EJCRIM
European Journal of Case Reports in Internal Medicine

SHOULD THE TRADITIONAL ALGORITHM FOR SYPHILIS SCREENING BE ABANDONED? NEUROSYPHILIS PRESENTING AS LIMBIC ENCEPHALITIS: A PROZONE FALSE-NEGATIVE RPR MISSED BY AN RPR-ONLY INITIAL SCREEN

Hidenori Sanayama[1], Yuka Hayashi[2], Takahiko Fukuchi[1]

[1] Division of General Medicine, Department of Comprehensive Medicine 1, Jichi Medical University Saitama Medical Center, Saitama, Japan
[2] Division of Neurology, Department of Comprehensive Medicine 1, Jichi Medical University Saitama Medical Center, Saitama, Japan

Corresponding author's e-mail: sanayama@jichi.ac.jp

Received: 26/08/2026
Accepted: 07/09/2026
Published: 28/09/2026

Conflicts of Interests: The Authors declare no conflict of interest.
Patient Consent: Written informed consent was obtained from the patient for the publication of their clinical history, diagnostic findings, and any accompanying images. A signed consent form is on file and available upon request.
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How to cite this article: Sanayama H, Hayashi Y, Fukuchi T. Should the traditional algorithm for syphilis screening be abandoned? Neurosyphilis presenting as limbic encephalitis: a prozone false-negative RPR missed by an RPR-only initial screen. EJCRIM 2026;13:doi:10.12890/2026_007473

ABSTRACT

Introduction: Neurosyphilis is a treatable mimic of viral and autoimmune limbic encephalitis. The prozone phenomenon—antibody excess preventing the antigen–antibody lattice—can render an undiluted non-treponemal test such as the rapid plasma reagin (RPR) test falsely negative, with reactivity restored on dilution.

Case description: A 37-year-old man presented with seizures and rapidly progressive limbic encephalitis; Brain magnetic resonance imaging (MRI) with fluid-attenuated inversion recovery sequences showed hyperintensities in the amygdalae, periventricular regions, left insula and left putamen. On admission, the possibility of a sexually transmitted infection was considered, but only an RPR was requested, and it was negative. When the encephalitis failed to respond to empirical antiviral, antibacterial and corticosteroid therapy, a *Treponema pallidum* haemagglutination assay was added; it was positive, and serially diluted serum yielded a reactive RPR (endpoint titre 1:32), revealing a prozone false negative. Cerebrospinal fluid studies confirmed neurosyphilis, and the patient recovered fully after penicillin.

Discussion: With an RPR-only screen, the non-treponemal/treponemal discordance that typically signals a prozone never arose, so the false negative was accepted at face value; the delay reflected the prozone compounded by the initial testing strategy. Because empirical ceftriaxone active against *T. pallidum* had been started on admission, effective treatment was not delayed.

Conclusion: When syphilis is suspected, a negative undiluted RPR does not exclude it; pairing a treponemal test with the RPR—or adopting a treponemal-first screening strategy—guards against prozone-related false negatives.

KEYWORDS

Neurosyphilis, prozone phenomenon, limbic encephalitis, rapid plasma reagin, syphilis serology

EFIM
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LEARNING POINTS

- When a sexually transmitted infection is being considered, obtain a careful, respectful sexual history and request non-treponemal and treponemal tests together; a rapid plasma reagin -only screen cannot reveal the non-treponemal/treponemal discordance that signals a prozone false negative. A treponemal-first (reverse-sequence) algorithm avoids this particular pitfall.
- A negative undiluted RPR does not exclude syphilis: the prozone phenomenon occurs even at low-to-moderate titres and in human immunodeficiency virus-negative patients, so serial dilution should be requested when clinical suspicion is high.
- Neurosyphilis is a treatable mimic of limbic encephalitis; outcome depends on prompt effective therapy, and including a treponemal-active agent (e.g. ceftriaxone) in empirical meningoencephalitis coverage may limit harm from diagnostic delay.

INTRODUCTION

Syphilis is resurging worldwide, and reported cases in Japan have risen sharply over the past decade[1]. Neurosyphilis, from invasion of the central nervous system by *Treponema pallidum*, produces protean manifestations[2]. Limbic encephalitis is an uncommon but increasingly recognised presentation whose mesiotemporal fluid-attenuated inversion recovery (FLAIR) hyperintensities can mimic herpes simplex and autoimmune or paraneoplastic encephalitis[3–5]. Serological diagnosis relies on both non-treponemal tests, such as the rapid plasma reagin (RPR) test, and treponemal tests, such as the *T. pallidum* haemagglutination assay (TPHA). The prozone phenomenon—antibody excess preventing formation of the antigen–antibody lattice—can render an undiluted non-treponemal test falsely negative, with reactivity restored on dilution[6]. We describe neurosyphilitic limbic encephalitis in which an RPR-only initial screen, combined with a prozone false negative, delayed the diagnosis.

