

# Multiple Neurosyphilitic Maladies

Subjects: Biology

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*Treponema pallidum* (*Tp*) subspecies pallidum causes syphilis, a sexually transmitted disease that infects more than 2.1 million pregnant women every year. Due to its maximum death rates of neonates, augmented risk of human immunodeficiency virus (HIV) infection, and continued morbidity particularly in low-income countries as well as in high-income countries, such as Japan, where the rate of cases is increasing at an alarming level in heterosexual men and women, syphilis is a disease of worldwide concern, the disease is still a matter of debate in many low- and high-income countries. The infection has three stages that lead to several complications if left untreated and can lead to many tertiary complications in the brain, eyes, ears, heart, and pregnancy. Principally, the infection is transmitted through sexual contact, exceptionally with blood transfusion and blood products, and transmits vertically from mother to child (Syphilis Transmission from Mother-to-Child (MTCT)) during pregnancy. The *Tp* spirochete transmits vertically to the fetus, leading to congenital syphilis infections in poorly treated or utterly treated pregnant women, and causes multiple clinical manifestations, including stillbirth and neonatal death, skin and visceral manifestations, and other asymptomatic infections. According to the World Health Organization (WHO), a recently published study estimating the burden of congenital syphilis showed more than half a million (almost 661,000) cases of congenital syphilis in 2016, consequently facing 200,000 stillbirths and neonatal deaths. Congenital syphilis is the second leading cause of preventable stillbirth globally, preceded only by "Malaria". Neurosyphilis (NS) is also known as the clinical result of infection of the central nervous system by *Tp* subspecies pallidum. It can evolve at any time and from any stage of syphilis exposure. NS involves all neurological disorders related to nervous system invasion by the *Tp* and can be seen during the primo-secondary (early NS) or tertiary stages. Importantly, NS has two forms: an early form often strikes the CSF, meninges, and vasculature; the late form hits the brain and spinal cord parenchyma, and in several cases, it goes unnoticed or unidentified, leading to multifarious neurological complications.

Keywords: *Treponema pallidum* ; Blood-Brain Barrier ; Neurosyphilitic Meningitis ; Syphilitic Myelitis ; Cerebral Syphilitic Gumma ; Early Syphilitic Complication ; Asymptomatic/Symptomatic Syphilis

## 1. Neurosyphilitic Meningitis or Syphilitic Meningitis/Meningovascular Syphilis (MVS)

Chronic and long-term disease and clinical outcomes of infection of the CNS by *Tp* can occur during any stage of neurosyphilitic meningitis. Approximately 30% of untreated syphilis cases have led to complications in neurology and psychiatry for the last two centuries <sup>[1][2]</sup>. Nevertheless, modern NS epidemiology is still not well-described because of the lack of data based on population. NS infections have been primarily identified in HIV patients <sup>[3]</sup>, but there have been cases in non-HIV patients. For example, these patients have had both symptomatic and asymptomatic syphilis, and the form of meningitis, with space-occupying gummas, vasculitis, strokes, cranial neuropathy, myelopathy, dementia, and seizures is hard to diagnose <sup>[3][4]</sup>. Asymptomatic neurosyphilis (ASN) is a type of CNS infection in which patients have confirmed syphilis and have a CSF pleocytosis event (an increase in WBC count in the CSF) but are neurologically asymptomatic. ASN patients with constant infection or without medication are at high risk for disease progression toward symptomatic neurosyphilis (SNS; 35% of ASN patients evolve SNS with the natural progression <sup>[5]</sup>), notably with symptomatic syphilitic meningitis, MVS, intracranial gummas, general paresis, and tabes dorsalis <sup>[2]</sup>. Syphilitic meningitis comprises meningeal irritability and increases intracranial pressure, causing headaches, back pain, neck pain, vision problems, nausea, and vomiting before antibiotic discovery. According to Merritt, CSF was classified into three primary forms—hydrocephalic, vertical, and basilar—to classify syphilitic meningitis <sup>[6]</sup>. Untreated syphilis appears in the secondary and later stages of the infection and implicates all nervous system elements with brain disorders, spinal cord, and cranial and peripheral nerves. With the arrival of antibiotic treatments, NS has relocated its clinical demonstration from chronic and delayed forms, including the CNS parenchyma, to an older way to affect the meninges and CNS blood vessels. These are an unusual pathological representation of inboard NS, MVS, or meningovascular neurosyphilis <sup>[1][6][7]</sup>. MVS is a distinct form of NS described by a meningo-encephalopathic syndrome with superimposed cerebrovascular or

myelovascular incidents and a fusion of chronic syphilitic meningitis and arthritis. MVS is an infection associated with inflammatory arteriopathy, causing outgoing damage to the blood vessels of the leptomeninges, brain, and spinal cord, leading to necrosis [8][9]. MVS can lead to dementia responsible for vascular dementia or hydrocephalus by clogging CSF permeation. The reason for syphilitic dementia is parietic neurosyphilis (or dementia paralytica, or general paralysis of the insane, or general paresis) [10].

