



Psychiatric Manifestations in a Patient with Neurosyphilis – The Role of Antibiotic Treatment by Benzathine Penicillin G

Dear Editor,

Syphilis infection, caused by the spirochete *Treponema pallidum*, is known as the “great imitator” due to its varied manifestations.¹ Neurosyphilis, which can present with symptoms such as poor vision, seizures, stroke, confusion, and personality changes, might be so subtle as to be overlooked.² Despite the widespread use of penicillin to treat syphilis, the incidence of syphilis has been steadily increasing over the past decade in both the United States and Taiwan.^{3,4} These trends highlight the significant resurgence of syphilis infections, underscoring the importance of continued vigilance and awareness of this ancient yet highly variable bacterium. Hereby, we report a case of a patient with neurosyphilis presenting with psychotic symptoms and cognitive deficits, and the effects of antibiotic treatment.

A 78-year-old female with a history of a major depressive disorder, receiving escitalopram 5 mg/day, visited our psychiatric clinic because of incoherent and irrelevant speech, tinnitus, and poor recent memory for about 2 months. Tests for hepatitis A virus, hepatitis B virus, hepatitis C virus, and HIV were all negative. The rapid plasma reagin (RPR) test (1:4) and *T. pallidum* particle agglutination assay (1:640) were positive. Given the abrupt onset and the positive RPR test, she was diagnosed with minor neurocognitive disorder due to another medical condition (neurosyphilis). After consultation, the infectious medicine specialist prescribed intramuscular (IM) benzathine penicillin G 7.2 million units for her latent syphilis, administered in 3 weekly doses of 2.4 million each. She continued her monthly follow-up at neurology outpatient clinic. Following treatment, her speech impairment resolved and recent memory (three-item recall), abstract thinking, and calculation abilities improved.

Three years later, at the age of 81, she experienced tinnitus, anxiety, and progressive cognitive decline for about 2 months. In addition, auditory hallucination and nihilistic delusion were noted for 2 weeks before her visit to our psychiatric outpatient department. Her Mini-Mental State Examination (MMSE) score was 19 out of 30. The patient was disoriented to place and person, with impaired registration, attention and calculation. The remainder of her neurologic examination was normal. Blood tests including electrolytes, hepatic, renal, and thyroid function were normal. Folate and Vitamins B12 were both beyond the upper limit of normal. The HIV test was negative, but the RPR test (1:4) and chemiluminescence immunoassays (index value =27.5) were both positive. The

infectious medicine specialist recommended three doses of IM benzathine penicillin of 2.4 million units per week. All the psychotic symptoms improved by the end of the treatment and her MMSE score recovered to 25 out of 30 a week after the antibiotic treatment. During follow-up at the neurology outpatient clinic for 3 years, she was free of psychosis and scored 27 out of 30 on the MMSE at the age of 84 years.

The incidence of syphilis declined substantially after the introduction of penicillin. However, it has been increasing over the past decade in both the United States and Taiwan. In Taiwan, the incidence rate rose from 28.7 / 100,000 population in 2011 to 37.1 / 100,000 population in 2016, with an average annual increase of 5.5%. In the United States, the total syphilis incidence increased from 35.1 / 100,000 population in 2018 to 62.0 / 100,000 population in 2022.⁴ Notably, the incidence of unknown duration or late syphilis reported cases nearly doubled, from 12.2 / 100,000 population in 2018 to 26.2 / 100,000 population in 2022, representing an increase of almost 80%.³ These trends underscore the importance of continued vigilance and awareness of syphilis, particularly in the context of its varied and often subtle presentations.

Previous research indicates that approximately 30.8% of patients with neurosyphilis exhibit psychiatric manifestations.⁵ Common presentations include personality changes (76%), memory impairment (62%), hostility (52%), hallucinations (48%), and delusions (19%).⁶ These psychiatric symptoms are not directly caused by the cytotoxic effects of *T. pallidum* but rather by immunological and inflammatory responses.⁷ One hypothesis suggests that oxidative stress, altered tryptophan catabolism, and homocysteine metabolism modifications contribute to these symptoms.⁸ Notably, a case study by Hung *et al.* reported successful resolution of auditory hallucinations and religious delusions in a neurosyphilis patient treated with penicillin alone.⁹ In addition, a recent cohort study found that 90% of otosyphilis patients experienced hearing loss, 73% had tinnitus, and 53% had vertigo.¹⁰