CASE DESCRIPTION

A 37-year-old man was brought to hospital after recurrent episodes of impaired consciousness and a generalised tonic–clonic seizure. Over the preceding day he had been uncharacteristically talkative and forgetful. His history included aspirin-exacerbated respiratory disease and eosinophilic sinusitis, treated with low-dose prednisolone and the anti-interleukin-5 receptor antibody benralizumab. On admission he was mildly drowsy (Glasgow Coma Scale 15) with neck stiffness and dysarthria; temperature was 37 °C. Over the first hospital days his mental state deteriorated: he became disoriented to time and place, disinhibited and confabulatory, produced incoherent speech and was unable to follow simple commands, a picture consistent with limbic encephalitis.

Cerebrospinal fluid (CSF) showed mononuclear pleocytosis (17 mononuclear cells/3 high-power fields), protein 115 mg/dl and glucose 57 mg/dl; herpes simplex and varicella-zoster polymerase chain reaction were subsequently negative. Brain magnetic resonance imaging (MRI) with FLAIR sequences showed hyperintensities in the bilateral amygdalae, the periventricular regions bordering the third ventricle, the left insular cortex and the left putamen *(Fig. 1)*. No sexual history had been available from his prior outpatient visits. Because he was living with a man, the possibility of a sexually transmitted infection was considered, and human immunodeficiency virus (HIV) antibody and an RPR were obtained on admission; both were negative. Notably, no treponemal test was sent at this point, and the RPR (manual card test) was read on undiluted serum.

Empirical intravenous acyclovir, ceftriaxone 2 g twice daily and levetiracetam were started, and the seizures ceased. Investigations for autoimmune, paraneoplastic and other causes were unremarkable *(Table 1)*; a neuronal-surface and onconeural antibody panel could not be obtained rapidly enough to guide acute management. High-dose methylprednisolone (1 g/day, days 3–5) produced no improvement.

Because syphilis remained a concern despite the negative

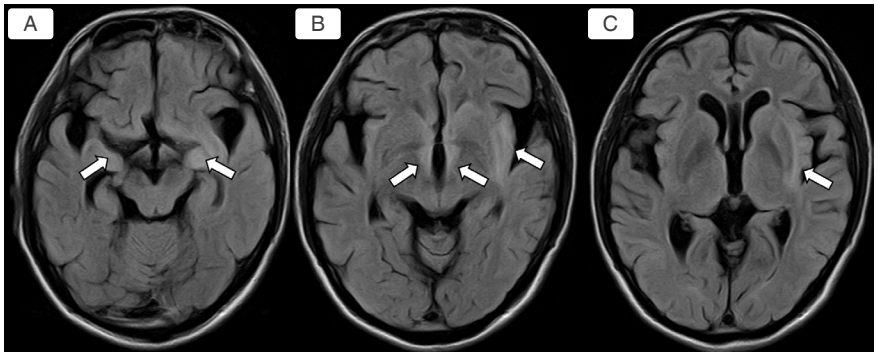


Figure 1. *Brain magnetic resonance imaging on admission. Axial fluid-attenuated inversion recovery images show hyperintensities in the bilateral amygdalae A) the periventricular regions bordering the third ventricle bilaterally and B) the left insular cortex, and C) the left putamen, consistent with limbic encephalitis with extension to the basal ganglia.*

Investigation	Result	Reference
Antinuclear antibody	<40×	<40×
Anti-SS-A/SS-B	Negative	Negative
Anti-aquaporin-4	Negative	Negative
Anti-glutamic acid decarboxylase	Negative	Negative
Soluble interleukin-2 receptor (U/ml)	203	157–474
MPO-ANCA / PR3-ANCA	Negative	Negative
C3/C4 (mg/dl)	101/19	65–135/13–35
Erythrocyte sedimentation rate (mm/h)	9	<15
TSH (µIU/ml)	3.12	0.61–4.23
Free T4 (ng/dl)	1.5	0.82–1.63
Anti-TPO / anti-thyroglobulin	Negative	Negative
Trunk CT (non-contrast)	No obvious malignancy	—

Table 1. *Investigations for alternative causes of limbic encephalitis (acute phase).*
Abbreviations: MPO/PR3-ANCA, myeloperoxidase/proteinase-3 antineutrophil cytoplasmic antibody; SS-A/SS-B, Sjögren's-syndrome-related antigen A/B; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; T4, Thyroxine; CT, computed tomography.

admission RPR, a TPHA and a repeat RPR were sent on day 9. The TPHA was positive, and serially diluted serum was reactive to an endpoint titre of 1:32, confirming that the admission result had been a prozone false negative. CSF RPR and CSF TPHA were reactive and positive and HIV antibody was negative, establishing neurosyphilis presenting as limbic encephalitis. On direct questioning prompted by the serological diagnosis, he disclosed a male sexual partner.

