Multiple Neurosyphilitic Maladies

Subjects: Biology

Contributor: Arun Kumar Jaiswal , Syed Babar Jamal , Lucas Gabriel Rodrigues Gomes , Rodrigo Profeta , Helioswilton Sales-Campos , Carlo Oliveira , Flavia Aburjaile , Sandeep Tiwari , Debmalya Barh , Marcos Vinicius da Silva , Siomar Soares , Vasco Azevedo

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.

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 [1][2]. 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 [3], 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 [3][4]. 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. ANS patients with constant infection or without medication are at high risk for disease progression toward symptomatic neurosyphilis (SNS; 35% of ANS patients evolve SNS with the natural progression [5]), notably with symptomatic syphilitic meningitis, MVS, intracranial gummas, general paresis, and tabes dorsalis [2]. 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 [6]. 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 [1][6][7]. 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 paretic 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]

Complication	Disorders	Case Report/References
	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]

References

1. Ropper, A.H. Neurosyphilis. N. Engl. J. Med. 2019, 381, 1358–1363.
2. Li, W.; Jiang, M.; Xu, D.; Kou, C.; Zhang, L.; Gao, J.; Qin, K.; Wu, W.; Zhang, X. Clinical and Laboratory Characteristics of Symptomatic and Asymptomatic Neurosyphilis in HIV-Negative Patients: A Retrospective Study of 264 Cases. BioMed Res. Int. 2019, 2019, 2426313.
3. Barragán, E.P.; Hernández, E.U.; Orozco, B.P.; González, M.S. Meningovascular neurosyphilis with basilar artery thrombosis in HIV patient. J. Infect. Public Health 2018, 11, 439–441.
4. Ahsan, S.; Burrascano, J. Neurosyphilis: An Unresolved Case of Meningitis. Case Rep. Infect. Dis. 2015, 2015, 634259.
5. Pastuszczak, M.; Zeman, J.; Jaworek, A.K.; Wojas-Pelc, A. Cerebrospinal Fluid Abnormalities in HIV-Negative Patients with Secondary and Early Latent Syphilis and Serum VDRL ≥ 1:32. Indian J. Dermatol. 2013, 58, 325.
6. Gonzalez, H.; Koralnik, I.J.; Marra, C.M. Neurosyphilis. Semin. Neurol. 2019, 39, 448–455.

7. Zamora, J.A.G.; Espinoza, L.A.; Nwanyanwu, R.N. Neurosyphilis with Concomitant Cryptococcal and Tuberculous Meningitis in a Patient with AIDS: Report of a Unique Case. Case Rep. Infect. Dis. 2017, 2017, 4103858.
8. Ha, T.; Tadi, P.; Dubensky, L. Neurosyphilis. In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2021.
9. Thibodeau, R.; Goel, A.; Jafroodifar, A.; Klumpp, M.; Mirchia, K.; Swarnkar, A. Cerebral syphilitic gumma presenting with intracranial gumma and pathologic vertebrae fractures. Radiol. Case Rep. 2021, 16, 916–922.
10. Nitrini, R.; de Paiva, A.R.B.; Takada, L.T.; Brucki, S.M.D. Did you rule out neurosyphilis? Dement. Neuropsychol. 2010, 4, 338–345.
11. Yuan, J.-L.; Wang, W.-X.; Hu, W.-L. Clinical features of syphilitic myelitis with longitudinally extensive myelopathy on spinal magnetic resonance imaging. World J. Clin. Cases 2019, 7, 1282–1290.
12. Wu, Y.; Wu, W. Neurosyphilis presenting with myelitis-case series and literature review. J. Infect. Chemother. 2020, 26, 296–299.
13. Dong, H.; Liu, Z.; Duan, Y.; Li, D.; Qiu, Z.; Liu, Y.; Huang, J.; Wang, C. Syphilitic meningomyelitis misdiagnosed as spinal cord tumor: Case and review. J. Spinal Cord Med. 2019, 44, 789–793.
14. Carlson, J.A.; Dabiri, G.; Cribier, B.; Sell, S. The immunopathobiology of syphilis: The manifestations and course of syphilis are determined by the level of delayed-type hypersensitivity. Am. J. Dermatopathol. 2011, 33, 433–460.
15. Daumas, A.; Coiffard, B.; Chartier, C.; Amara, A.B.; Alingrin, J.; Villani, P.; Mege, J.-L. Defective Granuloma Formation in Elderly Infected Patients. Front. Cell. Infect. Microbiol. 2020, 10, 189.
16. Cui, L.; Liu, J.; Zhang, W.; Xu, Z.; Hou, H. The Application of MR Spectroscopy and MR Perfusion in Cerebral Syphilitic Gumma: A Case Report. Front. Neurosci. 2020, 14, 544802.
17. Weng, C.; Huang, K.; Jiang, T.; Zhou, G.; Wu, T. Cerebral syphilitic gumma masquerading as cerebral metastatic tumors: Case report. Neurosurg. Focus 2019, 47, E15.
18. Ying, S.; Li-Min, L. Cerebral syphilis mimicking metastatic tumors: Report and review of the literature. Neurol. India 2018, 66, 1170.
19. Barahona, E.A.; Olvera, J.L.N.; Liquidano, M.A.E.; Cobos, A.M.; Arroyo, Á.D.R.; Apo, E.G. Left temporal cerebral syphilitic gumma: Case report and literature review. Rev. Médica Del Hosp. Gen. México 2017, 80, 119–124.
20. Mejdoubi, A.; Khoulali, M.; Raouzi, N.; Nasri, S.; Mebrouk, Y.; Oulali, N.; Moufid, F. Neurosyphilis revealed by compressive cervical spine syphilitic gumma: A case report. Spinal Cord Ser. Cases 2020, 6, 56.