Symptomatic and asymptomatic neurosyphilis are typically treated with aqueous penicillin for 10–14 days. The standard regimens include intravenous aqueous crystalline penicillin G, administered at 18–24 million units per day (3–4 million units every 4 h), or IM aqueous procaine penicillin G, combined with oral probenecid (500 mg four times a day), at a dose of 2.4 million units per day.^{11,12} These regimens are preferred due to their efficacy in achieving therapeutic levels in the cerebrospinal fluid. In this case, the patient was treated with

penicillin G benzathine, 2.4 million units IM once weekly for 3 weeks, which is the recommended regimen for latent syphilis. Although this regimen is effective for latent syphilis, it is not the first-line treatment for neurosyphilis.

According to the new guidelines published in 2021, lumbar puncture is no longer recommended for follow-up in controlled HIV patients or immunocompetent patients.¹³ In this case, the patient's auditory hallucinations resolved and cognitive decline improved, and she received regular follow-up at our neurology clinic after antibiotic treatment.

Given the increasing incidence of syphilis and neurosyphilis, it is essential to remain vigilant and consider these treatment protocols to manage and prevent the resurgence of this infection effectively. This case underscores the importance of recognizing and treating neurosyphilis, even in the era of widespread antibiotic use.

In conclusion, this case could serve as a reminder of how crucial it is to consider neurosyphilis symptomatology even in a patient with a previous psychiatric diagnosis. It is important for a psychiatrist to be more watchful when evaluating syphilis screening tests and take neurosyphilis into consideration as a differential diagnosis of mild cognitive impairment so as to enhance the therapeutic strategy for elderly patients and prevent the potentially irreversible complications it can cause.

Ethical approval statement

This study proposal was approved by the Institutional Review Board of Tri-Service General Hospital (IRB# C202215036) (May 26, 2022). The study was conducted in accordance with the Declaration of Helsinki.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

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REFERENCES

1. Saini HS, Sayre M, Saini I, Elsharkawy N. Neurosyphilis presenting as intermittent explosive disorder and acute psychosis. *Cureus* 2019;11:e6337.7.
2. Ropper AH. Neurosyphilis. *N Engl J Med* 2019;381:1358-63.
3. Prevention USCFDCa. CDC's 2022 STI Surveillance Report Underscores that STIs Must be a Public Health Priority; 2024. Available from: <https://www.cdc.gov/std/statistics/2022/default.htm>. [Last accessed on 2024 Aug 07].
4. Lai SK, Chen CM, Kuo HW, Liu DP. Epidemiology of syphilis and Gonorrhea in Taiwan, 2005-2016. *Epidemiol Bull* 2017;33:159.
5. Lin LR, Zhang HL, Huang SJ, Zeng YL, Xi Y, Guo XJ, *et al*. Psychiatric manifestations as primary symptom of neurosyphilis among HIV-negative patients. *J Neuropsychiatry Clin Neurosci* 2014;26:233-40.
6. Roberts MC, Emsley RA. Psychiatric manifestations of neurosyphilis. *S Afr Med J* 1992;82:335-7.
7. Ho EL, Lukehart SA. Syphilis: Using modern approaches to understand an old disease. *J Clin Invest* 2011;121:4584-92.
8. Bransfield RC. The psychoimmunology of lyme/tick-borne diseases and its association with neuropsychiatric symptoms. *Open Neurol J* 2012;6:88-93.
9. Hung HC, Chu JL, Lu T. Psychotic disorder due to neurosyphilis. *J Neuropsychiatry Clin Neurosci*

- 2013;25:E67-8.
10. Yimtae K, Srirompotong S, Lertsukprasert K. Orosyphilis: A review of 85 cases. *Otolaryngol Head Neck Surg* 2007;136:67-71.
 11. Arando Lasagabaster M, Otero Guerra L. Syphilis. *Enferm Infecc Microbiol Clin (Engl Ed)* 2019;37:398-404.
 12. Marra CM. Neurosyphilis. *Continuum (Minneapolis Minn)* 2015;21:1714-28.
 13. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, *et al.* Sexually transmitted

infections treatment guidelines, 2021. *MMWR Recomm Rep* 2021;70:1-187.

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