Intravenous penicillin G (24 million units/day) was given from day 9 to day 23 *(Fig. 2A)*. Cognition improved in parallel: the Mini-Mental State Examination rose from 18 (day 12) to 28 (day 23) and the Hasegawa Dementia Scale–Revised from 23 to 29, with resolution of disorientation, disinhibition and incoherent speech and a reduction in errors on the Trail Making Test. He was discharged home on day 25, independent in activities of daily living, and returned to work about 4 months after onset. Serial follow-up with an automated assay confirmed Treponema Pallidum Haemagglutination Assay a serological response *(Fig. 2B)*. The first serum RPR measured by the automated assay,8 months after diagnosis, was unexpectedly high (85.8 R.U.); because the manual dilution titre obtained at diagnosis and the automated value are not directly comparable, a second course of oral amoxicillin plus probenecid was given as a precaution. The titre subsequently declined to 7.6 R.U. by 30 months, and the neurological recovery had been complete well before the second course.

DISCUSSION

On admission, the possibility of a sexually transmitted infection was considered, yet only an RPR was requested. Because non-treponemal and treponemal antibodies behave differently, a prozone usually declares itself as a discordant result—non-treponemal-negative but treponemal-positive; with an RPR-only screen this discordance never arose, and the false negative was accepted at face value. Guidelines recommend pairing non-treponemal and treponemal testing when syphilis is suspected[7]; had a TPHA accompanied the initial RPR, the discrepancy would likely have prompted dilution and earlier recognition. The delay is therefore best attributed to the prozone compounded by an RPR-only strategy, rather than to the prozone alone. A specific sexual history was, moreover, not pursued at presentation and emerged only after serology prompted a more detailed interview; eliciting a careful, respectful and non-judgmental sexual history at the initial encounter might itself have shortened the delay.

A prozone is not confined to very high titres. Among 4,334 patients with a reactive RPR, 36 (0.83%) showed a prozone; endpoint titres ranged from 1:8 to 1:512, nearly one-third were 1:16 or lower, and neurosyphilis was associated with the phenomenon[8]. Our patient's endpoint titre was only 1:32 and he was HIV-negative. A negative undiluted RPR should therefore prompt serial dilution when clinical suspicion is high[6].

Distinguishing neurosyphilis from autoimmune limbic

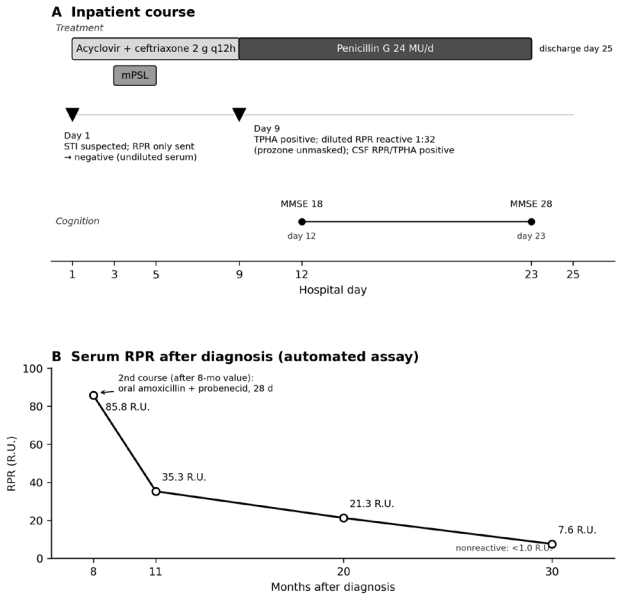


Figure 2. *Clinical course. A) Inpatient timeline showing continuous anti-treponemal therapy (ceftriaxone from day 1, then penicillin G to day 23), the rapid plasma reagin (RPR)-only admission screen with a prozone false negative, unmasking of the prozone on day 9, and cognitive recovery (Mini-Mental State Examination 18 to 28); B) Serum RPR by automated latex turbidimetric assay after diagnosis; Because the first automated value (85.8 R.U. at 8 months) appeared unexpectedly high, a second course of oral amoxicillin plus probenecid was given; the titre then declined without further intervention. R.U., RPR units.*

encephalitis is difficult, and the two are not mutually exclusive: neurosyphilis can secondarily induce neuronal-surface antibodies that resolve after antitreponemal therapy[9]. A positive autoantibody therefore does not exclude neurosyphilis, and—as in our patient, whose antibody panel was unavailable acutely—syphilis serology should be pursued in parallel.