21. Beauchemin, P.; Laforce, R. Neurocognitive Changes in Tertiary Neurosyphilis: A Retrospective Chart Review. Can. J. Neurol. Sci. 2014, 41, 452–458.
22. Crozatti, L.L.; de Brito, M.H.; Lopes, B.N.A.; de Campos, F.P.F. Atypical behavioral and psychiatric symptoms: Neurosyphilis should always be considered. Autops. Case Rep. 2015, 5, 34–47.
23. Wang, Y.; Shi, H.; Hou, L.; Zhong, X.; Chen, X.; Li, L.; Wu, Z.; Zheng, D.; Zhang, Y.; Tan, Y.; et al. Clinical and neuropsychological characteristics of general paresis misdiagnosed as primary psychiatric disease. BMC Psychiatry 2016, 16, 230.
24. Swain, K. 'Extraordinarily arduous and fraught with danger': Syphilis, Salvarsan, and general paresis of the insane. Lancet Psychiatry 2018, 5, 702–703.
25. Sharma, S.R.; Hussain, M.; Roy, D. General Paresis of Insane: A Forgotten Entity. Neurol. India 2020, 68, 487.
26. Read, P.J.; Donovan, B. Clinical aspects of adult syphilis. Intern. Med. J. 2012, 42, 614–620.
27. Antunes, A.P.; Dias, M.C.; Verdelho, A. Neuropsychiatric Symptoms in Reversible Dementias; Springer International Publishing: Basel, Switzerland, 2017; pp. 93–139.
28. Mehrabian, S.; Raycheva, M.; Traykova, M.; Stankova, T.; Penev, L.; Grigorova, O.; Traykov, L. Neurosyphilis with dementia and bilateral hippocampal atrophy on brain magnetic resonance imaging. BMC Neurol. 2012, 12, 96.
29. Chen, M.H.; Hsu, J.W.; Huang, K.L.; Bai, Y.M.; Ko, N.Y.; Su, T.P.; Li, C.T.; Lin, W.C.; Tsai, S.J.; Pan, T.L.; et al. Sexually Transmitted Infection Among Adolescents and Young Adults With Attention-Deficit/Hyperactivity Disorder: A Nationwide Longitudinal Study. J. Am. Acad. Child Adolesc. Psychiatry 2018, 57, 48–53.
30. Saini, H.S.; Sayre, M.; Saini, I.; Elsharkawy, N. Neurosyphilis Presenting as Intermittent Explosive Disorder and Acute Psychosis. Cureus 2019, 11, e6337.
31. De Bruijn, S.; Kenyon, C.; Léonard, N.; Vlieghe, E. The big imitator strikes again: A case report of neurosyphilis in a patient with newly diagnosed HIV. Acta Clin. 2017, 72, 372–374.
32. Prynn, J.; Hussain, A.; Winnett, A. Diagnosing neurosyphilis: A case of confusion. BMJ Case Rep. 2016, 2016, bcr2016216582.
33. Seo, E.H.; Yang, H.J.; Kim, S.H.; Park, J.H.; Yoon, H.-J. Psychotic mania as the solitary manifestation of neurosyphilis. Ann. Gen. Psychiatry 2018, 17, 24.
34. Neetu, R.; Sukhani, P.K.; Dubey, R. Neurosyphilis—A Forgotten Disease: Case Reports with Ten Years Follow-Up and Review of Literature. Neurol. India 2020, 68, 889–893.
35. Nguyen, A.; Berngard, S.C.; Lopez, J.P.; Jenkins, T.C. A Case of Ocular Syphilis in a 36-Year-Old HIV-Positive Male. Case Rep. Infect. Dis. 2014, 2014, 352047.

