serum treponemal tests are reactive along with CSF-VDRL [12]. In neurosyphilis especially in tabes dorsalis, the nontreponemal tests may be nonreactive. If there is clinical suspicion of late neurosyphilis, serum treponemal tests i.e. FTA-ABS, TPPA, or syphilis EIA should always be conducted. In patients with syphilis, these tests usually remain reactive, irrespective of previous treatment. If these tests are reactive, it suggests that the patient had syphilis any point of time in his or her life and there is a risk of neurosyphilis in these patients. The diagnostic criteria of neurosyphilis are as follows:

Definite neurosyphilis

1. Positive blood treponemal serology and
2. Positive CSF VDRL

Probable neurosyphilis

1. CSF mononuclear pleocytosis,
2. Neurological signs and symptoms compatible with neurosyphilis,
3. Positive blood treponemal serology and
4. Negative CSF VDRL

Possible neurosyphilis

1. CSF mononuclear pleocytosis,
2. Absent neurological signs and symptoms compatible with neurosyphilis,
3. Positive blood treponemal serology and
4. Negative CSF VDRL

Treatment of neurosyphilis

Centers for Disease Control and Prevention (CDC) has provided guidelines for the treatment of neurosyphilis [13].

1. Aqueous crystalline penicillin G, 18 to 24 million units per day, administered as 3 to 4 million

units intravenous (I/V) every four hours, or 24 million units daily as a continuous infusion for 10 to 14 days, or Procaine penicillin G, 2.4 million units intramuscular (IM) once daily plus probenecid 500 mg orally four times a day, both for 10 to 14 days.

2. An alternative treatment for patients who have a mild penicillin allergy is ceftriaxone 2 g IV or IM daily for 10 to 14 days, with careful observation for crossreactivity [14].

High dose doxycycline 200 mg orally twice a day for 21 to 28 days may also be used as an alternative (still not recommended by the CDC or European guidelines) option [15].

Conclusion

After the introduction of penicillin, there is marked reduction in neurosyphilis. Recently, upsurge is seen in neurosyphilis especially in HIV infected patients and homosexual population [16,17]. In current scenario, concurrent HIV and syphilis infections poses a major challenge as both conditions have similar modes of transmission and risk factors [18]. Apart from that, infection with one condition may enhance the transmission of the other [19,20]. It is very important to keep the possibility of neurosyphilis in patients with HIV and/or homosexual behaviour presenting with neurological problems. Apart from this, now a days, short course antibiotic use is common for various infective indications. This may lead to incomplete treatment in an undiagnosed syphilis patient which may lead to milder atypical forms or forme fruste of typical syndromes. This further complicates the issue and demands high clinical suspicion in relevant clinical scenario.

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