Reported cognitive outcomes vary and depend largely on the interval to effective treatment rather than on the presentation itself[3,9]. Our patient received anti-treponemal therapy from day 1: empirical ceftriaxone, an accepted alternative agent for neurosyphilis[10], was given for suspected bacterial meningitis before penicillin. Thus, although the diagnosis was delayed, effective treatment was not—a plausible reason for his full recovery and an argument for including a treponemal-active agent in empirical coverage of undifferentiated meningoencephalitis. The initial worsening followed by a plateau is consistent with the natural course of the encephalitis before treatment took effect; clinical response in neurosyphilis is conventionally assessed 1 month after treatment and evolves over weeks to months.

Syphilis screening algorithms have evolved differently worldwide, shifting from the traditional non-treponemal-first approach to the treponemal-first algorithm increasingly adopted in Europe and North America. Even within Japan, practice is not uniform, with some regional insurance review boards permitting simultaneous testing while others, including Tokyo, in practice enforce a sequential algorithm through non-reimbursement—as at the initial evaluation of our patient. A non-treponemal-first screen can be defeated by a prozone false negative, as here, whereas a treponemal immunoassay (enzyme immunoassay or chemiluminescence immunoassay) is more sensitive and unaffected by the prozone. Its trade-offs—detection of previously treated infection and, in low-prevalence populations, isolated treponemal-positive/non-treponemal-negative results requiring a further treponemal test—are real, and direct comparisons of the two algorithms remain limited[11]. Where workflow or reimbursement permits only one test, as often in Japan, a treponemal test is the safer choice when clinical suspicion is real, since a falsely negative RPR risks missing active disease.

REFERENCES

1. Komori A, Mori H, Xie W, Valenti S, Naito T. Rapid resurgence of syphilis in Japan after the COVID-19 pandemic: A descriptive study. PLoS One. 2024;19(3):e0298288. doi: 10.1371/journal.pone.0298288.
2. Ropper AH. Neurosyphilis. N Engl J Med. 2019;381(14):1358-1363. doi: 10.1056/NEJMra1906228. Erratum in: N Engl J Med. 2019;381(18):1789. doi: 10.1056/NEJMx190030. Erratum in: N Engl J Med. 2023;389(19):1828. doi: 10.1056/NEJMx230008.
3. Fujimoto H, Imaizumi T, Nishimura Y, Miura Y, Ayabe M, Shoji H, et al. Neurosyphilis showing transient global amnesia-like attacks and magnetic resonance imaging abnormalities mainly in the limbic system. Intern Med. 2001;40(5):439-42. doi: 10.2169/internalmedicine.40.439.
4. Shrimpton M, Malhotra A. Neurosyphilis presenting as limbic encephalitis. BMJ Case Rep. 2023;16(12):e258794. doi: 10.1136/bcr-2023-258794.
5. Abdelerahman KT, Santamaria DD, Rakocevic G. Pearls and oy-sters: neurosyphilis presenting as mesial temporal encephalitis. Neurology. 2012;79(24):e206-8. doi: 10.1212/WNL.0b013e318278b5a1.
6. Papp JR, Park IU, Fakile Y, Pereira L, Pillay A, Bolan GA. CDC Laboratory Recommendations for Syphilis Testing, United States, 2024. MMWR Recomm Rep. 2024;73(1):1-32. doi: 10.15585/mmwr.rr7301a1.
7. 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(4):1-187. doi: 10.15585/mmwr.rr7004a1. Erratum in: MMWR Morb Mortal Wkly Rep. 2023;72(4):107-108. doi: 10.15585/mmwr.mm7204a5.
8. Liu LL, Lin LR, Tong ML, Zhang HL, Huang SJ, Chen YY, et al. Incidence and risk factors for the prozone phenomenon in serologic testing for syphilis in a large cohort. Clin Infect Dis. 2014;59(3):384-9. doi: 10.1093/cid/ciu325.
9. Liao H, Zhang Y, Yue W. Case Report: A Case Report of Neurosyphilis Mimicking Limbic Encephalitis. Front Neurol. 2022;13:862175. doi: 10.3389/fneur.2022.862175.
10. Bettuzzi T, Jourdes A, Robineau O, Alcaraz I, Manda V, Molina JM, et al. Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France: a retrospective multicentre study. Lancet Infect Dis. 2021;21(10):1441-1447. doi: 10.1016/S1473-3099(20)30857-4. Erratum in: Lancet Infect Dis. 2021;21(10):e302. doi: 10.1016/S1473-3099(21)00477-1.
11. Cantor A, Nelson HD, Daeges M, Pappas M. Screening for Syphilis in Nonpregnant Adolescents and Adults: Systematic Review to Update the 2004 U.S. Preventive Services Task Force Recommendation [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 Jun. Report No.: 14-05213-EF-1.