36. Muylaert, B.; Almeidinha, Y.; Borelli, N.; Esteves, E.; Oliveira, A.R.; Cestari, M.; Garbelini, L.; Eid, R.; Michalany, A.; De Oliveira Filho, J. Malignant syphilis and neurosyphilis in an immunocompetent patient. J. Am. Acad. Dermatol. 2016, 74, AB152.
37. Su, S.; Mao, L.; Zhao, J.; Chen, L.; Jing, J.; Cheng, F.; Zhang, L. Epidemics of HIV, HCV and syphilis infection among synthetic drugs only users, heroin-only users and poly-drug users in Southwest China. Sci. Rep. 2018, 8, 6615.
38. Boyle, A.; Zafar, R.; Riley, V.; Lindesay, J. Neurosyphilis presenting with dissociative symptoms. J. Neurol. Neurosurg. Psychiatry. 1995, 59, 452–453.
39. Borges, C.R.; de Almeida, S.M.; Sue, K.; Koslyk, J.L.A.; Sato, M.T.; Shiokawa, N.; Teive, H.A.G. Neurosyphilis and ocular syphilis clinical and cerebrospinal fluid characteristics: A case series. Arq. De Neuro-Psiquiatria. 2018, 76, 373–380.
40. Arain, Z.; Abbas, Y.; Adams, A. Pediatric otosyphilis—An unusual cause of conductive hearing loss. Radiol. Case Rep. 2020, 15, 65–70.
41. De Goffau, M.J.; Doelman, J.C.; van Rijswijk, J.B. Unilateral sudden hearing loss due to otosyphilis. Clin. Pract. 2011, 1, 296–298.
42. Eren, F.; Aygül, R.; Ekmekci, H.; Öztürk, Ş. Neurosyphilis Presenting with Ptosis and Diplopia as the First Complaints: Case Report. Turk. J. Neurol. 2018, 24, 330–333.
43. Pozzobon, T.; Facchinello, N.; Bossi, F.; Capitani, N.; Benagiano, M.; di Benedetto, G.; Zennaro, C.; West, N.; Codolo, G.; Bernardini, M.; et al. Treponema pallidum (syphilis) antigen TpF1 induces angiogenesis through the activation of the IL-8 pathway. Sci. Rep. 2016, 6, 18785.
44. Akinci, E.; Oncu, F.; Topcular, B. Neurosyphilis in Psychiatric Settings: Three Case Reports. Turk. J. Psychiatry 2016, 28, 61–66.
45. Tatar, Z.B.; Cansiz, A.; Köksal, A.; Kurt, E. A Case of Neurosyphilis Presenting with Dementia and Psychiatric Symptoms. J. Neuropsychiatry Clin. Neurosci. 2014, 26, E39–E40.
46. Blažeković, A.; Ozretić, D.; Habek, M.; Bilić, E.; Borovečki, F. Neurosyphilis: The shape of a rising threat. Int. J. Infect. Dis. 2018, 76, 1–3.
47. Chen, S.F.; Wang, L.Y.; Chiang, J.H.; Shen, Y.C. Bipolar Disorder Is Associated With an Increased Risk of Sexually Transmitted Infections: A Nationwide Population-based Cohort Study. Sex. Transm. Dis. 2018, 45, 735–740.
48. Ghanem, K.G. Review: Neurosyphilis: A Historical Perspective and Review. CNS Neurosci. Ther. 2010, 16, e157–e168.
49. Lin, L.-R.; Zhang, H.-L.; Huang, S.-J.; Zeng, Y.-L.; Xi, Y.; Guo, X.-J.; Liu, G.-L.; Tong, M.-L.; Zheng, W.-H.; Liu, L.-L.; et al. Psychiatric Manifestations as Primary Symptom of Neurosyphilis Among HIV-Negative Patients. J. Neuropsychiatry Clin. Neurosci. 2014, 26, 233–240.

50. Medeiros, L.J.D.; Marchiori, E.; Bahia, P.R.V. Neurosyphilis manifesting as trigeminal nerve dysfunction. Rev. Soc. Bras. Med. Trop. 2018, 51, 404.
51. Bezalely, S.; Jacob, G.; Flusser, G.; Ablin, J. Syphilis: An unusual manifestation? Case Rep. 2014, 2014, bcr2014204871.