## 2. Syphilitic Myelitis (SM)

Syphilitic myelitis (SM) is a rare manifestation of NS caused by *Tp*. One-third (more than 30%) of early syphilitic patients have CNS manifestations. Recently, the reemergence of syphilis has been seen together with an increment in NS. Nevertheless, symptomatic syphilis, particularly SM and its clinical symptoms, has been occasionally mentioned, and fewer cases have been registered. Initial treatment and diagnosis are vital, as it demonstrates that myelopathy has a curable and perhaps irregular cause [11]. Unfortunately, most cases of SM are misdiagnosed, and there are not many research data available. Some articles describe its clinical manifestations and neuroimaging characteristics, but there are no consistent data on prognosis with long-term follow-up [12][13].

## 3. Cerebral Syphilitic Gumma (CSG)

A gumma is also known as granuloma and is formed during inflammation (immune response against foreign particles or microorganisms). Macrophages do not eliminate chronic disease [14][15]. If the pathogens can be removed, the gumma's progression can be comprehensively cellular but can sustain growth if its antigens persist. The surrounding epithelial cells vary in lymphocytes in number, macrophages, plasma cells, fibroblasts, and connective tissue scarring, depending on the lesion's progress stage. The gumma is a highly typical lesion of tertiary syphilis [14] that guides CSG as a demonstration of NS and is recognized to be infrequently included in the brain (first reported by Botalli in 1563 [16]). Due to its rare and miscellaneous features on imaging, CSG is mostly misdiagnosed, is comfortably confused with a brain tumor, and can be seen on any body part; misdiagnosis makes CSG identification difficult [17][18][19]. CSG is the consequence of the cellular immune response secondary to *Tp* invasion. Generally, it grows from the dura and pia mater (cerebro meningeal). Macroscopically, CSG is discovered as soft, well-defined lesions. It is considered a nonspecific, chronic inflammatory infiltrate, and the formation of an inflammatory "tumor-like" granulation possessing lymphocytes and plasma cells; abnormally, CSG intracerebral determines the problem of differential diagnosis with a malignant cerebral tumor [19][20]. Secret invasion, headache, nausea, and vomiting are the general clinical manifestations of CSG. The pathological signs of CSG are similar to tuberculosis, which comprises sizeable inflammatory intrusion of lymphocytes, plasma cells, and central caseous necrosis edged by epithelioid cells, multinucleated giant cells, and lymphocytes with intimal hyperplasia and peripheral arterial inflammation. CSG can be separated into multiple intracranial lesions growing from the meninges, with asymmetrical growth and surrounding edema that nearly resembles a brain tumor. CSG is infrequently misdiagnosed as a brain neoplasm, which requires surgery [16].

## 4. Atypical Behavior and Neuropsychiatric Symptoms in NS

Neurology and psychiatry both fight to employ disorders that evade different classifications. NS is one of the most extensive and deadly forms of degenerative mental complications. Neuropsychiatric symptoms of syphilis habitually occur in the late stage, representing tertiary syphilis, presumed as general paresis, also known as general paralysis of the insane paralytic dementia or meningoencephalitis—an outcome of direct *Tp* invasion into the brain [21][22][23][24][25]. Initial symptoms comprise memory loss, irritability, insomnia, and personality change. A developing dementia malady can grow over many years and lasts as confusion and disorientation, loss of judgment, seizures, and psychiatric symptoms, such as depression, mania, and psychosis. A physical check-up can be expected, but patients generally display various complications. Among them are dysarthria, hypomimia, limb hypotonia, facial and limb intention tremor, hyperreflexia, tabes dorsalis, sensory ataxia, and Argyll Robertson pupils, a small number of these mimic early-onset Alzheimer's disease [26][27][28]. Cases are mentioned in **Table 1**.

**Table 1.** Reported cases of multiple disorders in neurosyphilitic patients.

Complication	Disorders	Case Report/References
Neurosyphilitic Patients	Attention Deficit Disorder	[29]
	Anger/Violent Behavior	[30][31][32]
	Anxiety	[30]
	Bipolar Disorder	[33]
	Behavioral/Neuropsychiatric Changes	
	Complex Condition	[34]
	Drug/Alcohol	[35][36][37]
	Dissociative Disorder	[38]
	Hearing Disorder	[39][40][41]
	Hormonal Disabilities	[42][43]
	Memory Loss and Dementia	[44][45][46]
	Psychotic Mania and Hypomania	[33][47]
	Panic Disorder	
	Personality Disorder	[32]
	Post-Traumatic Disorder	
	Sleep Disorder/Insomnia	[48][49]
	Suicidal Thoughts	[30]
	Traumatic Brain Injury	
	Trigeminal Nerve Dysfunction	[50]
	Weight Loss	[51]

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